upstream processes. Downstream purification processes (e.g., Protein A) are capable of removal of HCPs; however, it has been shown that some HCPs can be co-purified with API molecules that have similar properties and are thus retained in trace quantities in the drug substance and drug product (K. Lee, et al., A Chinese Hamster Ovary Cell Host Cell Protein That Impacts PS-80 Degradation. AccBio Conference (2015). Presumably, lipases with high activity can result in significant polysorbate degradation even at undetectable levels. There are numerous ongoing efforts to identify and remove lipases from protein drugs by engineering cells with reduced lipase expression and via downstream processing steps (e.g., chromatography). However, the enzymatic degradation of PS20 and PS80 remains a significant challenge in biopharmaceutical development and there have been no significant efforts reported to identify optimal formulations for reducing hydrolytic or catalytic PS20 degradation.

[0009] Polysorbate degradation has numerous consequences that may impact the stability and shelf-life of protein drug formulations. Polysorbate degradants include poorly soluble fatty acids that may result in the formation of visible and subvisible particles in the solution. The loss of PS20 may also reduce the protective effects of PS20 for protein formulations. Additionally, a spiking study demonstrated that some of the PS20-related degradants can impact stability of protein drugs; however, no impact was observed under pharmaceutically relevant conditions (Kishore et al., *Pharm. Res.* 28:1194-1210 (2011).

[0010] What is needed is a method of reducing polysorbate degradation so that the protective effects of polysorbate on formulations (e.g., polypeptides) are maintained over time. This will result in more stable polypeptide formulations during processing, long-term storage, and during administration which in turn will lengthen the shelf life of polypeptide formulations and reduce waste caused by degraded and expired formulations.

[0011] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY

[0012] In one aspect, the invention provides a method of reducing polysorbate degradation in an aqueous formulation comprising a polysorbate, the method comprising adding a cyclodextrin to the formulation, wherein the resulting w/w ratio of cyclodextrin to polysorbate is greater than about 37.5:1. In some aspects, the invention provides a method of reducing polysorbate degradation in an aqueous formulation comprising a polysorbate, the method comprising adding a cyclodextrin to the formulation wherein the resulting w/w ratio of cyclodextrin to

polysorbate is greater than about 37.5:1, wherein the formulation comprises about 0.005%-0.4% polysorbate. In some aspects, the invention provides a method of reducing polysorbate degradation in an aqueous formulation comprising a polysorbate, the method comprising adding a cyclodextrin to the formulation to a concentration of about 0.01%-30%, wherein the resulting w/w ratio of cyclodextrin to polysorbate is greater than about 37.5:1, wherein the formulation comprises about 0.005%-0.4% polysorbate. In some aspects, the invention provides a method of reducing the amount of sub-visible and visible particles in an aqueous formulation comprising polysorbate, comprising adding a cyclodextrin to the formulation, wherein the resulting w/w ratio of cyclodextrin to polysorbate is greater than about 37.5:1. In some embodiments, the disclosure provides a method of reducing the amount of sub-visible and visible particles in an aqueous formulation comprising polysorbate, comprising adding a cyclodextrin to the formulation, wherein the resulting w/w ratio of cyclodextrin to polysorbate is greater than about 37.5:1, wherein the formulation comprises polysorbate and a polypeptide. In some aspects, the invention provides a method to disaggregate and solubilize polysorbate degradation products in an aqueous formulation comprising a polysorbate, the method comprising adding a cyclodextrin to the formulation, wherein the resulting w/w ratio of cyclodextrin to polysorbate is greater than about 37.5:1. In some embodiments the disclosure provides a method to disaggregate and solubilize polysorbate degradation products in an aqueous formulation comprising adding a cyclodextrin to the formulation, wherein the resulting w/w ratio of cyclodextrin to polysorbate is greater than about 37.5:1, wherein the formulation comprises polysorbate and a polypeptide.

[0013] In some embodiments of the above aspects, the polysorbate is polysorbate 20 or polysorbate 80. In some embodiments, the cyclodextrin is HP-β cyclodextrin, HP-γ cyclodextrin, or sulfobutyl ether β-cyclodextrin. In some embodiments, the concentration of polysorbate in the formulation is in the range of about 0.01% to 0.4%. In some embodiments, the concentration of polysorbate in the formulation is in the range of about 0.01% to 0.1%. In some embodiments, the concentration of polysorbate in the formulation is about 0.02%. In some embodiments, the concentration of cyclodextrin in the formulation is in the range of about 0.5-30%. In some embodiments, the concentration of cyclodextrin in the formulation is about 15%.

[0014] In some embodiments of the above aspects and embodiments, the polysorbate degradation is reduced by about 50%, about 75%, about 80%, about 85%, about 90%, about 95% or about 99%. In some embodiments, less than about 1,000, about 750, about 500, about 250, about 150, about 100, about 50, or about 25 polysorbate particles greater than about 2 microns in diameter/mL are formed.

[0015] In some embodiments of the above aspects and embodiments, the formulation comprises a polypeptide. In some embodiments, the polypeptide is an antibody. In some embodiments, the antibody is a polyclonal antibody, a monoclonal antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody or antibody fragment. In some embodiments, the polypeptide concentration in the formulation is about 1 mg/mL to about 250 mg/mL.

[0016] In some embodiments of the above aspects and embodiments, the formulation is stable at about 2 °C to about 8 °C for at least about six months, at least about 12 months, at least about 18 months, or at least about 24 months. In some embodiments, the formulation is stable at about 1°C to about 10 °C for at least about forty-eight months. In some embodiments, the formulation is stable at about 2 °C to about 8 °C for at least about forty-eight months.

[0017] In some embodiments, the formulation has a pH of about 4.5 to about 7.0. In some embodiments, the formulation has a pH of about 4.5 to about 6.0. In some embodiments, the formulation has a pH of about 6.0.

[0018] In some embodiments of the above aspects and embodiments, the formulation further comprises one or more excipients selected from the group consisting of a stabilizer, a buffer, a surfactant, and a tonicity agent. In some embodiments, the formulation is a pharmaceutical formulation suitable for administration to a subject. In some embodiments, the formulation is pharmaceutical formulation suitable for intravenous, subcutaneous, intramuscular, or intravitreal administration to a subject.

[0019] In some aspects, the invention provides an aqueous formulation comprising a polysorbate and a cyclodextrin, wherein the formulation has been stored at about 1 °C to about 10 °C for at least about six months, wherein the initial w/w ratio of cyclodextrin to polysorbate in the formulation is at least about 37.5:1 and wherein the amount of polysorbate in the formulation is at least about 80% of the initial amount of polysorbate in the formulation. In some embodiments, the disclosure provides an aqueous formulation comprising a polypeptide, a polysorbate and a cyclodextrin, wherein the formulation has been stored at about 1 °C to about 10 °C for at least about six months, wherein the initial w/w ratio of cyclodextrin to polysorbate in the formulation is at least about 37.5:1 and wherein the amount of polysorbate in the formulation is at least about 80% of the initial amount of polysorbate in the formulation. In some aspects, the invention provides an aqueous formulation comprising a polysorbate and a cyclodextrin, wherein the formulation has been stored at about 1 °C to about 10 °C for at least about six months, wherein the w/w ratio of cyclodextrin to polysorbate in the formulation is at least about 37.5:1 and wherein less than about 1% of the polysorbate has degraded. In some embodiments, the disclosure provides an aqueous formulation comprising a polypeptide, a polysorbate and a cyclodextrin, wherein the formulation has been stored at about 1 °C to about 10 °C for at least about six months, wherein the w/w ratio of cyclodextrin to polysorbate in the formulation is at least about 37.5:1 and wherein less than about 1% of the polysorbate has degraded.

[0020] In some embodiments of the above aspects, the cyclodextrin is HP-β cyclodextrin, HP-γ cyclodextrin, or sulfobutyl ether β-cyclodextrin. In some embodiments, the concentration of polysorbate in the formulation is in the range of about 0.01% to 0.4%. In some embodiments, the concentration of polysorbate in the formulation is in the range of about 0.01% to 0.1%. In some embodiments, the concentration of polysorbate in the formulation is about 0.02%. In some embodiments, the concentration of cyclodextrin in the formulation is in the range of about 0.5-30%. In some embodiments, the concentration of cyclodextrin in the formulation is about 15%.