evidence suggests that PNH and other complement-related disorders are alleviated through inhibition of complement activity.

[0008] While some therapeutic complement inhibitors are available to treat patients, most require frequent administrations by intravenous or subcutaneous delivery. These frequent, often daily, administrations reduce quality of life and patient compliance. There remains a need in the art for therapeutic formulations with less burdensome administration requirements. Embodiments of the present disclosure address this by providing related formulations and methods described herein.

SUMMARY

[0009] In one aspect, the present disclosure provides a sustained release formulation comprising: an active ingredient; and a release modulating matrix comprising a polymer, wherein the polymer comprises a release modulating matrix comprising a polymer, wherein the polymer comprises poly lactic-co-glycolic acid (PLGA).

[0009a] In another aspect, the present disclosure provides a method of preparing the sustained release formulation as described herein, the method comprising: preparing an organic phase solution, wherein the organic phase solution is prepared by combining an organic solvent, PLGA, and the active ingredient; preparing an aqueous phase solution, wherein the aqueous phase solution is prepared by combining an aqueous solution with an emulsion stabilizer; and preparing the sustained release formulation by preparing an emulsion of the organic phase solution and the aqueous phase solution.

[0009b] In another aspect, the present disclosure provides a use of the sustained release formulation as described herein in the manufacture of a medicament for treating a complement-related indication, comprising that the sustained release formulation is to be administered, wherein the active ingredient comprises a C5 inhibitor.

[0009c] In some examples, the present disclosure provides a sustained release formulation including: a polypeptide, wherein the polypeptide includes a C5 inhibitory cyclic polypeptide including the amino acid sequence of SEQ ID NO: 1; and a release modulating matrix including a polymer, wherein the polymer includes poly lactic-co-glycolic acid (PLGA). The release modulating matrix may include a particle. The particle may include a microparticle. The PLGA may include a ratio of poly lactic acid to poly glycolic acid of from about 25:75 to about 75:25. The PLGA may include a ratio of poly lactic acid to poly glycolic acid of about 50:50. The release modulating matrix may include an emulsion. The emulsion may include a single emulsion. The emulsion may include a double emulsion. The sustained release

formulation may include an excipient. The excipient may include a pore forming excipient (PFE). The pore forming excipient may be selected from the group consisting of medium chain triglycerides, PLURONIC® F-127, and poly (ethylene glycol) (PEG). The particle may include a diameter of from about 5 μm to about 200 μm. The polypeptide may include a cyclic bond. The polypeptide may include a modified lysine residue. The polypeptide may include a lipid moiety. The polypeptide may include a PEG moiety. The polypeptide may include zilucoplan. The sustained release formulation may include from about 10% to about 95% of the release modulating matrix by percent weight. The sustained release formulation may include from about 50% to about 90% of the release modulating matrix by percent weight. The sustained release formulation may include from about 10% to about 50% of the polypeptide by percent weight. The polypeptide may be uniformly distributed in the release modulating matrix.

[0010] In some examples, the present disclosure provides a method of preparing a sustained release formulation, the method including: preparing an organic phase solution, wherein the organic phase solution is prepared by combining an organic solvent, PLGA, and the polypeptide; preparing an aqueous phase solution, wherein the aqueous phase solution is prepared by combining an aqueous solution with an emulsion stabilizer; and preparing the sustained release formulation by preparing an emulsion of the organic phase solution and the aqueous phase solution. The organic solvent may include dichloromethane (DCM). The aqueous solution may include phosphate buffered saline. The emulsion stabilizer may include polyvinyl alcohol (PVA). The organic solvent may be removed from the emulsion by evaporation. The evaporation may be carried out by quench evaporation. The evaporation may be carried out by rotary evaporation. The particle may be formed as a result of the evaporation. The polypeptide may be uniformly distributed in the particle. The polypeptide may be combined in the organic phase solution at a concentration sufficient to yield from about 10% by weight to about 50% by weight of the polypeptide in the sustained release formulation. The polypeptide may be combined in the organic phase solution at a concentration sufficient to yield from about 36% by weight to about 38% by weight of the polypeptide in the sustained release formulation. The polypeptide may include zilucoplan. The sustained release formulation may include a zilucoplan-PLGA particle.

[0011] In some examples, the present disclosure provides a sustained release formulation prepared according to any of the methods described herein. The sustained release formulation may include a sustained release profile including low initial burst for release of a polypeptide and/or capability of achieving an effective concentration of a polypeptide in a medium where

the polypeptide is released from the sustained release formulation. The capability of achieving the effective concentration of the polypeptide in the medium where the polypeptide is released from the sustained release formulation may be extended over a specific period of time. The specific period of time may include from about one week to about three weeks. The effective concentration may be from about 4,000 ng/mL to about 12,000 ng/mL. The sustained release profile may include an initial burst for release of the polypeptide of from about 0% to about 20% of the total amount of the polypeptide included in the sustained release formulation.

[0012] In some examples, the present disclosure provides a method of administering a polypeptide, the method including administering a sustained release formulation described herein, wherein the polypeptide includes zilucoplan. The sustained release formulation may be administered by subcutaneous injection. The sustained release formulation may be administered weekly or biweekly. The polypeptide may be released from the sustained release formulation after administration. Release of the polypeptide may exhibit a burst of less than 5%. The sustained release formulation may be administered at a dose sufficient to administer from about 2 mg/kg to about 20 mg/kg of the polypeptide. The sustained release formulation may be administered at a dose sufficient to administer from about 100 mg to about 200 mg of zilucoplan.

[0013] In some examples, the present disclosure provides a method of reducing hemolysis in a subject, the method including administering a sustained release formulation described herein, wherein the sustained release formulation includes zilucoplan.

[0014] In some examples, the present disclosure provides a method of treating a complement-related indication, the method including administering a sustained release formulation described herein, wherein the sustained release formulation includes zilucoplan. The complement-related indication may include one or more of paroxysmal nocturnal hemoglobinuria, myasthenia gravis, an inflammatory indication, a wound, a burn, an autoimmune indication, a pulmonary indication, a cardiovascular indication, a neurological indication, a kidney-related indication, a diabetes-related indication, an ocular indication, and a pregnancy-related indication.

[0015] In some examples, the present disclosure provides a sustained release formulation including: an active ingredient; and a release modulating matrix including a polymer, wherein the polymer includes PLGA. The release modulating matrix may include a particle. The particle may include a nanoparticle or a microparticle. The PLGA may include a ratio of poly lactic acid to poly glycolic acid of from about 25:75 to about 75:25. The PLGA may include a

ratio of poly lactic acid to poly glycolic acid of about 50:50. The release modulating matrix may include an emulsion. The emulsion may include a single emulsion. The emulsion may include a double emulsion. The sustained release formulation may include an excipient. The excipient may include a PFE. The PFE may be selected from the group consisting of medium chain triglycerides, PLURONIC® F-127, and PEG. The particle may include a diameter of from about 5 μm to about 200 μm. The active ingredient may include a therapeutic agent. The active ingredient may include at least one non-natural amino acid. The at least one non-natural amino acid may be selected from any of those listed in Table 2 of United States Publication Number US 2011/0172126. The active ingredient may include a cyclic bond. The active ingredient may include a modified lysine residue. The active ingredient may include a lipid moiety. The active ingredient may include a PEG moiety. The active ingredient may be a peptidomimetic. The active ingredient may be a macrocyclic compound. The active ingredient may include a C5 inhibitor. The C5 inhibitor may be selected from the group consisting of any of those listed in Table 1 or any of those listed in Table 1 of United States Publication Number US 2017/0137468. The sustained release formulation may include from about 10% to about 95% of the release modulating matrix by percent weight. The sustained release formulation may include from about 50% to about 90% of the release modulating matrix by percent weight. The sustained release formulation may include from about 10% to about 50% of the active ingredient by percent weight. The active ingredient may be uniformly distributed in the release modulating matrix.

[0016] In some examples, the present disclosure provides a method of preparing a sustained release formulation described herein, the method comprising: preparing an organic phase solution, wherein the organic phase solution is prepared by combining an organic solvent, PLGA, and an active ingredient; preparing an aqueous phase solution, wherein the aqueous phase solution is prepared by combining an aqueous solution with an emulsion stabilizer; and preparing the sustained release formulation by preparing an emulsion of the organic phase solution and the aqueous phase solution. The organic solvent may include DCM. The aqueous solution may include phosphate buffered saline. The emulsion stabilizer may include PVA. The organic solvent may be removed from the emulsion by evaporation. The evaporation may be carried out by quench evaporation. The evaporation may be carried out by rotary evaporation. A particle may be formed as a result of the evaporation. The active ingredient may be uniformly distributed in the particle. The active ingredient may be combined in the organic phase solution at a concentration sufficient to yield from about 10% by weight to about 50% by weight of the active ingredient in the sustained release

formulation. The active ingredient may be combined in the organic phase solution at a concentration sufficient to yield from about 36% by weight to about 38% by weight of the active ingredient in the sustained release formulation.

[0017] In some examples, the present disclosure provides a sustained release formulation prepared according any of the methods described herein. The sustained release formulation may include a sustained release profile including low initial burst for release of the active ingredient and/or capability of achieving an effective concentration of the active ingredient in a medium where the active ingredient is released from the sustained release formulation. The capability of achieving the effective concentration of the active ingredient in the medium where the active ingredient is released from the sustained release formulation may be extended over a specific period of time. The specific period of time may include from about one week to about three weeks. The effective concentration may be from about 4,000 ng/mL to about 12,000 ng/mL. The sustained release profile may include an initial burst for release of the active ingredient of from about 0% to about 20% of the total amount of the active ingredient included in the sustained release formulation.

[0018] In some examples, the present disclosure provides a method of administering an active ingredient, the method comprising administering a sustained release formulation according to any of those described herein. The sustained release formulation may be administered by subcutaneous injection. The sustained release formulation may be administered weekly or biweekly. The active ingredient may be released from the sustained release formulation after administration. Release of the active ingredient may exhibit a burst of less than 5%. The sustained release formulation may be administered at a dose sufficient to administer from about 2 mg/kg to about 20 mg/kg of the active ingredient. The sustained release formulation may be administered at a dose sufficient to administer from about 100 mg to about 200 mg of the active ingredient.

[0019] In some examples, the present disclosure provides a method of reducing hemolysis in a subject by administering an active ingredient to the subject according to any of the methods described herein.

[0020] In some examples, the present disclosure provides a method of treating a complement-related indication in a subject by administering an active ingredient to the subject according to any of the methods described herein, wherein the active ingredient comprises a C5 inhibitor. The complement-related indication may include one or more of paroxysmal nocturnal hemoglobinuria, myasthenia gravis, an inflammatory indication, a wound, a burn, an autoimmune indication, a pulmonary indication, a cardiovascular

indication, a neurological indication, a kidney-related indication, a diabetes-related indication, an ocular indication, and a pregnancy-related indication.

BRIEF DESCRIPTION OF THE FIGURES

[0021] The foregoing and other objects, features and advantages of particular embodiments of the disclosure will be apparent from the following description and illustrations in the accompanying figures.

[0022] Fig. 1 is a graph of zilucoplan concentration in rat plasma samples obtained at various time points after administration of zilucoplan-PLGA formulations.

[0023] Fig. 2 is a graph of zilucoplan concentration in non-human primate plasma samples obtained at various time points after administration of zilucoplan-PLGA formulations.

[0024] Fig. 3 is a graph of zilucoplan concentration in non-human primate plasma samples obtained at various time points after administration of zilucoplan-PLGA formulations.

CLAIMS

What is claimed is:

1. A sustained release formulation comprising:

    an active ingredient; and

    a release modulating matrix comprising a polymer, wherein the polymer comprises poly lactic-co-glycolic acid (PLGA).

2. The sustained release formulation of claim 1, wherein the active ingredient is a polypeptide, and the polypeptide comprises a C5 inhibitory cyclic polypeptide comprising the amino acid sequence of SEQ ID NO: 1.

3. The sustained release formulation of claim 1 or 2, wherein:

(a) the release modulating matrix comprises a particle, wherein, optionally, the particle comprises a nanoparticle or a microparticle;

(b) the PLGA comprises a ratio of poly lactic acid to poly glycolic acid of from about 25:75 to about 75:25, wherein, optionally, the PLGA comprises a ratio of poly lactic acid to poly glycolic acid of about 50:50; and/or

(c) the release modulating matrix comprises an emulsion, wherein, optionally, the emulsion comprises a single or double emulsion.

4. The sustained release formulation of any one of claims 1-3, wherein:

(a) the sustained release formulation comprises an excipient, wherein, optionally, the excipient comprises a pore forming excipient (PFE), wherein, further optionally, the PFE is selected from the group consisting of medium chain triglycerides, PLURONIC® F-127, and polyethylene glycol (PEG);

(b) the particle comprises a diameter of from about 5 μm to about 200 μm; and/or

(c) the active ingredient comprises a therapeutic agent.

5. The sustained release formulation of any one of claims 1, 3 or 4, wherein:

(a) the active ingredient comprises at least one non-natural amino acid, wherein, optionally, the at least one non-natural amino acid is selected from any of those listed in Table 2 of United States Publication Number US 2011/0172126;

(b) the active ingredient comprises a cyclic bond, a modified lysine residue, a lipid moiety, and/or a PEG moiety;

(c) the active ingredient is a peptidomimetic and/or a macrocyclic compound; and/or

(d) the active ingredient comprises a C5 inhibitor, wherein, optionally, the C5 inhibitor is selected from the group consisting of any of those listed in Table 1 or any of those listed in Table 1 of United States Publication Number US 2017/0137468.

6. The sustained release formulation of any one of claims 1-5, wherein:

(a) the sustained release formulation comprises from about 10% to about 95% of the release modulating matrix by percent weight, wherein, optionally, the sustained release formulation comprises from about 50% to about 90% of the release modulating matrix by percent weight;

(b) the sustained release formulation comprises from about 10% to about 50% of the active ingredient by percent weight; and/or

(c) the active ingredient is uniformly distributed in the release modulating matrix.

7. A method of preparing the sustained release formulation of any one of claims 1-6, the method comprising:

preparing an organic phase solution, wherein the organic phase solution is prepared by combining an organic solvent, PLGA, and the active ingredient;

preparing an aqueous phase solution, wherein the aqueous phase solution is prepared by combining an aqueous solution with an emulsion stabilizer; and

preparing the sustained release formulation by preparing an emulsion of the organic phase solution and the aqueous phase solution.

8. The method of claim 7, wherein the organic solvent comprises dichloromethane (DCM), and/or the aqueous solution comprises phosphate buffered saline.

9. The method of claim 7 or 8, wherein the emulsion stabilizer comprises polyvinyl alcohol (PVA).

10. The method of claim 7 or 8, wherein the organic solvent is removed from the emulsion by evaporation, wherein, optionally, the evaporation is carried out by quench evaporation or rotary evaporation.

11. The method of claim 10, wherein a particle is formed as a result of the evaporation, wherein, optionally, the active ingredient is uniformly distributed in the particle.

12. The method of any one of claims 7-11, wherein the active ingredient is combined in the organic phase solution at a concentration sufficient to yield from about 10% by weight to about 50% by weight of the active ingredient in the sustained release formulation, wherein, optionally, the active ingredient is combined in the organic phase solution at a concentration sufficient to yield from about 36% by weight to about 38% by weight of the active ingredient in the sustained release formulation.

13. The sustained release formulation of any one of claims 1-6, wherein the sustained release formulation comprises a sustained release profile comprising low initial burst for release of the active ingredient and/or capability of achieving an effective concentration of the active ingredient in a medium where the active ingredient is released from the sustained release formulation, wherein, optionally:

(i) the capability of achieving the effective concentration of the active ingredient in the medium where the active ingredient is released from the sustained release formulation is extended over a specific period of time;

(ii) the specific period of time comprises from about one week to about three weeks;

(iii) the effective concentration is from about 4,000 ng/mL to about 12,000 ng/mL; and/or

(iv) the sustained release profile comprises an initial burst for release of the active ingredient of from about 0% to about 20% of the total amount of the active ingredient included in the sustained release formulation.

14. Use of the sustained release formulation according to any one of claims 1-6 and 13 in the manufacture of a medicament for treating a complement-related indication, comprising that the sustained release formulation is to be administered, wherein the active ingredient comprises a C5 inhibitor.

15. The use of claim 14, wherein:

(a) the sustained release formulation is to be administered by subcutaneous injection;

(b) the sustained release formulation is to be administered weekly or biweekly;

(c) the active ingredient is released from the sustained release formulation after administration, wherein, optionally, release of the active ingredient exhibits a burst of less than 5%;

(d) the sustained release formulation is to be administered at a dose sufficient to be administered from about 2 mg/kg to about 20 mg/kg of the active ingredient, wherein, optionally, the sustained release formulation is to be administered at a dose sufficient to be administered from about 100 mg to about 200 mg of the active ingredient; and/or

(e) the complement-related indication comprises one or more of paroxysmal nocturnal hemoglobinuria, myasthenia gravis, an inflammatory indication, a wound, a burn, an autoimmune indication, a pulmonary indication, a cardiovascular indication, a neurological indication, a kidney-related indication, a diabetes-related indication, an ocular indication, and a pregnancy-related indication.