COMPOSITION AND METHODS FOR STABILIZING LIQUID PROTEIN FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application No. 62/868,615, filed June 28, 2019, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present disclosure relates generally to stable liquid pharmaceutical formulations comprising polypeptides and surfactants and methods for making the same.

BACKGROUND

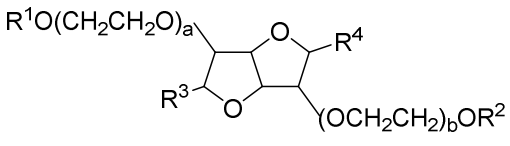
[0003] Polysorbates (PS), which are commonly used surfactants in biopharmaceutical protein formulations, have been shown to be susceptible to a variety of degradation pathways including: chemical hydrolysis, oxidation, and enzymatic hydrolysis. The degradation of PS can lead to the generation of various peroxides which subsequently oxidize amino acid residues (*e.g.*, methionine) in the protein during long-term storage. Levine et al. *Proc. Natl. Acad. Sci. U. S. A.* (1996) 93, 15036–15040. The oxidation of these amino acid residues has potentially negative impact on the biological activity of the protein, thereby limiting the protective effect of PS in protein formulations. In addition, because polysorbates are heterogeneous mixtures, the patterns of the degradation can be strikingly different between the different pathways. Therefore, there remains a need for a more efficient excipient for a surfactant in the development of pharmaceutical protein formulations.

SUMMARY ~~OF THE INVENTION~~

[0004] In one aspect, ~~T~~the present disclosure provides a liquid formulation comprising a polypeptide and a surfactant, wherein at least about 70% (wt%) of the surfactant are isosorbide polyoxyethylene (POE) fatty acid esters. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters comprise about 5-30 POE units. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters comprise about 20 POE units. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters comprise fatty acid chains selected from the group consisting of an optionally substituted C_{4-28} alkyl and an optionally substituted C_{4-28} alkenyl. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters are monoesters, diesters, or a mixture of the foregoing. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters are selected from the group

consisting of isosorbide POE monolaurate, isosorbide POE monomyristate, isosorbide POE monopalmitate, isosorbide POE monostearate, and isosorbide POE monooelate.

[0005] In some ~~embodiment~~examples, the isosorbide POE fatty acid ester is a compound of Formula (I):



(I);

wherein:

a and b are independently integers from 2 to 28, provided that the sum of a and b is an integer from 5-30;

R^1 and R^2 are independently selected from the group consisting of hydrogen and

-C(O)R", wherein R" is an optionally substituted C_{3-27} alkyl or an optionally substituted C_{3-27} alkenyl; and

R^3 and R^4 are independently hydrogen.

[0006] In some ~~embodiment~~examples, the sum of a and b is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some ~~embodiment~~examples, the sum of a and b is 9. In some ~~embodiment~~examples, the sum of a and b is 20. In some ~~embodiment~~examples, R^1 is H and R^2 is -C(O)R". In some ~~embodiment~~examples, R^2 is H and R^1 is -C(O)R". In some ~~embodiment~~examples, both R^1 and R^2 are -C(O)R". In some ~~embodiment~~examples, R" is an unsubstituted C_{3-27} alkyl. In some ~~embodiment~~examples, R" is an unsubstituted C_{11} alkyl. In some ~~embodiment~~examples, R" is an unsubstituted C_{3-27} alkenyl. In some ~~embodiment~~examples, R" is an unsubstituted C_{17} alkenyl.

[0007] In some ~~embodiment~~examples, the surfactant further comprises POE fatty acid esters. In some ~~embodiment~~examples, at least about 80% (wt%) of the surfactant are isosorbide POE fatty acid esters and POE fatty acid esters. In some ~~embodiment~~examples, at least about 85%, at least about 90% or at least about 95% (wt%) of the surfactant are isosorbide POE fatty acid esters and POE fatty acid esters. In some ~~embodiment~~examples, at least about 90% (wt%) of the surfactant are isosorbide POE fatty acid esters and POE fatty acid esters. In some ~~embodiment~~examples, the POE fatty acid ester comprises a fatty acid chains selected from the group consisting of an optionally substituted C_{4-28} alkyl and an optionally substituted C_{4-28} alkenyl. In some ~~embodiment~~examples, the POE fatty acid ester is selected from a group consisting of POE

monolaurate, POE monomyristate, POE monopalmitate, POE monostearate, and POE monooelate. In some ~~embodiment~~examples, less than about 20% of the surfactant are POE fatty acid esters. In some ~~embodiment~~examples, less than about 10% of the surfactant are POE fatty acid esters. In some ~~embodiment~~examples, the surfactant is about 0.0005% to 0.2% (w:v) in the liquid formulation. In some ~~embodiment~~examples, the surfactant comprises a greater amount of isosorbide POE fatty acid esters than POE fatty acid esters. In some ~~embodiment~~examples, the surfactant further comprises a sorbitan POE fatty acid ester. In some ~~embodiment~~examples, less than about 10%, less than about 8%, less than about 5%, less than about 3% or less than about 1% of the surfactant are sorbitan POE fatty acid esters.

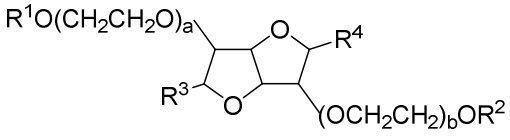
[0008] In some ~~embodiment~~examples, the polypeptide is a protein. In some ~~embodiment~~examples, the protein is an antibody selected from a group consisting of a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, and an antibody fragment. In some ~~embodiment~~examples, the antibody fragment is selected from the group consisting of Fab, Fab', $F(ab')_2$, and Fv fragments. In some ~~embodiment~~examples, the antibody concentration is about 0.001 mg/mL to about 300 mg/mL. In some ~~embodiment~~examples, the liquid formulation is a reconstituted lyophilized formulation. In some ~~embodiment~~examples, the liquid formulation is further diluted with an infusion solution to a concentration of about 0.001 mg/mL to about 100 mg/mL. In some ~~embodiment~~examples, the liquid formulation is substantially free of aggregates. In some ~~embodiment~~examples, the liquid formulation comprises less free fatty acid particle formation.

[0009] In another aspect, ~~A~~also provided herein is an article of manufacture comprising a container enclosing any liquid formulation described herein. In some ~~embodiment~~examples, the container is an IV bag. In some ~~embodiment~~examples, the IV bag comprises an injection device. In some ~~embodiment~~examples the IV bag comprises an infusion solution. In yet another aspect, the present disclosure provides a lyophilized formulation comprising a polypeptide and a surfactant, wherein at least about 70% (wt%) of the surfactant are isosorbide polyoxyethylene (POE) fatty acid esters and POE fatty acid esters; and wherein the lyophilized formulation is prepared by lyophilizing any liquid formulation disclosed herein. Also provided here is a lyophilized formulation comprising a polypeptide and a surfactant, wherein at least about 70% (wt%) of the surfactant are isosorbide POE fatty acid esters and POE fatty acid esters. In some ~~embodiment~~examples, the lyophilized formulation is prepared by lyophilizing any liquid formulation disclosed herein. In one aspect, the present disclosure provides an article of manufacture comprising a container enclosing the lyophilized formulation disclosed herein.

[0010] In one aspect, ~~A~~also provided herein is a method of making a liquid formulation comprising adding a polypeptide and a surfactant to an aqueous solution, wherein at least 70% (wt%) of the surfactant are isosorbide POE fatty acid esters. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters comprise about 5-30 POE units. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters comprise about 20 POE units. In some ~~embodiment~~examples, the isosorbide

POE fatty acid esters comprise fatty acid chains selected from the group consisting of an optionally substituted C_{4-28} alkyl and an optionally substituted C_{4-28} alkenyl. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters are monoesters, diesters, or a mixture of the foregoing. In some ~~embodiment~~examples, the isosorbide POE fatty acid esters are selected from the group consisting of isosorbide POE monolaurate, isosorbide POE monomyristate, isosorbide POE monopalmitate, isosorbide POE monostearate, and isosorbide POE monooelate.

[0011] In some ~~embodiment~~examples, the isosorbide POE fatty acid ester is a compound of Formula (I):



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R^3 and R^4 are independently hydrogen.

[0012] In some ~~embodiment~~examples, the sum of a and b is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In some ~~embodiment~~examples, the sum of a and b is 9. In some ~~embodiment~~examples, the sum of a and b is 20. In some ~~embodiment~~examples, R^1 is H and R^2 is -C(O)R". In some ~~embodiment~~examples, R^2 is H and R^1 is -C(O)R". In some ~~embodiment~~examples, both R^1 and R^2 are -C(O)R". In some ~~embodiment~~examples, R" is an unsubstituted C_{3-27} alkyl. In some ~~embodiment~~examples, R" is an unsubstituted C_{11} alkyl. In some ~~embodiment~~examples, R" is an unsubstituted C_{3-27} alkenyl. In some ~~embodiment~~examples, R" is an unsubstituted C_{17} alkenyl.

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POE fatty acid esters. In some ~~embodiment~~examples, the method further comprises adding a POE fatty acid ester. In some ~~embodiment~~examples, the POE fatty acid ester comprises a fatty acid chains selected from the group consisting of an optionally substituted C_{4-28} alkyl and an optionally substituted C_{4-28} alkenyl. In some ~~embodiment~~examples, the POE fatty acid ester is selected from a group consisting of POE monolaurate, POE monomyristate, POE monopalmitate, POE monostearate, and POE monooelate. In some ~~embodiment~~examples, less than about 20% of the surfactant are POE fatty acid esters. In some ~~embodiment~~examples, less than about 10% of the surfactant are POE fatty acid esters. In some ~~embodiment~~examples, the surfactant is about 0.0005% to 0.2% (w:v) in the liquid formulation. In some ~~embodiment~~examples, the surfactant comprises a greater amount of isosorbide POE fatty acid esters than POE fatty acid esters. In some ~~embodiment~~examples, the surfactant further comprises sorbitan POE fatty acid esters. In some ~~embodiment~~examples, less than about 10%, less than about 8%, less than about 5%, less than about 3% or less than about 1% of the surfactant are sorbitan POE fatty acid esters.

[0014] In some ~~embodiment~~examples, the polypeptide is a protein. In some ~~embodiment~~examples, the protein is an antibody selected from a group consisting of a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, and an antibody fragment. In some ~~embodiment~~examples, the antibody fragment is selected from the group consisting of Fab, Fab', $F(ab')_2$, and Fv fragments. In some ~~embodiment~~examples, the antibody concentration is about 0.1 mg/mL to about 300 mg/mL. In some ~~embodiment~~examples, the liquid formulation is a reconstituted lyophilized formulation. In some ~~embodiment~~examples, the liquid formulation is further diluted with an infusion solution to a concentration of about 0.1 mg/mL to about 2 mg/mL. In some ~~embodiment~~examples, the liquid formulation is further lyophilized to prepare a lyophilized formulation. In some ~~embodiment~~examples, the liquid formulation is substantially free of aggregates. In some ~~embodiment~~examples, the liquid formulation comprises less free fatty acid particle formation.

[0015] It is to be understood that one, some, or all of the properties of the various ~~embodiment~~examples described herein may be combined to form other ~~embodiment~~examples of the present ~~invention~~disclosure. These and other aspects of the ~~invention~~disclosure will become apparent to one of skill in the art. These and other ~~embodiment~~examples of the ~~invention~~disclosure are further described by the detailed description that follows.