CLAIMS

1. A microsphere formulation, comprising:

polymer microspheres, each polymer microsphere comprising:

(i) ~~a BTK inhibitor~~ibrutinib; and

(ii) a biodegradable polymer,

wherein each polymer microsphere comprises a drug load of the ~~BTK inhibitor~~ibrutinib of greater than ~~40~~30% by weight of the polymer microsphere, and

wherein the polymer microspheres have ~~an average~~a particle size of less than 110 μm (D_{50}).

~~2.~~ The microsphere formulation of claim 1~~, wherein the BTK inhibitor comprises ibrutinib.~~

~~3.~~2. ~~The microsphere formulation of claim 1 or 2~~, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide).

~~4.~~3. The microsphere formulation of ~~any of claims~~claim 1~~-3~~, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide) having a lactide:glycolide ratio of 50:50.

4. The microsphere formulation of ~~any of claims 1-~~claim 3, wherein the biodegradable polymer is ester-terminated.

5. The microsphere formulation of claim 1, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide) having a lactide:glycolide ratio of ~~75:25~~55:45.

6. The microsphere formulation of ~~any~~claim 5, wherein the biodegradable polymer is ester-terminated.

~~6.~~7. The microsphere formulation of ~~claims~~claim 1~~-3~~, wherein the biodegradable polymer comprises a poly(D,L-lactide-co-glycolide) having a lactide:glycolide ratio of 85:15.

~~7.~~ The microsphere formulation of claim ~~1 or 2, wherein the biodegradable polymer comprises a poly(D,L-lactide).~~

~~8. The microsphere formulation of any of the preceding claims, wherein the biodegradable polymer is acid-terminated.~~

~~9.~~8.~~The microsphere formulation of any of claims 1~~ 7, wherein the biodegradable polymer is ~~ester~~acid-terminated.

~~10.~~9. The microsphere formulation of ~~any of claims~~claim 1~~ 6, 8, or 9~~, wherein the biodegradable polymer has an inherent viscosity between about 0.2 dL/g and about 0.~~6~~24 dL/g.

~~11.~~ The microsphere formulation of ~~any of claims~~claim 1~~, 2, 7, 8, or 9, wherein the biodegradable polymer has an inherent viscosity between about 0.1 dL/g and 0.4 dL/g.~~

~~12.~~10. ~~The microsphere formulation of any of the preceding claims~~, wherein each polymer microsphere comprises a drug load of the ~~BTK inhibitor~~ibrutinib of ~~from~~ about ~~45% to about 65~~50% by weight of the polymer microsphere.

~~13.~~11. The microsphere formulation of ~~any of the preceding claims~~claim 1, wherein the polymer microspheres have ~~an average~~a particle size of between about ~~30~~20 μm (D_{50}) ~~to~~and about 60 μm (D_{50}).

~~14.~~12. The microsphere formulation of ~~any of the preceding claims~~claim 1, characterized in that about 75% to 100% of the ~~BTK inhibitor~~ibrutinib is released over a period of ~~between~~ about ~~7 and 28~~12 to about 16 days of injection into a subject, but not more than about 20% of the ~~BTK inhibitor~~ibrutinib has been released within ~~about~~ 24 hours of injection into the subject.

13. The microsphere formulation of claim 1, characterized in that about 75% to 100% of the ibrutinib is released over a period of between about 25 to about 31 days of injection into a subject, but not more than about 20% of the ibrutinib has been released within 24 hours of injection into the subject.

~~15.~~14. A pharmaceutical composition comprising the microsphere formulation of ~~any of the preceding claims~~claim 1.

~~16.~~15. The microsphere formulation of ~~any of the preceding claims~~claim 1 for use in the treatment of a B-cell malignancy.

~~17. A method for making a~~A microsphere formulation, ~~the method comprising the steps:~~

~~(i) contacting a BTK inhibitor with a biodegradable polymer comprising a poly(D,L-lactide-co-glycolide) having a co-monomer ratio of between about 50:50 and 85:15 and an inherent viscosity of between about 0.2 dL/g and 0.6 dL/g in the presence of an organic solvent system to form a dispersed phase;~~

~~(ii) combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion;~~

~~(iii) removing the organic solvent from the emulsion to form a microsphere formulation essentially free of organic solvent; and~~

~~(iv) subjecting the substantially organic solvent-free microsphere formulation to a drying process.~~

~~18. The method of claim 17, wherein the surfactant comprises polyvinyl alcohol.~~

~~19. The method of claim 17 or 18, wherein the surfactant comprises polyvinyl alcohol, and wherein the polyvinyl alcohol concentration in the aqueous phase prior to the combining is about 0.35% by weight.~~

~~20. A method for making a microsphere formulation, the method comprising the steps:~~

~~(i) contacting a BTK inhibitor with a biodegradable polymer comprising a poly(D,L-lactide) having an inherent viscosity of between about 0.1 dL/g and 0.4 dL/g in the presence of an organic solvent system to form a dispersed phase;~~

~~(ii) combining the dispersed phase with a continuous phase comprising water and surfactant in a homogenizer to form an emulsion;~~

~~(iii) removing the organic solvent from the emulsion to form a microsphere formulation essentially free of organic solvent; and~~

~~(iv) subjecting the substantially organic solvent-free microsphere formulation to a drying process.~~

~~21. The method of claim 20, wherein the surfactant comprises polyvinyl alcohol.~~

~~22. The method of claim 20 or 21, wherein the surfactant comprises polyvinyl alcohol, and wherein the polyvinyl alcohol concentration in the aqueous phase prior to the combining is about 0.35% by weight.~~

~~23.~~16. ~~A kit,~~ comprising:

polymer microspheres, each polymer microsphere comprising:

(i) ibrutinib; and

(ii) a biodegradable polymer comprising ~~a~~an ester-terminated poly(D,L-lactide-co-glycolide) having ~~an inherent viscosity between about 0.2 dL/g and 0.6 dL/g,~~ a lactide:glycolide ratio selected from 50:50, 55:45, and 75:25, or a combination thereof;

wherein each polymer microsphere comprises a drug load of the ibrutinib of ~~from~~ between about 30% and about ~~45% to about 65~~55% by weight of the polymer microsphere, and

wherein the polymer microspheres have ~~an average~~a particle size of ~~from~~between about ~~30~~25 μm (D_{50}) ~~to about 60~~and 40 μm (D_{50})~~).~~), and

~~24. A method for treating a B-cell malignancy,~~wherein the ~~method comprising:~~

~~administering by intramuscular or subcutaneous injection to the subject a~~ microsphere formulation ~~with a dosing schedule of from~~is characterized in that about ~~every 7~~75% to 100% of the ibrutinib is released over a period of between about 12 to about ~~every 28~~16 days~~,~~ of injection into a human subject, but not more than about 20% of the ibrutinib has been released within 24 hours of injection into the human subject.

17. A microsphere formulation, comprising:

polymer microspheres, each polymer microsphere comprising:

(i) ibrutinib; and

(ii) a biodegradable polymer comprising ~~a~~an acid-terminated poly(D,L-lactide-co-glycolide) having ~~an inherent viscosity between about 0.2 dL/g and 0.6 dL/g, a~~ lactide:glycolide ratio of 85:15;

wherein each polymer microsphere comprises a drug load of the ibrutinib of ~~from~~between about 45% ~~to~~and about ~~65~~55% by weight of the polymer microsphere, and

wherein the polymer microspheres have ~~an average~~a particle size of between about 30 μm (D_{50}) ~~to about 60~~and 40 μm (D_{50}~~).~~), and

wherein the microsphere formulation is characterized in that about 75% to 100% of the ibrutinib is released over a period of between about 25 to about 31 days of injection into a human subject, but not more than about 20% of the ibrutinib has been released within 24 hours of injection into the human subject.