INJECTABLE SLURRIES AND

METHODS OF MANUFACTURING AND USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No. 62/042,979, filed August 28, 2014, U.S. Provisional Patent Application Serial No. 62/121,329, filed February 26, 2015, and U.S. Provisional Patent Application Serial No. 62/121,472, filed February 26, 2015. This application contains disclosure that is related to International Application No. PCT/US2015/PCT/047292, filed on August 27, 2015 (Attorney Docket No. 051588-2221 lWO2(00387)). The entire disclosures of the aforementioned applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Although various devices and techniques seek to selectively target certain tissues, there remains a need for higher resolution and specificity in targeting selected tissues while avoiding harm to non-selected tissues.

SUMMARY

One aspect of the disclosure provides a slurry comprising: a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm, the plurality of sterile ice particles being substantially uniform in shape; and a biocompatible surfactant selected from glycerol, urea, polysorbates, or a combination thereof, the slurry having a mean temperature in the range of 0 °C to -15 °C.

This aspect of the disclosure can have a variety of examples. The plurality of sterile ice particles can have a largest cross-sectional dimension less than a value selected from the group consisting of: about 1.25 mm, about 1 mm, about 0.9 mm, about 0.8 mm, about 0.7 mm, about 0.6 mm, about 0.5 mm, about 0.4 mm, about 0.3 mm, about 0.2 mm, and about 0.1 mm.

The biocompatible surfactant can be one or more selected from the group consisting of: a solvent, a detergent, a wetting agent, an emulsifier, a foaming agent, and a dispersant. The biocompatible surfactant can be one or more selected from the group consisting of: anionic, cationic, amphoteric, and nonionic. The biocompatible surfactant can be glycerol. The biocompatible surfactant can be urea.

The plurality of ice particles can constitute between about 0.1% and about 75% of the slurry by weight. The plurality of ice particles can constitute a percentage by weight selected

from the group consisting of: between about 0.1% and 1%, between about 1% and 10%, between about 10% and about 20%, between about 20% and about 30%, between about 30% and about 40%, between about 40% and about 50%, between about 50% and about 60%, between about 60% and about 70%, and greater than about 50%. The plurality of ice particles can constitute between about 0.1% and about 50% of the slurry by weight.

The slurry can further include a therapeutic compound.

The therapeutic compound can be selected from the group consisting of: an anesthetic and an analgesic. The therapeutic compound can be a water-soluble anesthetic. The therapeutic compound can be selected from the group consisting of: prilocaine, bupivacaine, prilocaine, tetracaine, procaine, mepivicaine, etidocaine, lidocaine, QX-314, and a nonsteroidal antiinflammatory drugs (NSAID).

The therapeutic compound can be a vasoconstrictor. The vasoconstrictor can be selected from the group consisting of: epinephrine, norepinephrine, a selective adrenergic agonist, a nonselective adrenergic agonist, and a corticosteroid.

The slurry can further include one or more selected from the group consisting of: microbubbles, nanobubbles, and biodegradable solids.

The slurry can further include a toxin. The toxin can be ethanol.

The slurry can be hypertonic. The slurry can be hypotonic.

The slurry can have a mean temperature selected from the group consisting of:

about +10° C, about +9° C, about +8° C, about +7° C, about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

The slurry can have a mean temperature of about +5° C or lower.

Also provided is a slurry comprising: a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm, the plurality of sterile ice particles being substantially uniform in shape; a biocompatible surfactant; and a foam comprising a plurality of gas bubbles, the slurry having a mean temperature in the range of 8° C to -15° C.

This aspect of the disclosure can have a variety of examples. The slurry can have a mean temperature selected from the group consisting of: about +10° C, about +9° C,

about +8° C, about +7° C, about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

Disclosed is a slurry comprising: a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm; and a biocompatible excipient.

This example can have a variety of examples. The slurry can have a mean temperature selected from the group consisting of: about +10° C, about +9° C, about +8° C, about +7° C, about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

Disclosed is a slurry comprising: a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm; and a lipolytic agent.

This example can have a variety of examples. The lipolytic agent can be a detergent. The detergent can be deoxycholate. The lipolytic agent can be an alcohol. The lipolytic agent can be an organic solvent.

The slurry can have a mean temperature selected from the group consisting of:

about +10° C, about +9° C, about +8° C, about +7° C, about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

Another aspect of the disclosure provides a slurry as described herein for use in therapy.

Another aspect of the disclosure provides a slurry as described herein for use in treating a subject, wherein the slurry is to be injected into a treatment region of the subject. Also disclosed is a method of treating a subject. The use or method includes: injecting a slurry as described herein into a treatment region of the subject.

This aspect of the disclosure can have a variety of examples. The treatment region can be selected from the group consisting of: proximate to a nerve, proximate to subcutaneous

about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

The slurry can be hypotonic relative to the treatment region. The slurry can be isotonic relative to the treatment region. The slurry can be hypertonic relative to the treatment region.

Another aspect of the disclosure provides a slurry as described herein for use in treating a subject, wherein the slurry has a temperature and cooling capacity sufficient to non-selectively disrupt tissue and is to be injected into a treatment region of the subject. Also disclosed is a method of treating a subject. The use or method includes: injecting the slurry as described herein having a temperature and cooling capacity sufficient to non-selectively disrupt tissue into a treatment region of the subject.

This aspect of the disclosure can have a variety of examples. The treatment region can be selected from the group consisting of: a prostate, a kidney, a heart, and a fibroadenoma.

The slurry can have a mean temperature selected from the group consisting of:

about +10° C, about +9° C, about +8° C, about +7° C, about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

The slurry can be hypotonic relative to the treatment region. The slurry can be isotonic relative to the treatment region. The slurry can be hypertonic relative to the treatment region.

Disclosed is use of a slurry in the manufacture of a medicament for treating a subject, wherein the slurry is to be injected into a treatment region of the subject selected from the group consisting of: proximate to a nerve, proximate to subcutaneous adipose tissue, proximate to breast tissue, proximate to visceral fat, fatty tissue proximate to the pharynx, fatty tissue proximate to the palate, fatty tissue proximate to the tongue, proximate to a spinal cord lipoma, proximate to a lipomyelomeningocele, proximate to visceral fat, proximate to lipomastia, proximate to a tumor, proximate to cardiac tissue, proximate to pericardial fat, and proximate to epicardial fat. Also disclosed is a method of treating a subject. The method includes injecting a slurry into a treatment region of the subject selected from the group consisting of: proximate to a nerve, proximate to subcutaneous adipose tissue, proximate to breast tissue, proximate to visceral fat, fatty tissue proximate to the pharynx, fatty tissue proximate to the palate, fatty tissue proximate to the tongue, proximate to a spinal cord lipoma, proximate to a lipomyelomeningocele, proximate to visceral fat, proximate to lipomastia, proximate to a tumor, proximate to cardiac tissue, proximate to pericardial fat, and proximate to epicardial fat.

This example can have a variety of examples. The slurry can include an ionic component.

The slurry can have a temperature and cooling capacity sufficient to non-selectively disrupt tissue into a treatment region of the subject. The slurry can have a mean temperature selected from the group consisting of: about +10° C, about +9° C, about +8° C, about +7° C,

about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

Another aspect of the disclosure provides a method of preparing a slurry comprising: freezing a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm in one or more micromolds, the plurality of sterile ice particles being substantially uniform in shape; and mixing the plurality of sterile ice particles with one or more biocompatible surfactants selected from glycerol, urea, polysorbates, or a combination thereof; the slurry having a mean temperature in the range of 0 °C to -15 °C.

This aspect of the disclosure can have a variety of examples. The plurality of sterile ice particles can have a substantially uniform shape. The one or more micromolds can be fabricated from one or more materials selected from the group consisting of: polymers, plastics, elastomers, silicons, silicones, and metals. The method can further include applying mechanical strain, stress waves, shock waves, or centripetal force to remove the plurality of sterile ice particles from the one or more micromolds.

The slurry can have a mean temperature selected from the group consisting of:

about +10° C, about +9° C, about +8° C, about +7° C, about +6° C, about +5° C, about +4° C, about +3° C, about +2° C, about +1° C, about 0° C, about -1° C, about -2° C, about -3° C, about -4° C, about -5° C, about -6° C, about -7° C, about -8° C, about -9° C, about -10° C, about -11° C, about -12° C, about -13° C, about -14° C, about -15° C, between about -15° C and about -25° C, between about -25° C and about -50° C, and between about -50° C and about -75° C.

Disclosed is a slurry comprising: a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm; and an ionic component selected from the group consisting of: hydrogen ions, lactate, phosphate, zinc ions, sulfur ions, nitrate, ammonium, hydroxide, iron ions, barium ions.

BRIEF DESCRIPTION OF THE DRAWINGS

For a fuller understanding of the nature and desired objects of the present invention, reference is made to the following detailed description taken in conjunction with the

CLAIMS

1. A slurry comprising:

a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm, the plurality of sterile ice particles being substantially uniform in shape; and

a biocompatible surfactant selected from glycerol, urea, polysorbates, or a combination thereof;

the slurry having a mean temperature in the range of 0 °C to -15 °C.

2. The slurry of claim 1, wherein the plurality of sterile ice particles have a largest cross-sectional dimension less than a value selected from the group consisting of: about 1.25 mm, about 1 mm, about 0.9 mm, about 0.8 mm, about 0.7 mm, about 0.6 mm, about 0.5 mm, about 0.4 mm, about 0.3 mm, about 0.2 mm, and about 0.1 mm.

3. The slurry of claim 1, wherein the biocompatible surfactant is one or more selected from the group consisting of: a solvent, a detergent, a wetting agent, an emulsifier, a foaming agent, and a dispersant.

4. The slurry of claim 1, wherein the biocompatible surfactant is one or more selected from the group consisting of: anionic, cationic, amphoteric, and nonionic.

5. The slurry of claim 1, wherein the biocompatible surfactant is glycerol.

6. The slurry of claim 1, wherein the biocompatible surfactant is urea.

7. The slurry of claim 1, wherein the plurality of ice particles constitute between 0.1% and 75% of the slurry by weight.

8. The slurry of claim 1, wherein the plurality of ice particles constitute a percentage by weight selected from the group consisting of: between 0.1% and 1%, between 1% and 10%, between 10% and 20%, between 20% and 30%, between 30% and 40%, between 40% and 50%, between 50% and 60%, between 60% and 70%, and greater than 50%.

9. The slurry of claim 1, wherein the plurality of ice particles constitute between 0.1% and 50% of the slurry by weight.

10. The slurry of claim 1, further comprising:

a therapeutic compound.

11. The slurry of claim 10, wherein the therapeutic compound is selected from the group consisting of: an anesthetic and an analgesic.

12. The slurry of claim 10, wherein the therapeutic compound is a water-soluble anesthetic.

13. The slurry of claim 10, wherein the therapeutic compound is selected from the group consisting of: prilocaine, bupivacaine, tetracaine, procaine, mepivicaine, etidocaine, lidocaine, QX-314, and a nonsteroidal anti-inflammatory drugs (NSAID).

14. The slurry of claim 10, wherein the therapeutic compound is a vasoconstrictor.

15. The slurry of claim 14, wherein the vasoconstrictor is selected from the group consisting of: epinephrine, norepinephrine, a selective adrenergic agonist, a nonselective adrenergic agonist, and a corticosteroid.

16. The slurry of claim 1, further comprising:

one or more selected from the group consisting of: microbubbles, nanobubbles, and biodegradable solids.

17. The slurry of claim 1, further comprising:

a toxin.

18. The slurry of claim 17, wherein the toxin is ethanol.

19. The slurry of claim 1, wherein the slurry is hypertonic relative to the treatment region.

20. The slurry of claim 1, wherein the slurry is hypotonic relative to the treatment region.

21. The slurry of claim 1, wherein the slurry has a mean temperature selected from the group consisting of: about 0 °C, about -1 °C, about -2 °C, about -3 °C, about -4 °C, about -5 °C, about -6 °C, about -7 °C, about -8 °C, about -9 °C, about -10 °C, about -11 °C, about -12 °C, about -13 °C, about -14 °C, and about -15 °C.

22. The slurry of claim 1, wherein the slurry has a mean temperature of about -5° C or lower.

23. The slurry of claim 1, further comprising

a foam comprising a plurality of gas bubbles.

24. The slurry of claim 23, wherein the slurry has a mean temperature selected from the group consisting of: about 0 °C, about -1 °C, about -2 °C, about -3 °C, about -4 °C, about -5 °C, about -6 °C, about -7 °C, about -8 °C, about -9 °C, about -10 °C, about -11 °C, about -12 °C, about -13 °C, about -14 °C, and about -15 °C.

25. A slurry of any one of claims 1-24 for use in therapy.

26. A slurry of any one of claims 1-24 for use in treating a subject, wherein the slurry is to be injected into a treatment region of the subject.

27. The slurry for use of claim 26, wherein the treatment region is selected from the group consisting of: proximate to a nerve, proximate to subcutaneous adipose tissue, proximate to breast tissue, proximate to visceral fat, fatty tissue proximate to the pharynx, fatty tissue proximate to the palate, fatty tissue proximate to the tongue, proximate to a spinal cord lipoma, proximate to a lipomyelomeningocele, proximate to visceral fat, proximate to lipomastia, proximate to a tumor, proximate to cardiac tissue, proximate to pericardial fat, and proximate to epicardial fat.

28. The slurry for use of claim 26, wherein the treatment region comprises one or more tissues selected from the group consisting of: connective, epithelial, neural, joint, cardiac, adipose, hepatic, renal, vascular, cutaneous, and muscle.

29. The slurry for use of claim 26, further comprising:

measuring a temperature of the slurry prior to injection.

30. The slurry for use of claim 26, wherein the slurry is to be injected via gravity flow.

31. The slurry for use of claim 26, wherein the slurry is to be injected via pressure injection.

32. The slurry for use of claim 26, wherein the slurry is to be injected through one or more selected from the group consisting of: a syringe, a cannula, a catheter, and tubing.

33. The slurry for use of claim 26, wherein

the treatment region is to be pre-cooled prior to the injecting step.

34. The slurry for use of claim 26, wherein

energy is to be applied adjacent to the target tissue, wherein the energy protects tissue adjacent to the treatment region from undesired cooling, wherein the energy is selected from the group consisting of radiofrequency (RF) energy, energy from coherent light, energy from incoherent light, energy from heated fluid, energy from a resistive (Ohmic) heater, energy from a microwave generator, energy from an ultrasound generator, and combinations thereof.

35. The slurry for use of claim 26, wherein

suction is to be applied to the treatment region to remove melted slurry.

36. The slurry for use of claim 26, wherein the injecting step comprises injecting a sufficient volume of the slurry to cause tumescent swelling of the treatment region.

37. The slurry for use of claim 26, wherein the injecting step is to be repeated a plurality of times.

38. The slurry for use of claim 26, further comprising:

calculating a desired amount of slurry to be injected based on a desired amount of disruption to the treatment region.

39. The slurry for use of claim 26, wherein the slurry cools the treatment region adjacent to an injection site at a rate greater in magnitude than about -2 °C per minute.

40. The slurry for use of claim 26, wherein the use thickens septa.

41. The slurry for use of claim 26, further comprising:

mixing the slurry with relatively warmer liquid prior to the injecting step.

42. The slurry for use of claim 26, wherein the slurry is isotonic relative to the treatment region.

43. A slurry of any one of claims 1-24 for use in treating a subject, wherein the slurry

has a temperature and cooling capacity sufficient to non-selectively disrupt tissue and is to be injected into a treatment region of the subject.

44. The slurry for use of claim 43, wherein the treatment region is selected from the group consisting of: a prostate, a kidney, a heart, and a fibroadenoma.

45. A method of preparing a slurry, the method comprising:

freezing a plurality of sterile ice particles having a largest cross-sectional dimension less than about 1.5 mm in one or more micromolds, the plurality of sterile ice particles being substantially uniform in shape; and

mixing the plurality of sterile ice particles with one or more biocompatible surfactants selected from glycerol, urea, polysorbates, or a combination thereof;

the slurry having a mean temperature in the range of 0 °C to -15 °C.

46. The method of claim 45, wherein the one or more micromolds are fabricated from one or more materials selected from the group consisting of: polymers, plastics, elastomers, silicons, silicones, and metals.

47. The method of claim 45, further comprising:

applying mechanical strain, stress waves, shock waves, or centripetal force to remove the plurality of sterile ice particles from the one or more micromolds.

48. The method of claim 45, wherein the slurry has a mean temperature selected from the group consisting of: about 0 °C, about -1 °C, about -2 °C, about -3 °C, about -4 °C, about -5 °C, about -6 °C, about -7 °C, about -8 °C, about -9 °C, about -10 °C, about -11 °C, about -12 °C, about -13 °C, about -14 °C, and about -15 °C.