within the working time of the PGSU reaction without compromising uniformity or precision, and/or an elastomer loaded with up to 90% w/w API that provides controlled release of the API for at least three months.

SUMMARY

[0009] Examples are directed to processes that form poly(glycerol sebacate) urethane (PGSU) having a degradation rate and corresponding API release kinetics that are both tunable by selection of the starting PGS polyol structure and the process conditions to form the API-loaded PGSU.

[0010] Examples are directed to PGSU formulations that incorporate high API loading and provide sustained API release, independent of loading concentration, to maintain therapeutic levels over the course of many months.

[0011] Examples are directed to manufacturing methods for PGSU that eliminate any use of high temperature or solvent, thereby permitting incorporation of thermolabile and form-sensitive APIs into the PGSU.

[0012] According to an example, a process forms an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient. The process includes homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend. The process also includes selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25. The process further includes homogeneously combining the resin blend with the isocyanate to form a reaction mixture and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient. In one aspect, the present disclosure refers to a process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and

injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is loaded with at least 40% w/w of the active pharmaceutical ingredient. In another aspect, the present disclosure refers to a process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient; wherein the catalyst is selected from the group consisting of a potassium catalyst, potassium tartrate, and potassium citrate. In yet another aspect, the present disclosure refers to a process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient; wherein the injecting further comprises removing generated gasses, entrained gasses, entrapped gasses, or combinations thereof. In a further aspect, the present disclosure refers to a process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient; wherein the resin blend includes no more than 50% w/w of a solvent.

[0013] According to another example, an implantable product includes a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient. The implantable product releases the

active pharmaceutical ingredient by surface degradation of the poly(glycerol sebacate) urethane at a predetermined release rate for at least three months under physiological conditions.

[0014] According to yet another example, an implantable product includes a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient. The poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25. In another aspect, the present disclosure refers to an implantable product comprising a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25 and wherein the active pharmaceutical ingredient is at least 40% w/w of the implantable product. In yet another aspect, the present disclosure refers to an implantable product comprising a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25 and wherein the implantable product comprises more than one compartment. In a further aspect, the present disclosure refers to an implantable product comprising a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25 and wherein the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient forms a plurality of fibers.

[0015] Various features and advantages of the present invention will be apparent from the following more detailed description, taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 shows viscosity as a function of reaction time for a water-mediated PGS polymerization process and a non-water-mediated PGS polymerization process.

[0017] FIG. 2 shows Fourier-transform infrared (FTIR) spectra for a variety of PGS resin types.

[0018] FIG. 3 shows GPC spectra for high-molecular-weight PGS resins formed by either a water-mediated process or a non-water-mediated process.

[0019] FIG. 4 shows PGSU crosslinking level as a PGS:HDI mass ratio based on FTIR spectra and a multiple linear regression model for PGSU made from a variety of PGS resin types.

[0020] FIG. 5 shows PGSU crosslinking density as determined by Flory-Rehner swell testing for PGSU made from a variety of PGS resin types.

[0021] FIG. 6 shows elastic modulus for PGSU films made from a variety of PGS resin types.

[0022] FIG. 7 shows strain at break for PGSU made from a variety of PGS resin types.

[0023] FIG. 8 shows weight-average molecular weight and polydispersity index of extractables collected from PGSU films from a variety of PGS resin types.

[0024] FIG. 9 shows mass and mass percentage of extractables collected from PGSU films, made from a variety of PGS resin types, based on the mass of the PGSU film.

Claims

What is claimed is:

1. A process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising:

homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend;

selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25;

homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and

injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is loaded with at least 40% w/w of the active pharmaceutical ingredient.

2. The process of claim 1, wherein the weight average molecular weight of the flowable poly(glycerol sebacate) resin is greater than 10,000 Da.

3. The process of claim 1, wherein the homogeneous combining comprises shear mixing.

4. The process of claim 1, wherein the injecting comprises reaction injection molding.

5. The process of claim 1, wherein the injecting further comprises removing generated gasses, entrained gasses, entrapped gasses, or combinations thereof.

6. The process of claim 5, wherein the removing occurs under vacuum.

7. The process of claim 5, wherein the removing occurs under sonication.

8. The process of claim 1, wherein the process occurs at a temperature of 60 °C or less.

9. The process of claim 1, wherein the homogeneous mixing occurs in the absence of a solvent.

10. The process of claim 1, wherein the flowable poly(glycerol sebacate) resin is free of a solvent.

11. The process of claim 1, wherein the resin blend includes no more than 50% w/w of a solvent.

12. The process of claim 11 further comprising evaporating the solvent from the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient at a temperature of up to 40 °C for up to 6 days.

13. The process of claim 1, wherein the injecting comprises injecting the reaction mixture into a mold.

14. The process of claim 1 further comprising crosslinking the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient for up to 24 hours at up to 40 °C to form the implantable product.

15. The process of claim 1, wherein the catalyst is selected from the group consisting of a potassium catalyst, potassium tartrate, and potassium citrate.

16. An implantable product comprising a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25 and wherein the active pharmaceutical ingredient is at least 40% w/w of the implantable product.

17. The implantable product of claim 16, wherein the implantable product comprises more than one compartment.

18. The implantable product of claim 17, wherein the implantable product comprises a second active pharmaceutical ingredient.

19. The implantable product of claim 16, wherein the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient forms a plurality of fibers.

20. The implantable product of claim 16, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) resin having a molecular weight greater than 10,000 Da.

21. The implantable product of claim 16, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) resin having a polydispersity index less than 12.

22. The implantable product of claim 16, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) resin having a glycerol-to-sebacic acid

stoichiometric ratio of between 1:0.5 and 1:1.5.

23. The implantable product of claim 16, wherein the isocyanate is a blocked isocyanate.

24. The implantable product of claim 16, wherein the implantable product releases the active pharmaceutical ingredient by surface degradation of the poly(glycerol sebacate) urethane at a predetermined release rate for at least three months under physiological conditions.

25. A process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient; wherein the injecting further comprises removing generated gasses, entrained gasses, entrapped gasses, or combinations thereof.

26. The process of claim 25, wherein the removing occurs under vacuum.

27. The process of claim 25, wherein the removing occurs under sonication.

28. A process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient; wherein the resin blend includes no more than 50% w/w of a solvent.

29. The process of claim 28 further comprising evaporating the solvent from the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient at a temperature of up to 40° C for up to 6 days.

30. The process of claim 28, wherein the homogeneous mixing occurs in the absence of a solvent.

31. The process of claim 28, wherein the flowable poly(glycerol sebacate) resin is free of a solvent.

32. A process of forming an implantable product comprising poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, the process comprising: homogeneously mixing a flowable poly(glycerol sebacate) resin with the active pharmaceutical ingredient and a catalyst to form a resin blend; selecting an amount of isocyanate such that an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25; homogeneously combining the resin blend with the isocyanate to form a reaction mixture; and injecting the reaction mixture to form the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient; wherein the catalyst is selected from the group consisting of a potassium catalyst, potassium tartrate, and potassium citrate.

33. An implantable product comprising a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25 and wherein the implantable product comprises more than one compartment.

34. The implantable product of claim 33, wherein the implantable product comprises a second active pharmaceutical ingredient.

35. An implantable product comprising a poly(glycerol sebacate) urethane loaded with an active pharmaceutical ingredient, wherein the poly(glycerol sebacate) urethane is formed from a poly(glycerol sebacate) reacted with an isocyanate at an isocyanate-to-hydroxyl stoichiometric ratio is in the range of 1:0.25 to 1:1.25 and wherein the poly(glycerol sebacate) urethane loaded with the active pharmaceutical ingredient forms a plurality of fibers.