poly(DL-ladide-co-glycolide) with a molar ratio of lactide to glycolide of 75/25 (Birmingham Polymer, Inc.) was dissolved in NMP to give a solution with 45% polymer by weight. This solution was combined and mixed with leuprolide acetate to result in a flowable and injectable viscous formulation. As shown in the present application, a significant amount leuprolide related substances or impurities were unexpectedly observed from this type of formulation over a short period of time which would adversely compromise the quality of the drug product. More surprisingly, the major impurities generated were not the reaction between bioactive substances and the poly(DL-lactide-co-glycolide) as disclosed in the prior art, but the direct reaction between bioactive substances and the residual or unreacted lactidie monomers of the polymer.

[0008] According to ICH guidelines , any impurity (individual impurity) in new drug product greater than 0.1% has to be reported. Based on maximum daily dose, any impurity greater than 0.1 %, 0.2%, 0.5%, or 1% has to be identified. If the impurity in a new drug product is more than a given qualification threshold level, those impurities should be identified and adequately tested for their adverse effects and biological safety. Therefore, any impurity generation exceeding the corresponding qualification threshold will raise regulatory compliance issues. Characterization and qualification of these impurities for their adverse effects and biological safety can be very expensive and time-consuming.

[0009] US Patent 8,343,513 disclosed several ways to eliminate or reduce impurities in microspheres. It describes that "the following general considerations should be kept in mind in any efforts to eliminate or reduce impurities in

such as glycolide; ring-opening-polymerization of lactide in the further presence of a hydroxycarboxylic acid derivative of which carboxyl group is protected (for example, International Patent Publication WO00/35990); ring-opening-polymerization of lactide in which a catalyst is added under heat to lactide to cause ring-opening polymerization (for example, J. Med. Chem., 16, 897 (1973)); and other methods for copolymerization of lactide with glycolide and/or other monomers.

[0075] The polymerization can be carried out by bulk polymerization in which lactide and other co-monomers are melted, or by solution polymerization in which lactide and other co-monomers are dissolved in a suitable solvent. The solvent for dissolving lactide in solution polymerization includes, but not limited to, aromatic hydrocarbons, such as benzene, toluene, xylene and the like, decalin, dimethylformamide and the like.

[0076] Polymer molecular weight is important because it determines many physical properties. Some examples include the temperatures for transitions from liquids to waxes to rubbers to solids, and mechanical properties, such as stiffness, strength, viscoelasticity, toughness, and viscosity. It is important to select an appropriate polymer with suitable molecular weight for a specific application.

[0077] The terms "weight-average molecular weight, Mw" and "number-average molecular weight, Mn" are well-known to those of skill in the art. The term "polydispersity index, PDI" as used herein is defined as the weight-average molecular weight of a polymer divided by the number-average molecular weight of the polymer (PDI = Mw/Mn). The polydispersity index is well-known to characterize the distribution of molecular weights in a polymer. PDI provides an idea about the homogeneity of a polymer. The polymers whose molecules have nearly same

Example 5: Leuprolide stability in solution with PLGA containing different amount of D,L-lactide monomers

[00128] US patent 8,343,513 claims a nucleophilic compound in a dispersed phase in an organic solvent and a polymer having acid numbers of at least 5, can be stabilized. The present invention shows the higher acid number does not prevent the formation of the impurities and lactide conjugates with leuprolide. A PLGA polymer, PLGA5050 containing different amount of residual lactide monomers was used to measure the difference in formulation stability.

[00129] Table 8 shows the properties of this polymer.

Table 8: Polymer Properties

Polymer	IV	Composition Lac:Gly	MW	Residual Lactide (%)	Acid No
PLGA5050-1	0.37	51 :49	27k	0.02	5 mgKOH/g
PLGA5050-2	0.37	51 :49	27k	0.32	5 mgKOH/g

[00130] 50% polymer solutions of PLGAs containing different amounts of residual D, L-lactide were prepared by dissolving the polymers in suitable amount of NMP.

[00131] Formulations were made by mixing leuprolide acetate (CSBio, #GF1122) into the polymer solutions. Table 9 shows the formulation compositions.

Table 9: Leuprolide formulation composition

Formulation	leuprolide (mg)	Polymer Solution (mg)
LA-50%PLGA5050-1/NMP	77.8	572.1
LA-50%PLGA5050-2/NMP	80.9	603.1

[00132] The solutions were mixed well and stored at 37°C. At specified time points, purity of the solution was analyzed by UPLC and polymer molecular weight was analyzed by GPC.

[00133] Table 10 shows the relative retention times (RRT) for the peaks seen with the formulations at the specified time points.

Polymer	Number of Purification Cycle	D,L-lactide content - - percentage by weight - -
8515DLG2CE-P	1	0.3
8515DLG2CE-P1	2	0.10
8515DLG2CE-P2	3	0.03
8515DLG2CE-P3	4	<0.01
9010DLPG	0	1.72
100DLPLA-1	1	0.16

[00149] Table 16 shows the monomer content is reduced for each subsequent purification of PLGA 8515DLG2CE-P. Formulations were made with leuprolide mesylate (LAMS) according to Table 17.

Table 17: LAMS/PLGA formulation compositions

Formulation	LAMS (SP-002) (mg)	Polymer Solution (mg)
LAMS(SP002)-60% 8515DLG2CE-P/NMP	51.3	585.5
LAMS(SP002)-60% 8515DLG2CE-P1/NMP	51.5	602.7
LAMS(SP002)-60% 8515DLG2CE-P2/NMP	57.6	663.3
LAMS(SP002)-60% 8515DLG2CE-P3/NMP	52.2	603.8
LAMS(SP002)-55% 9010DLPG /NMP	51.3	558.5
LAMS(SP002)-57.5% 100DLPLA/NMP	55.6	638.8

[00150] Formulations were stored in glass vials at 37°C. At specified time points, the leuprolide stability was measured and the sum of the impurities generated from the D,L-lactide monomer was tabulated as a percentage of the total AUC from the HPLC chromatogram as seen in Table 18.

Table 18: Sum of lactide-leuprolide implurities (%) for formulations in Table 17 at 37°C

Time (days)	*LAMS-55% 9010DLPG /NMP*	*LAMS-60% 8515DLG2CE-P/NMP*	*LAMS-57.5% 100DLPLA /NMP*	*LAMS-60% 8515DLG2CE-P1/NMP*	*LAMS-60% 8515DLG2CE-P2/NMP*	*LAMS-60% 8515DLG2CE -P3/NMP*
3	4.834	1.945	1.037	0.559	0.141	0.050

What is claimed:

1 . A process for making an injectable composition for controlled release drug delivery comprising:

combining a lactate-based polymer having a weight average molecular weight between 5,000 and 50,000 dalton, an acid number of less than 3 mgKOH/g and the content of residual lactide monomers in the lactate-based polymer of less than 0.3% by weight; with

a pharmaceutically acceptable organic solvent; and

a bioactive substance or a salt thereof that contains an amino acid serine in the molecular structure that is capable of reacting with lactide monomer to form a conjugate,

with the proviso that no acid additive is added in making the composition.

2. The process of claim 1 where the lactide in the lactate-based polymer is D-lactide, D,L-lactide, L,D-lactide, L-lactide, (R,R)-Lactide, (S,S)-lactide and meso-lactide or any combination thereof.

3. The process of claim 1 where the lactate-based polymer has the content of residual lactide monomers of less than 0.2% by weight.

4. The process of claim 1 where the lactate-based polymer has the content of residual lactide monomers of less than 0.1 % by weight.

5. The process of claim 1 where the lactate-based polymer has an acid number of less than 2 mgKOH/g.

6. The process of claim 1 , wherein the lactate-based polymer is poly(lactic acid) or polylactide (PLA).

7. The process of claim 1 , wherein the lactate-based polymer is poly(lactide-co-glycolide) (PLGA) having the ratio of lactide/glycolide from 50/50 to 100/0.

8. The process of claim 1 where the bioactive substance is selected from the group consisting of luteinizing hormone releasing hormone (LHRH), LHRH analogs, agonists, and antagonists, or salt thereof.

9. The process of claim 1 where the bioactive substance is leuprolide, or salt thereof.

10. The process of claim 1 where the pharmaceutically acceptable organic solvent is selected from the group of N-methyl-2-pyrrolidone, dimethylsulfoxide, dimethylacetamide, glycofurol, methoxypolyethylene glycol 350, polyethylene glycol esters, benzyl benzoate, benzyl alcohol, ethyl benzoate, esters of citric acid, triacetin, diacetin, triethyl citrate, acetyl triethyl citrate, and mixtures thereof.

11 . The process of claim 1 where the pharmaceutically acceptable organic solvent is N-methyl-2-pyrrolidone.

12. An injectable composition for controlled release drug delivery comprising:

a. a lactate-based polymer having a weight average molecular weight between 5,000 and 50,000 dalton, an acid number of less than 3 mgKOH/g and the content of residual lactide monomers in the lactate-based polymer of less than 0.3% by weight;

b. a pharmaceutically acceptable organic solvent; and

c. a bioactive substance or a salt thereof that contains an amino acid serine in the molecular structure that is capable of reacting with lactide monomer to form a conjugate,

with the proviso that no acid additive is added in producing the composition, and the composition reduces the formation of the conjugate.

13. The injectable composition of claim 12 where the lactide in the lactate-based polymer is D-lactide, D,L-lactide, L,D-lactide, L-lactide, (R,R)-Lactide, (S,S)-lactide and meso-lactide or any combination thereof.

14. The injectable composition of claim 13 where the lactate-based polymer has an acid number of less than 2 mgKOH/g.

15. The injectable composition of claim 13 where the lactate-based polymer has the content of residual lactide monomers in the lactate-based polymer of less than 0.2% by weight.

16. The injectable composition of claim 13 where the lactate-based polymer has the content of residual lactide monomers in the lactate-based polymer of less than 0.1 % by weight.

17. The injectable composition of claim 13, wherein the lactate-based polymer is poly(lactic acid) or poly(lactide) (PLA).

18. The injectable composition of claim 13, wherein the lactate-based polymer is poly(lactide-co-glycolide) (PLGA) having the ratio of lactide/glycolide from 50/50 to 100/0.

19. The injectable composition of claim 13 where the bioactive substance is selected from the group consisting of luteinizing hormone releasing hormone (LHRH), LHRH analogs, agonists, and antagonists, or salt thereof.

20. The injectable composition of claim 13 where the bioactive substance is leuprolide or its salts thereof.

21. The injectable composition of claim 13 where the pharmaceutically acceptable organic solvent is selected from the group of N-methyl-2-pyrrolidone, dimethylsulfoxide, dimethylacetamide, glycofurol, methoxypolyethylene glycol 350, polyethylene glycol esters, benzyl benzoate, benzyl alcohol, ethyl benzoate, esters of citric acid, triacetin, diacetin, triethyl citrate, acetyl triethyl citrate, and mixtures thereof.

22. The injectable composition of claim 13 where the pharmaceutically acceptable organic solvent is N-methyl-2-pyrrolidone.