FIG. 2

(57) Abstract: Particles for delivery of tramadol formed from tramadol and a hydrophobic matrix, as well as methods for making and using such particles. Tramadol is an opioid receptor agonist and centrally acting synthetic analgesic used to treat moderate to moderately severe pain. Tramadol has a wide range of applications, including treatment of rheumatoid arthritis, restless legs syndrome, motor neuron disease, and fibromyalgia.
TRAMADOL PARTICLE FORMULATIONS AND METHODS

Cross Reference to Related Applications


Statement of Government Interest

[0002] This invention was made with government support under Award No. 1R43DA032294-01 awarded by National Institutes of Health. The United States government has certain rights in the invention.

BACKGROUND

[0003] Inadequate management of postsurgical pain affects every one out of two patients in the United States and has significant clinical consequences that dramatically increase total cost of care. Current multi-modal postsurgical pain management techniques often fail to adequately manage postsurgical pain and are associated with dangerous and costly opioid-related adverse events (ORAE). Most analgesics require multiple oral administrations per day which frequently leads to poor compliance and insufficient control over pharmacokinetic profiles. In addition, the increased reliance on analgesic opioids for chronic pain management has led to increased levels of dependence and abuse. While injectable formulations offer improved compliance and reduced risk of abuse, they typically result in drug ‘burst’, followed by imprecise pharmacokinetics resulting in a lack of tight control over the concentration of these drugs in the blood.

SUMMARY

[0004] The present disclosure relates to particles and methods for delivery of tramadol and methods for making such particles.

[0005] Tramadol is a µ-opioid receptor agonist and centrally acting synthetic analgesic used to treat moderate to moderately severe pain. Tramadol has a wide range of applications, including treatment of rheumatoid arthritis, restless legs syndrome, motor neuron disease, and fibromyalgia.

[0006] In one embodiment, a composition is provided comprising particles, wherein the particles comprise tramadol and a hydrophobic matrix. The tramadol is dispersed in the hydrophobic matrix and the particles have a melting temperature of at least 45°C. Furthermore,
the particles are substantially free of water have a mean particle size diameter of less than 250 μm.

[0007] In another embodiment, the above composition further comprises a densifier.

[0008] In another embodiment, any of the above compositions further comprise a stabilizer. For example, the stabilizer is chosen from one or more of cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, microcrystalline cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, chitin, chitosan, pectin, polyacrylates, polymethacrylates, polyvinyl acetate, EVA resins, acetate phthalate, polyanhydrides, polyvinylalcohols, and silicone elastomers. The stabilizer can be from about 0.1% to about 10% by weight of the particle.

[0009] In another embodiment, any of the above compositions may further comprise a release modifier. For example, the release modifier is chosen from one or more of stearic acid, sodium stearate, magnesium stearate, glycercy1 monostearate, castor oil, cremophor, oleic acid, sodium oleate, lauric acid, sodium laurate, myristic acid, sodium myristate, vegetable oils, coconut oil, mono-, di-, tri-glycerides, stearyl alcohol, span 20, span 80, and polyethylene glycol (PEG).

[0010] In another embodiment, any of the above composition may further comprise a liquid vehicle. For example, the liquid vehicle may include tramadol, tramadol freebase, an analgesic other than tramadol, or any combination thereof.

[0011] In any of the above embodiments, the particles have a diameter with no more than a 25% standard deviation from the mean particle diameter, a diameter with no more than a 15% standard deviation from the mean particle diameter, or a diameter with no more than a 10% standard deviation from the mean particle diameter.

[0012] In any of the above embodiments, particles have mean particle size diameter of less than 200 μm.

[0013] In any of the above embodiments, the active ingredient is present in an amount from about 10% to about 90% by weight of the particles.

[0014] In any of the above embodiments, the hydrophobic matrix is a hydrophobic wax material, a lipid material, or a glycol polymer. In one instance, the hydrophobic matrix is a hydrophobic wax material chosen from one or more of ceresine wax, beeswax, ozokerite, microcrystalline wax, candelilla wax, montan wax, carnauba wax, paraffin wax, cauassu wax, Japan wax, and Shellac wax. In another instance, the hydrophobic matrix is a lipid material.
chosen from one or more of glycerol fatty acid esters, triacylglycerols, tripalmitin, tristearin, glyceryl trilaurate, coconut oil, glycerins, glycerides, glyceryl trimyristate, glyceryl tripalmitate, glyceryl tristearate, hydrogenated fats, ceramides, and organic esters. In yet another instance, the hydrophobic matrix is a glycol polymer chosen from one or more of high molecular weight glycols, polyethylene glycol with a minimum of 20 repeating units, cellulose ethers, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, microcrystalline cellulose, cellulose esters, cellulose acetate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyacrylates and derivatives thereof, polymethacrylates and derivatives thereof, poloxamers, starch and derivatives thereof.

[0015] In any of the above embodiments, the hydrophobic matrix is present in amount from about 30% to about 80% by weight of the particles.

[0016] In any of the above embodiments, the particles comprise a layer disposed on the surface of the particle.

[0017] In any of the above embodiments, the particles are configured to have sustained release of the active ingredient over a period of 10 hours or more and in some instances, over a period of 24 hours or more.

[0018] In any of the above embodiments, the particles comprise a water content of less than 2.0% w/w, less than 1.0% w/w, or less than 0.5% w/w. In some instances, the particles may have a water content that is undetectable by currently available methods.

[0019] The present disclosure also provides a method comprising administering to a subject a therapeutically effective amount of any of the above described compositions.

[0020] The features and advantages of the present invention will be readily apparent to those skilled in the art. While numerous changes may be made by those skilled in the art, such changes are within the spirit of the invention.

**DRAWINGS**

[0021] Figure 1 is (A) In vitro release kinetics of wax-tramadol microspheres over a 7-day period (n=2; average ±S.D.) (B) Wax-tramadol microspheres (Carnauba wax with 7% Tramadol HCl) with a mean diameter of 150 μm.

[0022] Figure 2 shows in vivo performance of wax-tramadol microspheres. Free tramadol and Tramadol HCL extended release (200 mg) (manufactured by Patriot Pharmaceuticals) exhibited large bursts and fast elimination, whereas microsphere formulations
demonstrated a smooth ramp in concentration and sustained blood levels. Results represented as average ±S.D.

[0023] Figure 3 is a graph showing release of tramadol. Particles were suspended in sesame-oil at 100 mg/mL, injected into dialyzer cassettes, and sampled daily for 7 days.

[0024] While the present disclosure is susceptible to various modifications and alternative forms, specific example embodiments have been shown in the figures and are described in more detail below. It should be understood, however, that the description of specific example embodiments is not intended to limit the invention to the particular forms disclosed, but on the contrary, this disclosure is to cover all modifications and equivalents as illustrated, in part, by the appended claims.

DESCRIPTION

[0025] The present disclosure relates to particles and methods for delivery of tramadol and methods for making such particles.

[0026] The present disclosure provides, according to certain embodiments, compositions comprising particles, the particles comprising tramadol and a hydrophobic matrix. The present disclosure also provides methods for making and using such particles. The particles of the present disclosure may be useful, among other things, for sustained release formulations of tramadol. Unless otherwise specified, the term “tramadol” refers generally to any form of tramadol, including both salt and freebase forms of tramadol.

[0027] Drug delivery systems that allow for long-term release of pain relievers, including analgesics and opioids, reduce the risk of patient non-compliance and abuse, but often result in difficult to control drug release kinetics. Attempts to sustain and control the concentration of these drugs in the blood via controlled release formulations have typically resulted in drug ‘burst’, followed by marginal control over the ensuing pharmacokinetics.

[0028] The present disclosure is based in part on the observation that Precision Particle Fabrication technology (See, e.g., U.S. Patent No. 6,669,961; 7,368,130) may produce uniform microspheres encapsulating tramadol provide sustained delivery of tramadol without drug ‘burst’.

[0029] According to certain embodiments, the present disclosure provides compositions comprising particles, the particles comprising tramadol and a hydrophobic matrix; wherein the tramadol is dispersed in the hydrophobic matrix; wherein the particles have a
melting temperature of at least 45°C; wherein the particles are substantially free of water; and wherein the particles have a mean particle size diameter of less than 250 μm.

[0030] As noted above, the tramadol is disposed within the hydrophobic wax matrix. The tramadol may be dispersed within hydrophobic wax matrix via a molten or solubilized form. The tramadol also may be dispersed within the hydrophobic matrix in a molecular dispersed form, i.e. as a solid solution, in fine crystalline dispersed form, in a glassy amorphous phase, or dispersed as a fine amorphous powder, as well as in a eutectic mixture. The tramadol also may be dispersed within hydrophobic wax matrix as small particulates. Alternatively, the tramadol may be disposed substantially within the hydrophobic wax matrix in a core-shell configuration in which the hydrophobic wax matrix is the shell. The particles of the present disclosure are substantially free of water or other aqueous solvent.

[0031] In general, the tramadol may be present in the particles in an amount sufficient to provide any suitable dosage. The active ingredient may be present in the particles in an amount in the range of from about 10% to about 90%, about 15% to about 80%, 20% to about 60%, or 30% to about 40% by weight of the particles.

[0032] In certain embodiments, the entire dose of the tramadol may be provided by the tramadol in the particle. In other embodiments, the particle provides a partial does of the tramadol. In such embodiments, the remainder of the does may be included in the composition apart from the particles. For example, the tramadol may be included in a liquid vehicle in which the particles are suspended. In certain specific embodiments, the tramadol included in the liquid vehicle may be the freebase of tramadol.

[0033] In general, the particles of the present disclosure have a melting temperature of at least 45°C and a mean particle size diameter suitable for injection (e.g., from about 20 μm to about 250 μm). In certain embodiments, the particles have a mean particle size diameter of from about 50 μm to about 100 μm. In other embodiments, the particles may be substantially monodisperse with a relatively narrow particle size distribution with a 25% or less standard deviation from the mean particle size. In other embodiments, the particles may be substantially monodisperse with a relatively tight particle size distribution within a 5%, 10%, 15%, or 20% standard deviation from the mean particle size. In a specific embodiment, the mean particle diameter may range from 25 μm to 100 μm. In some embodiments, two or more populations of
substantially monodisperse particle sizes may be used. The particular particle size, or mixture of particle sizes, will depend on the desired release profile.

[0034] In some embodiments, relatively tight particle size distributions may be preferred. Such particle size distributions benefit from the lack of “fines.” Particle fines are small particles left over from a manufacturing process. Their small effective surface area results in faster dissolution rates. As used herein, the term “fines” refers to particulates having a particle size at or below 10% of the mean particle size diameter. Accordingly, formulations having particle fines are not substantially monodisperse and may not provide the desired dissolution properties and/or bioavailability.

[0035] The hydrophobic matrix may be a hydrophobic wax material, a lipid material, a glycol polymer, or a combination thereof. In certain embodiments, suitable hydrophobic matrix materials have a melting point at or above about 45°C and a viscosity when melted sufficient to allow spraying.

[0036] Suitable lipid materials should be solid at room temperature and have a melting temperature at or above about 45°C. Examples of suitable lipid materials include, but are not limited to, glycerol fatty acid esters, such as triacylglycerols, tripalmitin, tristearin, glyceryl trilaurate, coconut oil, glycerins, glycerides, glyceryl trimeyrurate, glyceryl tripalmitate, glyceryl tristearate, hydrogenated fats, ceramides, and organic esters from and/or derived from plants, animals, minerals.

[0037] Suitable glycol polymers should be solid at room temperature and have a melting temperature at or above about 45°C. Examples of suitable glycol polymers include, but are not limited to, high molecular weight glycols (e.g., polyethylene glycol with a minimum of 20 repeating units), cellulose ethers (e.g., ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, microcrystalline cellulose), cellulose esters (e.g., cellulose acetate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate), polyacrylates derivatives, polymethacrylates derivatives, poloxamers, and starch and its derivatives.

[0038] In certain embodiments, the hydrophobic matrix may be a hydrophobic wax material. The hydrophobic wax matrix may be any wax-like material suitable for use with the active ingredient. Examples of suitable hydrophobic waxes include, but are not limited to, ceresine wax, beeswax, ozokerite, microcrystalline wax, candelilla wax, montan wax, carnauba wax, paraffin wax, cauassu wax, Japan wax, and Shellac wax.
In certain embodiments of particles employing a hydrophobic wax matrix, the particles further comprise a densifier. A densifier may be used to increase the density of a particle. For example, a densifier may be used to make a particle heavier so that it will approach or be closer to the density of a liquid vehicle in which the particles may be suspended. Examples of suitable densifiers include, but are not limited to, titanium dioxide, calcium phosphate, and calcium carbonate. In one embodiment, the one or more densifiers may be present in the particles in an amount in the range of from about 0% to about 40% by weight of the particles.

The hydrophobic matrix may be present in the particles in an amount in the range of from about 5% to about 90%, about 5% to about 30%, about 20% to about 80%, or about 40% to about 60% by weight of the particle. In another embodiment, the hydrophobic matrix may be present in the particles in an amount sufficient to provide sustained release of the active ingredient over a period ranging between about 8 hour to about 24 hours or more. For example, the wax may be present in the particles in an amount sufficient to provide sustained release of the hydrophilic active ingredient over a period of about 8 hours, 10 hours, 12 hours, 18 hours, 24 hours, 30 hours, 36 hours, 48 hours, or longer. In certain embodiments, the hydrophobic matrix may be increased or decreased depending on the particular release characteristics desired. In addition, more than one hydrophobic matrix layer may be used to achieve the particular sustained release desired. In general, higher hydrophobic matrix concentrations favor longer, more sustained release of the tramadol and lower concentrations favor faster, more immediate release.

In certain embodiments, the particles of the present disclosure comprise a stabilizer. The stabilizer may improve the properties of the hydrophobic wax matrix and provide improved stability of the particles over time, as well as improved dissolution profiles. Changes in particles can occur over time that affect the particle’s performance. Such changes include physical, chemical, or dissolution instability. These changes are undesirable as they can affect a formulation’s shelf stability, dissolution profile, and bioavailability of the active ingredient. For example, the hydrophobic wax matrix or tramadol may relax into a lower energy state, the particle may become more porous, and the size and interconnectivity of pores may change. Changes in either the tramadol or hydrophobic wax matrix may affect the performance of the particle. The present disclosure is based, at least in part, on the observation that a stabilizer added to the hydrophobic wax matrix improves the stability and performance of the particles of the
present disclosure. By way of explanation, and not of limitation, it is believed that the stabilizer interacts with the hydrophobic wax material making it resistant to physical changes. Accordingly, the particles of the present disclosure comprise a stabilizer. Examples of suitable stabilizers include but are not limited to, cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, microcrystalline cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, chitin, chitosan, pectin, polyacrylates, polymethacrylates, polyvinyl acetate, Elvax® EVA resins, acetate phthalate, polyanhydrides, polyvinylalcohols, silicone elastomers, and mixtures thereof. Stabilizers may be used alone or in combination. The stabilizer may be present in the particles in an amount from about 0.1% to about 10% by weight of the particle. For example, the stabilizer may be present in an amount from about 0.1% to about 5%, about 0.5% to about 2.5%, and about 5% to about 10% by weight of the particle.

[0042] In certain embodiments, the particles of the present disclosure also comprise a release modifier. A release modifier improves the performance of hydrophobic wax matrix particles particularly during the later stages of the active ingredient’s release. The release modifier is believed also to interact with the stabilizer (e.g., improve the stabilizer’s solubility) to facilitate preparation of the particles. It is also believed that the release modifier may adjust the relative hydrophobicity of the hydrophobic wax material. Examples of suitable release modifiers include but are not limited to, stearic acid, sodium stearate, magnesium stearate, glyceryl monostearate, castor oil (e.g., cremophor), oleic acid, sodium oleate, lauric acid, sodium laurate, myristic acid, sodium myristate, vegetable oils, coconut oil, mono-, di-, tri-glycerides, stearyl alcohol, span 20, span 80, and polyethylene glycol (PEG). Release modifiers may be used alone or in combination. For example, in certain embodiments, the release modifier may be a combination of stearic acid and glyceryl mono stearate. The release modifier may be present in the particles in an amount from about 0.5% to about 90% by weight of the particle. For example, the release modifier may be present in an amount from about 0.5% to about 10%, about 1% to about 5%, about 2.5% to about 5%, about 5% to about 10%, about 10% to about 25%, about 20% to about 90%, about 40% to about 80%, about 50% to about 70%, about 60% to about 80%, and about 80% to about 90% by weight of the particle. In general, higher release modifier concentrations favor faster release of the tramadol and lower concentrations favor longer, sustained release.
[0043] In some embodiments, the particles of the present disclosure may further comprise pharmaceutically acceptable inactive ingredients. The term “pharmaceutically acceptable,” when used in connection with the pharmaceutical compositions of the disclosure, refers to molecular entities and compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. For example, “pharmaceutically acceptable” may refer to inactive ingredients approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. Examples of inactive ingredients that may be included in particles or formulations of the present disclosure include but are not limited to, buffers, preservative, suspending agents, dyes, antioxidants, surfactants, and the like.

[0044] In some embodiments, the particles of the present disclosure may comprise an additional layer disposed on the surface of the particle. Such layers may be used to reduce or delay the release of active ingredient from the particles or to mask the taste of the active ingredient. The additional layer may be a coating applied to the surface of the particle. Such coating may be formed from any material capable of being applied to a pharmaceutical composition. Coatings may be applied to the particles using techniques known in the art such as, for example, Wurster coating and techniques described in U.S. Pat. Nos. 6,669,961, 7,309,500, and 7,368,130, all of which are incorporated by reference.

[0045] Examples of suitable materials that may be applied to the surface of the particle to, among other things, reduce or delay the release of active ingredient from the particles include, but are not limited to, polymethacrylates, materials from Eudragit®️, Surelease®️️ or Kollicoat®️ series, and cellulose materials (e.g., ethyl cellulose, hydroxypropylmethyl cellulose).

[0046] Examples of suitable materials that may be applied to the surface of the particle to, among other things, mask the taste of the active ingredient include, but are not limited to, mono-, di-, or polysaccharides, sugar alcohols, or other polyols such as lactose, glucose, raffinose, melezitose, lactitol, mannitol, maltitol, trehalose, sucrose, and starch; ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxybutyl methylcellulose, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, polymethyl methacrylate, polyethyl methacrylate, polyphenyl methacrylate, polymethyl acrylate,
polyisopropyl acrylate, polyisobutyl acrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyphenyl methacrylate, polyvinyl acetate, polyvinyl isobutyl ether, polyvinyl alcohol, polyethylene terephthalate, polyethylene oxide, polyethylene glycol, polyethylene, polypropylene, polyoctadecyl acrylate, polyvinyl chloride, and polyvinyl pyrrolidone.

[0047] In one embodiment, the additional layer may comprise the hydrophobic matrix and optionally tramadol or other active ingredients. The additional layer also may further comprise a stabilizer or a release modifier or both. When included, the tramadol may be present the same or different amounts than is present in the remainder of the particle. Such additional layer may further include a coating as described above.

[0048] In certain embodiments, the particles of the present disclosure are stable. Stability is often a consideration for pharmaceutical formulations. For particulate dosage forms, like certain embodiments of the particles of the present disclosure, stability may be measured with reference to dissolution. Dissolution testing is an in vitro method that characterizes how an active ingredient is extracted out of a solid dosage form. It can indicate the efficiency of in vivo dissolution. Dissolution can be measured using standard protocols. For example, the stability of the particle of the present disclosure may be evaluated by studying the release profile at any given time point during the course of dissolution when placed at 40°C for up to at least 4 weeks as measured by, for example, United States Pharmacopeia (USP) dissolution protocols (e.g., USP II or IV).

[0049] The present disclosure also provides formulations comprising particles of the present disclosure. Such formulations may be in the form of a suspension of particles or any other suitable means of formulating particulates into dosage forms suitable for administration to a patient. In certain embodiments, formulations of the present disclosure may have a range of particle concentrations suitable or optimized for a particular application, dosage, and mode of administration. In certain embodiments, the particle concentration may result in viscous formulations. In general, the formulations of the present disclosure may be delivered to a subject by injection (e.g., subcutaneous, intramuscular, positive displacement). In certain embodiments, the particles may be formulated for delivery to a subject in the form of an implant, depot, pump, programmable drug administration device, or other delivery approaches known in the art.

[0050] In general, the particles of the present disclosure may be made using methods comprising melting the particle components together followed by particle fabrication. Such
procedures may be performed in essentially a single step and without the use of water or other aqueous solvent. This has several advantages. For example, the resulting particles are dry and ready for further processing or formulation. Similarly, the resulting particles are substantially free of water, which may improve the stability of the active ingredient. Thus, water is not introduced artificially in the Precision Particle Fabrication process, and water content will generally be dependent on the raw active ingredient. For example, if the active ingredient is hygroscopic, such as guaifenesin, then the particle will likely have some water content based almost entirely on guaifenesin. However, if, for example, a tramadol freebase oil is used as the active ingredient, the water content may approach undetectable levels. Accordingly, in some embodiments, the resulting particles comprise a water content of less than about 5.0% w/w, less than about 4.0% w/w, less than about 3.0% w/w, less than about 2.0% w/w, less than about 1.0% w/w, or less than about 0.5% w/w, and in some instance, the water content may be undetectable using current moisture content measurement methods. Water content can be tested by coulometric Karl Fischer titration (756 KF Coulometer, Metrohm Ion Analysis, Herisau, Switzerland). Briefly, the coulometric Karl Fischer titration is a version of the classical water determination method developed by Karl Fischer. The traditional method utilizes a methanolic solution of iodine, sulfur dioxide and a base as buffer. Several reactions are run in the titration of a water-containing sample and can be summarized by the following overall equation: H2O + I2+ [RNH]SO3CH3+ 2 RN ⇌ [RNH]SO4CH3+ 2 [RNH]I. According to the above equation, I2 reacts quantitatively with H2O. This chemical relation forms the basis of the water determination.

[0051] The lack of water in the particles prevents the occurrence of pores or voids in the particle resulting from evaporation of water droplets within the particle. Because the particles can be made without water or an emulsion step, the particles can be formed more efficiently and with fewer manufacturing artifacts. These procedures also allow higher concentrations of active ingredient to be loaded in the hydrophobic wax matrix. Additionally, the procedure provides particles substantially free of fines, the presence of which can adversely affect the active ingredient’s release profile.

[0052] In certain embodiments, the particles of the present disclosure may be made by melting the components together using a melt-assisted dissolution of the active ingredient approach followed by particle fabrication. For example, particles of the present disclosure may
be made by adding to a preheated vessel the following components: a hydrophobic matrix and an active ingredient, and optionally a releasing agent. The active may be added in a solid form (for melt processing), or in a solubilized form (for creating a solid dispersion). The components are then melted and allowed to equilibrate at a temperature of close to or higher than the melting temperature of the hydrophobic matrix. The stabilizer may be added and allowed to dissolve into the mixture. The temperature of the resulting mixture is then allowed cool to a lower temperature at which the melted solution or suspension still remains processable for particle fabrication. The particle fabrication may use the techniques disclosed in techniques described in U.S. Pat. Nos. 6,669,961; 7,309,500; and 7,368,130, all of which are incorporated by reference. Particle fabrication also may use other techniques known in the art such as, for example, a spinning disk atomizer, centrifugal coextrusion, prilling, spray congealing, spray cooling, melt atomization, and melt congealing.

[0053] In certain embodiments, the particles of the present disclosure may be made by melting the components together using a solvent-assisted dissolution of the active ingredient approach followed by particle fabrication. Such approaches are particularly suited for active ingredients with very high melting temperatures. For example, particles of the present disclosure may be made by adding to a preheated vessel the following components: a hydrophobic matrix and a releasing agent. The components are then melted and allowed to equilibrate at a temperature close to or higher than the melting temperature of the hydrophobic matrix. The stabilizer may be added and allowed to dissolve into the mixture. Finally, the drug is solubilized separately in a mild non-flammable solvent and added to the vessel. The solvent is then evaporated from the vessel under constant stirring over a desired duration. The temperature of the resulting mixture is then allowed cool to a lower temperature at which the melted solution or suspension still remains processable for particle fabrication. The particle fabrication is then performed using the techniques herein.

[0054] In another embodiment, the particles of the present disclosure may be used in a similar melt-assisted dissolution of the active ingredient approach in which the releasing agent and stabilizer are introduced into a preheated vessel and allowed to solubilize at a temperature close to or higher than the melting temperature of the hydrophobic matrix (e.g., for about 5-20 minutes). In operation, the releasing agent in its molten form may be used to substantially solubilize the stabilizer. If needed, this mixture’s temperature is then reduced to lower values
close to or higher than the melting temperature of the hydrophobic matrix and the hydrophobic wax and tramadol are then added. The resulting combination is mixed well (e.g., 1 hour) while the temperature is maintained. After mixing, the temperature of the mixture is allowed to cool to a lower temperature at which the melted solution or suspension still remains processable before starting the particle fabrication using techniques described above.

[0055] In certain embodiments, after particle fabrication the particles may be treated to reduce the occurrence of pores on the surface of the particle. In this approach, the particles are allowed to cool to room temperature (e.g., over about 6 to 24 hours) then exposed to a brief heat treatment at, for example, 65°C or other temperature slightly lower than the melting temperature of the hydrophobic matrix or other component of the particle having the lowest melting temperature. Such heat treatment may reduce the occurrence of a burst of active ingredient in the release profile of the particle.

[0056] To further illustrate various illustrative embodiments of the present disclosure, the following examples are provided.

EXAMPLES

[0057] The examples herein are illustrations of various embodiments of this invention and are not intended to limit it in any way.

[0058] Uniform microspheres were prepared using Orbis’ Melt-Spray Precision Particle Fabrication technology, and as disclosed in U.S. Pat. Nos. 6,669,961; 7,309,500; and 7,368,130, each of which is incorporated by reference. Briefly, Tramadol-HCL (“tramadol”) was first dissolved in dichloromethane (DCM) and then dispersed into molten Generally Accepted As Safe (GRAS) wax matrix material. DCM was subsequently evaporated to create a fine tramadol-wax solid dispersion. Tramadol-loaded wax suspensions were sprayed through a coaxial Precision Particle Fabrication nozzle. Simultaneously, the wax matrix jet was acoustically excited using an ultrasonic transducer (Sonics and Materials, Newtown, CT) controlled by a frequency generator (Agilent, Santa Clara, CA) that produced regular disruptions in the wax-tramadol jet. Wax-tramadol particles air-cooled and were collected in an empty vessel positioned approximately 4 feet below the nozzle. The dried particles were either stored at -20°C or used immediately for dissolution testing.

[0059] In vitro tramadol release from the microsphere/sesame oil ‘vehicle’ (exactly as it was given to the dogs) was injected into Slide-A-Lyzer Dialysis cassettes with a 10,000 MW
cutoff. The cassettes were submerged in DI water in a glass beaker at 37°C and sampled daily after the first 12 and 24 hour time points. Cumulative release was found by normalizing incremental release to total loaded drug, both determined by HPLC.

[0060] In vivo studies were designed for testing the controlled release of tramadol from wax microspheres. All pharmacokinetic studies were conducted using beagle dogs. The tramadol-loaded microspheres, having an average particle size of 150 μm diameter and 7 wt% drug loading, were compared to injection of free tramadol and to Ultram® tablets. Both free tramadol and tramadol-loaded microspheres were suspended in an oil ‘vehicle’ immediately prior to injection. After delivery, plasma samples were taken with decreasing frequency during the first 24 hours, then every 8 hours for 7 days.

[0061] In vitro tramadol release from Precision Particle Fabrication wax microspheres demonstrated low initial burst (<10%), followed by steady release until day 7 (Figure 1A). Only 20% of the loaded drug was released over 7 days. Uniform microspheres (Figure 1B) were produced in a single-step process – requiring no additional lyophilization or post-processing steps, which are typically required with traditional encapsulation techniques.

[0062] The performance of the tramadol-loaded wax microspheres was then compared in vivo to free tramadol injection and to Ultram® tablets dosed orally. At the onset of administration, dogs dosed with Ultram® and free tramadol experienced a spike in plasma concentrations well beyond the therapeutic window, whereas this ‘burst’ was minimized with the microsphere formulation (Figure 2). By the end of the first 24-hour period, tramadol was undetectable in dogs administered the free drug or tablets; however, dogs with the microsphere injection showed a steadily declining plasma concentration through 7 days. The pharmacokinetic analysis is provided in Table 1 and supported the observed profiles, revealing a tramadol half-life of the microsphere formulation that was 13 times longer than the free drug injection, with an average burst concentration approximately 3 times lower. The microencapsulated tramadol also exhibited a slightly higher AUC, which suggested near complete release in vivo – an interesting observation considering the lack of complete release observed in vitro (Figure 1A).
Table 1. Pharmacokinetic analysis for Tramadol HCl administration in canine species.

<table>
<thead>
<tr>
<th></th>
<th>t 1/2 (hrs)</th>
<th>t max (hrs)</th>
<th>Cmax (ng/mL)</th>
<th>AUC Last (ng*hr/mL)</th>
<th>AUC Obs (ng*hr/mL)</th>
</tr>
</thead>
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<tr>
<td>Free Tramadol</td>
<td>2.0 ± 0.3</td>
<td>2.0 ± 1.4</td>
<td>1015.5 ± 106.7</td>
<td>5867.6 ± 789.3</td>
<td>9885.6 ± 744.3</td>
</tr>
<tr>
<td>Microspheres</td>
<td>25.6 ± 2.0</td>
<td>4.0 ± 0.0</td>
<td>368.8 ± 164.2</td>
<td>7582.0 ± 2185.6</td>
<td>7683.0 ± 2192.7</td>
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<tr>
<td>Ultram®</td>
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<td>8.0</td>
<td>139.8</td>
<td>3161.7</td>
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</table>

*NOTE: Out of range data prevented full analysis. Example kinetics from one dog after oral dosing on Day 3.

[0063] Compared to the Ultram® group, the microspheres were able to achieve faster action while minimizing the ‘burst’ release. In addition, the microspheres were able to outperform both free tramadol and Ultram® groups by sustaining blood levels via slow release of tramadol from the microspheres (Figure 2).

[0064] Melt-Spray Precision Particle Fabrication was successfully used to create uniform wax-tramadol microsphere depots that eliminated ‘burst’ and sustained drug plasma concentrations. Traditional controlled-release polymers (such as polyesters), which usually require a wet process of microencapsulation, fail to provide acceptable drug loading and release.

[0065] Therefore, the present invention is well adapted to attain the ends and advantages mentioned as well as those that are inherent therein. The particular embodiments disclosed above are illustrative only, as the present invention may be modified and practiced in different but equivalent manners apparent to those skilled in the art having the benefit of the teachings herein. Furthermore, no limitations are intended to the details of construction or design herein shown, other than as described in the claims below. It is therefore evident that the particular illustrative embodiments disclosed above may be altered or modified and all such variations are considered within the scope and spirit of the present invention.

[0066] While compositions and methods are described in terms of “comprising,” “containing,” or “including” various components or steps, the compositions and methods can also “consist essentially of” or “consist of” the various components and steps.

[0067] All numbers and ranges disclosed above may vary by some amount. Whenever a numerical range with a lower limit and an upper limit is disclosed, any number and any included range falling within the range is specifically disclosed. In particular, every range of values (of the form, “from about a to about b,” or, equivalently, “from approximately a to b,” or, equivalently, “from approximately a-b”) disclosed herein is to be understood to set forth every number and range encompassed within the broader range of values.
[0068] Also, the terms in the claims have their plain, ordinary meaning unless otherwise explicitly and clearly defined by the patentee. Moreover, the indefinite articles “a” or “an”, as used in the claims, are defined herein to mean one or more than one of the element that it introduces. If there is any conflict in the usages of a word or term in this specification and one or more patent or other documents that may be incorporated herein by reference, the definitions that are consistent with this specification should be adopted.
What is claimed is:

1. A composition comprising particles, the particles comprising tramadol and a hydrophobic matrix; wherein the tramadol is dispersed in the hydrophobic matrix; wherein the particles have a melting temperature of at least 45°C; wherein the particles are substantially free of water; and wherein the particles have a mean particle size diameter of less than 250 μm.

2. The composition of claim 1, further comprising a densifier.

3. The composition of claim 1, further comprising a stabilizer.

4. The composition of claim 3, wherein the stabilizer chosen from one or more of cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, microcrystalline cellulose, cellulose acetate, cellulose phthalate, methyl cellulose, chitin, chitosan, pectin, polyacrylates, polymethacrylates, polyvinyl acetate, EVA resins, acetate phthalate, polyanhydrides, polyvinylalcohols, and silicone elastomers.

5. The composition of claim 3, wherein the stabilizer is from about 0.1% to about 10% by weight of the particle.

6. The composition of claim 1, further comprising a release modifier.

7. The composition of claim 6, wherein the release modifier is chosen from one or more of stearic acid, sodium stearate, magnesium stearate, glyceryl monostearate, castor oil, cremophor, oleic acid, sodium oleate, lauric acid, sodium laurate, myristic acid, sodium myristate, vegetable oils, coconut oil, mono-, di-, tri-glycerides, stearyl alcohol, span 20, span 80, and polyethylene glycol (PEG).

8. The composition of claim 1, further comprising a liquid vehicle.

9. The composition of claim 8, wherein the liquid vehicle comprises tramadol, an analgesic other than tramadol, or both.

10. The composition of claim 8, wherein the liquid vehicle comprises tramadol freebase.

11. The composition of any of claims 1-10, wherein the particles have a diameter with no more than a 25% standard deviation from the mean particle diameter.

12. The composition of any of claims 1-10, wherein the particles have a diameter with no more than a 15% standard deviation from the mean particle diameter.

13. The composition of any of claims 1-10, wherein the particles have a diameter with no more than a 10% standard deviation from the mean particle diameter.
14. The composition of any of claims 1-10, wherein the particles have mean particle size diameter of less than 200 μm.

15. The composition of any of claims 1-10, wherein the active ingredient is present in an amount from about 10% to about 90% by weight of the particles.

16. The composition of any of claims 1-10, wherein the hydrophobic matrix is a hydrophobic wax material, a lipid material, or a glycol polymer.

17. The composition of any of claims 1-10, wherein the hydrophobic matrix is present in amount from about 30% to about 80% by weight of the particles.

18. The composition of any of claims 1-10, wherein the hydrophobic matrix is a hydrophobic wax material chosen from one or more of ceresine wax, beeswax, ozokerite, microcrystalline wax, candelilla wax, montan wax, carnauba wax, paraffin wax, cauassu wax, Japan wax, and Shellac wax.

19. The composition of any of claims 1-10, wherein the hydrophobic matrix is a lipid material chosen from one or more of glycerol fatty acid esters, triacylglycerols, tripalmitin, tristearin, glyceryl trilaurate, coconut oil, glycerins, glycerides, glyceryl trimyristate, glyceryl tripalmitate, glyceryl tristearate, hydrogenated fats, ceramides, and organic esters.

20. The composition of any of claims 1-10, wherein the hydrophobic matrix is a glycol polymer chosen from one or more of high molecular weight glycols, polyethylene glycol with a minimum of 20 repeating units, cellulose ethers, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, microcrystalline cellulose, cellulose esters, cellulose acetate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, polyacrylates and derivatives thereof, polymethacrylates and derivatives thereof, poloxamers, starch and derivatives thereof.

21. The composition of any of claims 1-10, wherein the particles comprise a layer disposed on the surface of the particle.

22. The composition of any of claims 1-10, wherein the particles are configured to have sustained release of the active ingredient over a period of 10 hours or more.

23. The composition of any of claims 1-10, wherein the particles are configured to have sustained release of the active ingredient over a period of 24 hours or more.
24. The composition of any of claims 1-10, wherein the particles comprise a water content of less than 2.0% w/w.

25. The composition of any of claims 1-10, wherein the particles comprise a water content of less than 1.0% w/w.

26. The composition of any of claims 1-10, wherein the particles comprise a water content of less than 0.5% w/w.

27. A method comprising administering to a subject a therapeutically effective amount of a composition according to any one of claims 1-26.
### INTERNATIONAL SEARCH REPORT

**PCT/US2014/043202**

#### A. CLASSIFICATION OF SUBJECT MATTER
- IPC(8) - A61K 9/22 (2014.01)
- CPC - A61K 9/16 (2014.09)

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

#### B. FIELDS SEARCHED

- Minimum documentation searched (classification system followed by classification symbols)
  - IPC(8) - A61K 9/16, 9/20, 9/22, 9/26, 9/48 (2014.01)
  - CPC - A61K 9/16, 9/20, 9/48 (2014.09)

- Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
  - USPC - 424/424, 469, 470, 480, 494, 495, 498, 502

- Electronic database consulted during the international search (name of database and, where practicable, search terms used)
  - Orbit, Google Patents, Google Scholar

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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</table>

Further documents are listed in the continuation of Box C.

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

<table>
<thead>
<tr>
<th>Date of the actual completion of the international search</th>
<th>Date of mailing of the international search report</th>
</tr>
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<tbody>
<tr>
<td>09 September 2014</td>
<td>07 OCT 2014</td>
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</table>

Name and mailing address of the ISA/US

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Form PCT/ISA/210 (second sheet) (July 2009)
### INTERNATIONAL SEARCH REPORT

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

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

1. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 27 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

#### Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)