CLAIMS

1. A polyelectrolyte nanocomplex (PNC) comprising one or more neuromodulators, a carrier molecule, and a counter ion polymer, wherein the counter ion polymer has a charge enabling it to bind electrostatically to the one or more neuromodulators.

2. A nanoparticle comprising the polyelectrolyte nanocomplex (PNC) of claim 1 and a non-water-soluble biodegradable polymer, wherein the polyelectrolyte nanocomplex (PNC) is distributed throughout the non-water-soluble biodegradable polymer.

3. The PNC of claim 1 or the nanoparticle of claim 2, wherein the one or more neuromodulators comprise a therapeutically active derivative of Clostridial neurotoxin, optionally wherein the Clostridial neurotoxin comprises a therapeutically active derivative of a botulinum toxin, further optionally wherein the botulinum toxin is selected from the group consisting of therapeutically active derivatives of botulinum toxin types A, B, C, including C_1, D, E, F and G, and subtypes and mixtures thereof.

4. The PNC or nanoparticle of claim 3, wherein the one or more neuromodulators is selected from the group consisting of onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxin A, prabotulinumtoxin A, rimabotulinumtoxin B, and combinations thereof.

5. The PNC or nanoparticle of any one of claims 1-4, wherein:

(a) the carrier molecule comprises a polyelectrolyte selected from the group consisting of a cationic polymer, a protein, and a polysaccharide, optionally wherein the protein is selected from the group consisting of IgG, collagen, gelatin, and serum albumin;

(b) a weight ratio of the carrier molecule to the one or more neuromodulators can vary from about 1:1 to about 2000:1, optionally wherein the weight ratio of the carrier molecule to the one or more neuromodulators is about 500:1;

(c) the counter ion polymer is selected from the group consisting of dextran sulfate (DS), heparin (heparin sulfate), hyaluronic acid, and combinations thereof; and/or

(d) the biodegradable polymer is a copolymer selected from the group consisting of poly(L-lactic acid) (PLLA), polyglycolic acid (PGA), poly (D,L-lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), their PEGylated block copolymers, and combinations thereof, optionally wherein the biodegradable polymer is selected from the group consisting of polyethylene glycol (PEG)-*b*-PLLA, PEG-*b*-PLGA, PEG-*b*-PCL, and combinations thereof, further optionally wherein the nanoparticle comprises one of: onabotulinumtoxinA (BoNTA): carrier protein: dextran sulfate (DS): PEG-*b*-PLGA in a m:1:1:n ratio, whereas m = 0.0005 to 1, and n = 3 to 10; (BoNTA+carrier):DS:PEG-b-PLGA is 1:1:5; or BoNTA:carrier is 1:1 to 1:2000.

6. A microgel comprising:

a polyelectrolyte nanocomplex (PNC) of claim 1 or the nanoparticle of claim 2 comprising one or more neuromodulators, a carrier molecule, and a counter ion polymer, wherein the counter ion polymer has a charge enabling it to bind electrostatically to the one or more neuromodulators; and

a crosslinked hydrophilic polymer, wherein the polyelectrolyte nanocomplex (PNC) of claim 1 or nanoparticle of claim 2 is distributed throughout the crosslinked hydrophilic polymer.

7. The microgel of claim 6, wherein the microgel:

(a) comprises the polyelectrolyte nanocomplex (PNC) of claim 1 or the nanoparticle of claim 2, wherein the microgel has a weight ratio of polyelectrolyte nanocomplex (PNC) to nanoparticle ranging from about 0 to about 1; or

(b) comprises a composite of the crosslinked hydrophilic polymer and a nanofiber, optionally wherein the composite comprises a plurality of polycaprolactone fibers having a mean length of less than about 200 micrometers, which are covalently linked to the crosslinked hydrophilic polymer.

8. The microgel of claim 6 or 7, wherein the crosslinked hydrophilic polymer comprises a hydrogel, optionally wherein the hydrogel comprises a natural or synthetic hydrophilic polymer selected from the group consisting of hyaluronic acid, chitosan, heparin,

alginate, fibrin, polyvinyl alcohol, polyethylene glycol, sodium polyacrylate, an acrylate polymers, and copolymers thereof, further optionally wherein the hydrogel comprises a crosslinked hyaluronic acid.

9. The microgel of any one of claims 6-8, wherein:

(a) the microgel comprises a plurality of microgel particles having a spherical or asymmetrical shape, optionally wherein the plurality of microgel particles have a nominal size ranging from about 10 μm to about 1,000 μm;

(b) the microgel or the plurality of microgel polymers has a shear storage modulus from about 10 Pa to about 10,000 Pa;

(c) the microgel comprises a polyelectrolyte nanocomplex (PNC) having a nominal size ranging from about 20 nm to about 900 nm; and/or

(d) the PNC or the nanoparticle comprises a biodegradable polymer selected from the group consisting of poly(L-lactic acid) (PLLA), polyglycolic acid (PGA), poly (D,L-lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), their PEGylated block copolymers, and combinations thereof, optionally wherein the biodegradable polymer is selected from the group consisting of polyethylene glycol (PEG)-*b*-PLLA, PEG-*b*-PLGA, PEG-*b*-PCL, and combinations thereof, further optionally wherein the microgel comprises a nanoparticle having a nominal size ranging from about 20 nm to about 900 nm.

10. The microgel of any one of claims 6-9, wherein the crosslinked hydrophilic polymer further comprises one or more neuromodulators added directly thereto, optionally wherein the one or more neuromodulators added directly to the crosslinked hydrophilic polymer is a fraction of an amount of the one or more neuromodulators in the nanoparticle or polyelectrolyte nanocomplex (PNC), further optionally wherein the fraction of the one or more neuromodulators added directly to the crosslinked hydrophilic polymer has a range from about 0 to about 1.

11. A process for preparing a neuromodulator-encapsulated polyelectrolyte nanocomplex (PNC), the process comprising:

(a) mixing the aqueous solution of one or more neuromodulators and the aqueous solution of the carrier molecule to form a protein solution; and

(b) mixing the protein solution with a counter ion polymer by a flash nanocomplexation (FNC) process to form a neuromodulator-encapsulated polyelectrolyte nanocomplex (PNC).

12. The process of claim 11, wherein the one or more neuromodulators comprise a therapeutically active derivative of Clostridial neurotoxin, optionally wherein the Clostridial neurotoxin comprises a therapeutically active derivative of a botulinum toxin, further optionally wherein the botulinum toxin is selected from the group consisting of therapeutically active derivatives of botulinum toxin types A, B, C, including C_1, D, E, F and G, and subtypes and mixtures thereof.

13. The process of claim 12, wherein the one or more neuromodulators is selected from the group consisting of onabotulinumtoxin A, abobotulinumtoxin A, incobotulinumtoxin A, prabotulinumtoxin A, rimabotulinumtoxin B, and combinations thereof.

14. The process of any one of claims 11-13, wherein:

(a) the carrier molecule comprises a polyelectrolyte selected from the group consisting of a cationic polymer, a protein, and a polysaccharide, optionally wherein the protein is selected from the group consisting of IgG, collagen, gelatin, and serum albumin;

(b) a weight ratio of the carrier molecule to the one or more neuromodulators varies from about 1:1 to about 2000:1, optionally wherein the weight ratio of the carrier molecule to the one or more neuromodulators is about 500:1; and/or

(c) the counter ion polymer is selected from the group consisting of dextran sulfate (DS), heparin (heparin sulfate), hyaluronic acid, and combinations thereof.

15. The process of any one of claims 11-14, comprising:

(a) an encapsulation efficiency of about 80% to about 99%; and/or

(b) a loading level of about 10% to about 70%.

16. The process of any one of claims 11-15, wherein the neuromodulator-encapsulated polyelectrolyte nanocomplexes (PNCs) have a release duration of about 1 day to about 7 days.

17. A process for generating a plurality of nanoparticles, the process comprising:

(a) forming a polyelectrolyte nanocomplex (PNC) by mixing a preformed solution of one or more neuromodulators and one or more carrier molecules and a counter ion polymer using a first continuous mixing process;

(b) co-precipitating the polyelectrolyte nanocomplex (PNC) with a non-water soluble biodegradable polymer using a second continuous mixing process; and

(c) forming a plurality of nanoparticles, wherein the polyelectrolyte nanocomplex (PNC) comprising the one or more neuromodulators, one or more carrier molecules, and counter ion polymer is distributed throughout the non-water-soluble biodegradable polymer.

18. The process of claim 17, wherein:

(i) step (a) and step (b) proceed simultaneously;

(ii) the first continuous mixing process comprises a flash nanocomplexation (FNC) process;

(iii) the forming of the polyelectrolyte nanocomplex (PNC) is by electrostatic attraction between the one or more neuromodulators and the counter ion polymer;

(iv) the mixing of the polyelectrolyte nanocomplex (PNC) and the non-water soluble biodegradable polymer is by solvent-induced flash nanoprecipitation (FNP); or

(v) the forming of the plurality of nanoparticles occurs by the precipitation of the non-water-soluble biodegradable polymer together with the polyelectrolyte nanocomplex (PNC).

19. The process of any one of claims 11-18, wherein:

(a) the neuromodulator-encapsulated polyelectrolyte nanocomplexes (PNCs) in any one of claims 11-16 or the plurality of nanoparticles in claim 17 or 18 have a Z-average particle size of about 20 nm to about 900 nm, and with a size distribution (PDI) of about 0.1 to about 0.4; and/or

(b) the neuromodulator-encapsulated polyelectrolyte nanocomplexes (PNCs) in any one of claims 11-16 or the plurality of nanoparticles in claim 17 or 18 have a negative surface charge with an average zeta potential of about -10 mV to about -35 mV.

20. The process of any one of claims 17-19:

(a) comprising an encapsulation efficiency of about 60% to about 95%;

(b) comprising a loading level of about 2% to about 50%; and/or

(c) wherein the plurality of nanoparticles have a release duration of about 7 days to about 180 days.

21. A process for generating a plurality of microgel particles, the process comprising:

(a) mixing a nanoparticle or polyelectrolyte nanocomplex (PNC) comprising one or more neuromodulators, a carrier molecule, and a counter ion polymer, and optionally a biodegradable polymer, with a hydrogel precursor;

(b) forming a hydrogel comprising the nanoparticle or polyelectrolyte nanocomplex (PNC) comprising one or more neuromodulators, a carrier molecule, and a counter ion polymer, and optionally a biodegradable polymer; and

(c) mechanically breaking the hydrogel into a plurality of microgel particles; optionally, wherein the plurality of microgel particles has a nominal size ranging from about 10 μm to 1,000 μm.

22. The nanoparticle of any of claims 1-5 or the microgel of any one of claims 6-10 for use as a medicament.

23. Use of the nanoparticle of any one of claims 1-5 or the microgel of any one of claims 6-10 in the preparation of a medicament for the treatment of a disease or condition in a subject in need of treatment thereof, wherein the disease or condition:

(a) is selected from the group consisting of a cosmetic condition, focal dystonias, cervical dystonia (CD), chronic sialorrhea, and muscle spasticity, optionally wherein the muscle spasticity is related to an overactive muscle movement selected from the group consisting of cerebral palsy, post-stroke spasticity, post-spinal cord injury spasticity, spasms of the head and neck, eyelid, vagina, limbs, jaw, and vocal cords, clenching of muscles associated with muscles of the esophagus, jaw, lower urinary tract and bladder, and anus, and refractory overactive bladder;

(b) comprises a muscle disorder selected from the group consisting of strabismus, blepharospasm, hemifacial spasm, infantile esotropia, restricted ankle motion due to lower-limb spasticity associated with stroke in adults, and lower-limb spasticity in pediatric patients two years of age and older;

(c) comprises excessive sweating; or

(d) is selected from the group consisting of a headache, a migraine headache, neuropathic pain, chronic pain, osteoarthritis pain, arthritic pain, allergy symptoms, depression, and premature ejaculation.

24. The use of claim 23, wherein two or more formulations of the nanoparticle or microgel are to be administered each having a different release profile.

25. A pharmaceutical composition comprising a nanoparticle of any of claims 1-5 or the microgel of any one of claims 6-10 and a pharmaceutically acceptable carrier.

26. A kit comprising a PNC or nanoparticle of any of claims 1-5 and/or a microgel of any one of claims 6-10.

27. A sustained release formulation comprising the PNC or nanoparticle of any of claims 1-5 or the microgel of any one of claims 6-10, wherein the formulation provides an

effective concentration of the one or more neuromodulators in soft tissue for a period of time between about 3 days to about 200 days.

28. Use of the nanoparticle of any one of claims 1-5 or the microgel of any one of claims 6-10 in the preparation of a medicament for the treatment of a disease or condition, wherein the medicament comprises a sustained release formulation comprising the PNC or nanoparticle of any of claims 1-5 or the microgel of any one of claims 6-10 and the medicament is for local administration by injection of the sustained release formulation, wherein the one or more neuromodulators is released from the sustained release formulation over a period of time from about 3 days to about 200 days, thereby treating a disease or condition with a measurable effect over 2 weeks to 40 weeks, optionally wherein the disease or condition is selected from the group consisting of a cosmetic condition, focal dystonias, cervical dystonia (CD), chronic sialorrhea, and muscle spasticity.