SUMMARY

[0009] It was previously discovered that injectable biodegradable polymeric compositions comprising peptide agents in the form of a salt formed with a strong acid (e.g., hydrochloric acid or methanesulfonic acid) exhibit much higher stability than those in the form of a salt formed with a weak acid (e.g., acetic acid) or in the form of the free base. Such beneficial salts of peptide agents may be formed through the neutralization of any basic groups of the peptide agents with a strong acid. When such beneficial salts of peptide agents formed with a strong acid were formulated into injectable biodegradable polymeric compositions, the interactions/reactions between the peptide agents and the polymer are minimized or prevented. Using such beneficial salts of peptide agents formed with a strong acid allows for the preparation of a stabilized injectable composition pre-filled in a single syringe in a ready-to-use configuration with satisfactory storage stability.

[0010] It was unexpectedly discovered that the polymers of such compositions degraded faster once injected in an aqueous environment than the polymers of compositions using a salt formed with a weak acid. This is surprising since the compositions comprising peptide agents in the form of a salt formed from a strong acid have a much higher storage stability and shelf-life, both in peptide purity and polymer molecular weight stability, than do the compositions formed using salts formed with weak acids. This finding can be used to formulate compositions of formulations with tailored release durations.

[0011] According to the product package insert, the commercially available product ELIGARD® is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver leuprolide acetate at a controlled rate over a one-, three-, four or six-month therapeutic period.

[0012] ELIGARD® is prefilled and supplied in two separate, sterile syringes. One syringe contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. ATRIGEL® is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly (DL-lactide-co-glycolide) (PLGH or PLGA) polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP).

[0013] The contents of two separate syringes are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. The mixture is not stable so it has to be used immediately or it has to be discarded if not used within 30 min. ELIGARD® is administered subcutaneously, where it forms a solid drug delivery depot.

[0014] PLGAH polymer is used for one-month product, while PLGA polymers are used in the three-, four- or six-month products. PLGH copolymer (with a molar ratio of DL-lactide to Glycolide = 50:50) contains carboxyl end groups which expedite the degradation of the polymer. PLGA copolymer for 3 and 4-month products has a molar ratio of DL-lactide to Glycolide = 75:25, while the PLGA copolymer for 6-month product has a molar ratio of DL-lactide to Glycolide = 85:15. PLGA copolymers are manufactured with hexanediol as an initiator resulting in the PLGA copolymer with hydroxyl end groups at both ends.

[0015] The present inventors have found that by using a leuprolide salt formed with a strong acid in place of leuprolide acetate, the stability of the resulting formulation can be significantly improved. The stabilized final formulation can be prefilled in a single syringe with a suitable storage shelf-life.

[0016] However, although the formulation containing leuprolide mesylate or other strong acid salts is more stable during storage than that containing leuprolide acetate or other weak acid salts, it was surprisingly found that the PLGA polymers in the formulation containing leuprolide mesylate degraded faster than those in the formulation containing

leuprolide acetate during *in vitro* and *in vivo* release. This property is quite counter intuitive and unexpected. This property can be advantageously used to tailor and fine tune the formulation to prepare better and improved products.

[0016a] In one aspect, the present invention provides a pharmaceutical composition comprising: a) a combination of a strong acid salt and a weak acid salt of a LHRH agonist or antagonist, wherein the molar ratio of (strong acid anion + weak acid anion) to LHRH is ≤ 2:1 and the molar ratio of the strong acid anion to the LHRH agonist or antagonist is from 1:1 to 2:1; b) a biodegradable polymer selected from the group of a homopolymer polylactide or polylatic acid, and a copolymer poly (lactic acid-co-glycolic acid) or poly (lactide-co-glycolide), wherein the ratio of lactide:glycolide (or lactic acid:glycolic acid) of the copolymer is from 50:50 to 100:0; and c) N-methyl-2-pyrrolidone (NMP), wherein the pharmaceutical composition having a selected release duration ranging from one month to 6 months can be prepared by varying the ratios of a strong acid salt and a weak acid salt of a LHRH agonist or antagonist.

[0016b] In another aspect, the present invention provides a pharmaceutical composition comprising: a) a combination of leuprolide mesylate and leuprolide acetate, wherein the molar ratio of (mesylate + acetate) to leuprolide is ≤ 2:1 and the molar ratio of mesylate anion to leuprolide is from 1:1 to 2:1; b) a biodegradable polymer selected from the group of a homopolymer polylactide or polylatic acid, and a copolymer poly (lactic acid-co-glycolic acid) or poly (lactide-co-glycolide), wherein the ratio of lactide:glycolide (or lactic acid:glycolic acid) of the copolymer is from 50:50 to 100:0; and c) N-methyl-2-pyrrolidone (NMP); wherein the pharmaceutical composition having a selected release duration ranging from one month to 6 months can be prepared by varying the ratios of mesylate to leuprolide.

[0016c] In another aspect, the present invention provides a pharmaceutical composition comprising: a) a combination of leuprolide mesylate and leuprolide formate, wherein the

molar ratio of (mesylate + formate) to leuprolide is ≤ 2:1 and the molar ratio of mesylate anion to leuprolide is from 1:1 to 2:1; b) a biodegradable polymer selected from the group of a homopolymer polylactide or polylatic acid, and a copolymer poly (lactic acid-co-glycolic acid) or poly (lactide-co-glycolide), wherein the ratio of lactide:glycolide (or lactic acid:glycolic acid) of the copolymer is from 50:50 to 100:0; and c) N-methyl-2-pyrrolidone (NMP); wherein the pharmaceutical composition having a selected release duration ranging from one month to 6 months can be prepared by varying the ratios of mesylate to leuprolide.

[0017] Accordingly, the present disclosure provides a stabilized injectable biodegradable polymeric composition for forming an economical, practical, and efficient controlled release delivery system for a LHRH agonist or antagonist. The present disclosure also provides a method of manufacturing and a method of use thereof. According to the present disclosure, the drug delivery system is produced easily and delivered conveniently to a subject such as a mammal or human. The compositions deliver a therapeutic amount of peptide over a desired, extended period of time, based on the specific composition of the biodegradable polymer used in the composition with the salt of a peptide formed from a strong acid. The compositions are both biocompatible and biodegradable, and disappear harmlessly after delivering the dose of the peptide agents.

[0018] The compositions in accordance with the present disclosure comprise a) a salt of a LHRH agonist or antagonist formed with a strong acid that minimizes or prevents the interaction/reaction between the peptide and the polymer in an organic solution; b) a biodegradable polymer; c) a pharmaceutically acceptable organic solvent, that when formulated together can deliver the LHRH agonist or antagonist over a 1-, 3-, 4- or 6-month period. According to the disclosure, the pharmaceutical composition may optionally include excipients to achieve optimal delivery of the peptide agent. The

pharmaceutical composition may be a viscous or non-viscous liquid, gel or semisolid that moves as a fluid so that it may be injected using a syringe. The pharmaceutical composition may be pre-filled into one syringe to form a product in a ready-to-use configuration.

[0019] The compositions in accordance with the present disclosure comprise a) a mixture of a salt of a LHRH agonist or antagonist formed with a strong acid and a salt of a LHRH agonist or antagonist formed with a weak acid, wherein the molar ratio of strong acid to LHRH agonist or antagonist is from 1:1 to 2:1, wherein the composition does not contain excess acid in addition to the acids used to form the strong acid to LHRH agonist or antagonist; b) a biodegradable polymer; c) a pharmaceutically acceptable organic solvent, that when formulated together can deliver the LHRH agonist or antagonist over a 1-, 3-, 4- or 6-month period. According to the disclosure, the pharmaceutical composition may optionally include excipients to achieve optimal delivery of the peptide agent. The pharmaceutical composition may be a viscous or non-viscous liquid, gel or semisolid that moves as a fluid so that it may be injected using a syringe. The pharmaceutical composition may be pre-filled into one syringe to form a product in a ready-to-use configuration.

[0020] LHRH such as leuprolide, triptorelin, and goserelin contains two basic functional group, i.e., histidine and arginine which can form ion pairs with a suitable counter ion. A salt of a LHRH agonist or antagonist formed with a strong acid can achieve a stoichiometric normal ratio of strong acid to LHRH agonist or antagonist that equals to 2:1. The salt of a LHRH agonist or antagonist can also be prepared to contain a mixture of a strong acid and a weak acid, but the ratio of (strong acid + weak acid) to LHRH agonist or antagonist is less than or equal to 2:1. In the case of salt mixture, the molar ratio of strong acid to LHRH agonist or antagonist is from 1:1 to 2:1. By varying salt mixture composition or ratio, the release profile of an LHRH in an aqueous environment

or human body can be tailored to achieve desired storage stability and drug delivery duration. The salt of a LHRH agonist or antagonist as disclosed herein has a pH (50 mg/mL in water) as determined by USP<791> method greater than 3, preferably greater than 4.

[0021] According to one example of the present disclosure, the LHRH agonist or antagonist has either an N-terminal primary amine or side chain primary amine group covalently modified with hydrophilic and/or lipophilic moieties that may be produced through pegylation, acylation, and the like. Furthermore, both N-terminal primary amine and side chain primary amine groups of the peptide agents may also be covalently modified simultaneously with hydrophilic and/or lipophilic moieties through pegylation, acylation, and the like.

[0022] The strong acid may be any acid having a pKa in water less than 3, preferably less than 0. For example, a strong acid may be selected from, but not limited to, the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, organic sulfuric acids, alkyl sulfuric acids of 1-40 carbons, nitric acid, chromic acid, methanesulfonic acid, trifluromethane sulfonic acid, organic sulfonic acids, trichloroacetic acid, dichloroacetic acid, bromoacetic acid, chloroacetic acid, cyanoacetic acid, 2-chloropropanoic acid, 2-oxobutanoic acid, 2-chlorobutanoic acid, 4-cyanobutanoic acid, perchloric acid, phosphoric acid, hydrogen iodide, and the like. The preferable strong acid is either hydrochloric acid or methanesulfonic acid.

[0023] The biodegradable polymer can be any biocompatible and pharmaceutically acceptable polymers. The biodegradable polymers may be thermoplastic, which melts upon heating and solidifies upon cooling. The biodegradable polymers of the disclosure are substantially insoluble in aqueous or body fluid, but are capable of substantially dissolving or dispersing in a water-miscible organic solvent to form a solution or suspension. Upon contact with an aqueous fluid, the water-miscible organic solvent

diffuses/dissipates from the inventive composition, which causes the coagulation of the polymer to form a gel, or solid matrix encapsulating the peptide agent. According to the present disclosure the biodegradable polymer may be a linear polymer, or a branched polymer, or a mixture of the two. Preferably, the polymer is a lactate-based polymer. The lactate-based polymer includes homopolymers of lactic acid or lactide monomers (poly(lactic acid) or polylactide, PLA), and copolymers of lactic acid (or lactide) with other monomers (for example, glycolic acid, glycolide (poly(lactide-co-glycolide), PLG or PLGA) and the like). Examples of the polymers suitable for the present composition includes, without limitation, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(maleic anhydride), and copolymers, terpolymers, or combinations or mixtures therein. Lactic acid-based polymers, and copolymers of lactic acid and glycolic acid (PLGA), including poly(D,L-lactide-co-glycolide) and poly(L-lactide-co-glycolide) are preferably used in the present disclosure. In some embodiments, the PLGA polymers have weight average molecular weights of between about 2,000 to about 100,000 and monomer ratios of lactic acid to glycolic acid of between about 50:50 to about 100:0. The preferred polymers of the present disclosure are PLA with molecular weight of between 11,000 and about 18,000 for a controlled delivery of 6 months, and a PLGA with molecular weight of between 10,000 and 25,000 dalton having a lactide content of 80-90% for a 3- or 4-month delivery.

[0024] The pharmaceutically acceptable organic solvents may be selected from a group consisting of N-methyl-2-pyrrolidone, dimethylacetamide, methoxypolyethylene glycol, alkoxypolyethylene glycol, polyethylene glycol esters, glycofurol, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide,

tetrahydrofuran, caprolactam, decylmethylsulfoxide, benzyl benzoate, ethyl benzoate, triacetin, diacetin, tributyrin, triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, triethylglycerides, triethyl phosphate, diethyl phthalate, diethyl tartrate, ethyl lactate, propylene carbonate, ethylene carbonate, butyrolactone, and 1-dodecylazacyclo-heptan-2-one, and combinations thereof.

[0025] According to the present disclosure, one or more excipients may be incorporated in the inventive composition to achieve optimal delivery of the peptide agent. Suitable excipients may include release rate modifying agents, burst effect reducing materials, buffering materials, antioxidants, and the like.

[0026] According to the present disclosure, suitable release rate modifying agents include, but are not limited to, amphiphilic compounds or copolymers, such alkanecarboxylic acid, oleic acid, alkyl alcohol, polar lipids, surfactants, copolymers of polyethyleneglycol and polylactide or poly(lactide-co-glycolide), poloxamers, polyvinylpyrrolidone, polysorbates, and the like; esters of mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, benzyl benzoate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as polyethylene glycol, sorbitol, and the like; fatty acids; triesters of glycerol, such as triglycerides, medium-chain triglycerides such as MIGLYOL 810, 812, 818, 829, 840, and the like. Mixtures of rate modifying agents can also be used in the polymer systems of the disclosure.

[0027] According to the present disclosure, suitable buffering agents include, but are not limited to, inorganic and organic salts including calcium carbonate, calcium hydroxide, calcium myristate; calcium oleate, calcium palmitate, calcium stearate, calcium phosphate, magnesium carbonate, magnesium hydroxide, magnesium phosphate, magnesium myristate, magnesium oleate, magnesium palmitate, magnesium stearate,

zinc carbonate, zinc hydroxide, zinc myristate, zinc oleate, zinc palmitate, zinc stearate, zinc phosphate, and combinations thereof.

[0028] According to the present disclosure, suitable antioxidants include, but are not limited to, d-alpha tocopherol acetate, ascorbyl palmitate, butylated hydroxyanidole, butylated hydroxyanisole, butylatedhydroxyquinone, hydroxycomarin, butylated hydroxytoluene, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propylhydroxybenzoate, trihydroxybutylrophenone, vitamin E, pegylated vitamin E or vitamin E-TPGS, and the like.

[0029] The present disclosure further provides methods of making and using such compositions. For example, a method of making such compositions comprising the neutralization of basic amine groups of peptide agents to form a beneficial salt to minimize or prevent the interaction/reaction of the basic amine group with the polymer; and the combination of the beneficial salt with other components and optionally one or more excipients. Preferably, the beneficial salt of the peptide agent is formed first, and then combined with the polymer dissolved in an organic solvent. Such compositions are physico-chemically stable prior to and during the fabrication process of a controlled delivery system such as microparticle formation or other implantable matrix formation. Preferably, such injectable compositions are physico-chemically stable during preparation, storage, and subsequent administration to a subject and form consistent and controlled release implants upon administration to a tissue site. The compositions of the present disclosure contain a biodegradable polymer, such that the duration of the release of the peptide is controlled over a period of up to 6 months.

[0030] The present disclosure further provides a kit for administration of the injectable composition to form a consistent and controlled release depot system, the kit comprises: a biodegradable polymer dissolved in a pharmaceutically acceptable solvent; a beneficial salt of a the LHRH agonist or antagonist formed with a strong acid

dissolved or dispersed in the polymeric vehicle; and optionally one or more excipients. The uniform mixture of all the components is packaged into one container. Preferably, the container is a syringe. Accordingly, the present disclosure also provides a method comprising a step of filling a syringe with the composition to form a stable product in a ready-to-use configuration.

[0031] The present disclosure further provides a method for *in-situ* forming implant capable of functioning as a controlled release delivery system of the LHRH agonist or antagonist in a subject over a period of 1 month, 3 months, 4 months or 6 months. The LHRH agonist or antagonist is preferably incorporated into the *in situ* formed implant, and subsequently released into the surrounding tissue fluids and to the pertinent body tissue or organ as the polymer degrades. The method comprises: administration of the injectable compositions of the present disclosure to an implant site by any suitable method for applying a liquid, as for example, by means of a syringe, needle, cannula, catheter, pressure applicator, and the like.

BRIEF DESCRIPTION OF THE FIGURES

[0032] Figure 1. *In vitro* release of leuprolide mesylate from different polymers compared with Eligard® 45 mg release

[0033] Figure 2. Mean Serum Concentration-Time Profiles of Leuprolide in Male Rats after a Single Subcutaneous Administration

[0034] Figure 3: *In vitro* release of LAMS and LAAc from PLA/NMP solution

[0035] Figure 4. LAMS release from Eligard® 45mg polymer solution compared with Eligard® 45 mg release

[0036] Figure 5. *In vitro* release of leuprolide mesylate from different PLGA polymers compared with release from PLA polymer

[0037] Figure 6. *In vitro* release of LAMS from 8515PLGA polymers

[0049] The term “peptide agent” is meant to include any peptide agents having diagnostic and/or therapeutic properties including, but not limited to, antimetabolic, antifungal, anti-inflammatory, antitumoral, antiinfectious, antibiotics, nutrient, agonist, and antagonist properties.

[0050] Specifically, the peptide agents of the invention may be any peptides capable of forming a beneficial salt with a strong acid, in particular a peptide agent containing an electron donor base group, such as a basic nitrogen atom, e.g. an amine, imine or ring nitrogen. The peptide agents preferably contain one or more exposed protonatable amine functionalities. Peptide agents useful in the preparation of the compositions of the present invention include, but are not limited to, oxytocin, vasopressin, adrenocorticotropic hormone (ACTH), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), prolactin, luteinising hormone, luteinizing hormone releasing hormone (LHRH), LHRH agonists, LHRH antagonists, growth hormones (including human, porcine, and bovine), growth hormone releasing factor, insulin, erythropoietin (including all proteins with erythropoietic activity), somatostatin, glucagon, interleukin (which includes IL-2, IL-11, IL-12, etc.), interferon-alpha, interferon-beta, interferon-gamma, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin releasing hormone (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), exenatide, peptide YY (PYY), renin,

weight. More preferably concentration of the polymer in the compositions is between 30 to 60% by weight.

[0066] Poly(lactic acid), and copolymers of lactic acid and glycolic acid (PLGA), including poly(D,L-lactide-co-glycolide) and poly(L-lactide-co-glycolide) are preferably used in the present invention. The polymers (or thermoplastic polyesters) have monomer ratios of lactic acid to glycolic acid of between about 50:50 to about 100:0 and weight average molecular weights of between about 2,000 to about 100,000. The biodegradable thermoplastic polyesters can be prepared using the methods known in the art, e.g., polycondensation and ring-opening polymerization (e.g., U.S.Pat. No. 4,443,340; 5,242,910; 5,310,865, which are all incorporated herein by reference). The terminal groups of the poly(DL-lactide-co-glycolide) can either be hydroxyl, carboxylic, or ester depending upon the method of polymerization. The suitable polymers may include a monofunctional alcohol or a polyol residue and may not have a carboxylic acid terminus. Examples of monofunctional alcohols are methanol, ethanol, or 1-dodecanol. The polyol may be a diol, triol, tetraol, pentaol and hexaol including ethylene glycol, 1,6-hexanediol, polyethylene glycol, glycerol, saccharides, reduced saccharides such as sorbitol, and the like.

[0067] The copolymers of lactic acid and glycolic acid or lactide and glycolide include poly(D,L-lactide-co-glycolide) (PLGA) and poly(L-lactide-co-glycolide). The copolymers have monomer molar ratios of lactic acid to glycolic acid of between about 50:50 to about 100:0. When the molar ratio of 85:15 is used, it indicates the copolymer contains 80 – 90% of lactic acid or lactide and 10 – 20% of glycolic acid or glycolide. When the molar ratio of 75:25 is used, it indicates the copolymer contains 70 – 80% of lactic acid

Such cavities include the cavities created after a surgery or natural body cavity such as vagina, anus, and the like.

[00101] In another aspect, the present invention provides a stabilized liquid biodegradable polymeric composition for forming an economical, practical, and efficient controlled release delivery system for LHRH agonists or antagonists comprising a) a beneficial salt of a LHRH agonist or antagonist formed with a strong acid which minimizes or prevents the interaction/reaction between the LHRH agonist or antagonist and the polymer in an organic solution; b) a biodegradable polymer; c) an organic solvent; and d) optionally one or more excipients to achieve optimal delivery of the peptide agent. The liquid biodegradable polymeric composition may be fabricated into implantable polymeric matrices. Wherein the liquid biodegradable polymeric composition retains at least 90%, preferably 95%, of their original molecular weight, structure and/or biological activity before and during the fabrication process.

[00102] As used herein, the term of "implantable polymeric matrices " is intended to include particles, films, pellets, cylinders, discs, microcapsules, microspheres, nanospheres, microparticles, wafers, and other known polymeric configurations used for drug delivery.

[00103] Methods for forming various pharmaceutically acceptable polymer carriers are well known in the art. For examples, various methods and materials are described in US Patents: 6,410,044; 5,698,213; 6,312,679; 5,410,016; 5.529,914; 5,501,863; and PCT Publication No. WO 93/16687; 4.938,763; 5,278,201; 5,278,202; EP 0,058,481; which are all incorporated herein by reference.

What is claimed is:

1. A pharmaceutical composition comprising:

    a) a combination of a strong acid salt and a weak acid salt of a LHRH agonist or antagonist, wherein the molar ratio of (strong acid anion + weak acid anion) to LHRH is ≤ 2:1 and the molar ratio of the strong acid anion to the LHRH agonist or antagonist is from 1:1 to 2:1;

    b) a biodegradable polymer selected from the group of a homopolymer polylactide or polylatic acid, and a copolymer poly (lactic acid-co-glycolic acid) or poly (lactide-co-glycolide), wherein the ratio of lactide:glycolide (or lactic acid:glycolic acid) of the copolymer is from 50:50 to 100:0; and

    c) N-methyl-2-pyrrolidone (NMP);

    wherein the pharmaceutical composition having a selected release duration ranging from one month to 6 months can be prepared by varying the ratios of a strong acid salt and a weak acid salt of a LHRH agonist or antagonist.

2. The pharmaceutical composition of claim 1 wherein the LHRH agonist is selected from a group consisting of leuprolide, triptorelin, and goserelin.

3. The pharmaceutical composition of claim 1 wherein the LHRH agonist is leuprolide.

4. The pharmaceutical composition of claim 1 wherein the strong acid is selected from a group consisting of methanesulfonic acid, HCl, and sulfuric acid.

5. The pharmaceutical composition of claim 1 wherein the strong acid is sulfuric acid and the molar ratio of the sulfate anion to the LHRH agonist or antagonist is from 0.5:1 to 1:1.

6. The pharmaceutical composition of claim 1 wherein the weak acid is selected from a group consisting of acetic acid and formic acid.

7. A pharmaceutical composition comprising:

   a) a combination of leuprolide mesylate and leuprolide acetate, wherein the molar ratio of (mesylate + acetate) to leuprolide is ≤ 2:1 and the molar ratio of mesylate anion to leuprolide is from 1:1 to 2:1;

   b) a biodegradable polymer selected from the group of a homopolymer polylactide or polylatic acid, and a copolymer poly (lactic acid-co-glycolic acid) or poly (lactide-co-glycolide), wherein the ratio of lactide:glycolide (or lactic acid:glycolic acid) of the copolymer is from 50:50 to 100:0; and

   c) N-methyl-2-pyrrolidone (NMP);

   wherein the pharmaceutical composition having a selected release duration ranging from one month to 6 months can be prepared by varying the ratios of mesylate to leuprolide.

8. A pharmaceutical composition comprising:

   a) a combination of leuprolide mesylate and leuprolide formate, wherein the molar ratio of (mesylate + formate) to leuprolide is ≤ 2:1 and the molar ratio of mesylate anion to leuprolide is from 1:1 to 2:1;

b) a biodegradable polymer selected from the group of a homopolymer polylactide or polylatic acid, and a copolymer poly (lactic acid-co-glycolic acid) or poly (lactide-co-glycolide), wherein the ratio of lactide:glycolide (or lactic acid:glycolic acid) of the copolymer is from 50:50 to 100:0; and

c) N-methyl-2-pyrrolidone (NMP);

wherein the pharmaceutical composition having a selected release duration ranging from one month to 6 months can be prepared by varying the ratios of mesylate to leuprolide.

9. The pharmaceutical composition of claims 7 and 8 wherein the molar ratio of mesylate anion to leuprolide is from 1.4:1 to 2:1.

10. The pharmaceutical composition of claims 7 and 8 wherein the molar ratio of mesylate anion to leuprolide is from 1.5:1 to 1.8:1.

11. The pharmaceutical composition of claims 1, 7 and 8 wherein the biodegradable polymer has at least one hydroxyl terminal group.

12. The pharmaceutical composition of claims 1, 7 and 8 wherein the biodegradable polymer has 30 – 60% of the composition by weight, has an average molecular weight of 8,000 to 50,000, and has a polydispersity less than or equals to 2.5.