approaches rely on small inorganic ions as additives to either neutralize the degradant products or prevent protein interactions with the degradant species from PLGA hydrolysis, without providing protection as excipients to protein.

[0006] What is needed is the use of polymeric excipients for stabilizing proteins in spray dried formulations at elevated temperature and also to neutralize the low pH environment created within PLGA.

[0007] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

BRIEF SUMMARY

[0008] In one aspect, the disclosure provides a formulation comprising a polypeptide and a hydroxypropyl methylcellulose acetate succinate (HPMCAS). In some examples, the HPMCAS comprises from about 8% to about 12% acetate and from about 7% to about 15% succinate. In some examples, the HPMCAS comprises about 8% acetate and about 15% succinate (HPMCAS-LF). In other examples, the HPMCAS comprises about 12% acetate and about 7% succinate (HPMCAS-HF). In some examples, the ratio of the HPMCAS to protein in the formulation is about 10:1 (mg/mg) to about 1:10 (mg/mg). In some examples, the ratio of the HPMCAS to protein in the formulation is from about 4:1 (mg/mg) to about 1:4 (mg/mg). In some examples, the ratio of the HPMCAS to protein in the formulation is about 4:1 (mg/mg). In some examples, the ratio of the HPMCAS to protein in the formulation is about 1:1 (mg/mg). In some examples, the ratio of the HPMCAS to protein in the formulation is about 1:4 (mg/mg). In some examples, the ratio of the HPMCAS to protein in the formulation is about 1:1 (mg/mg) to about 1:5 (mg/mg). In some examples, the formulation further comprises a histidine buffer. In some examples, the histidine buffer is a histidine HCl buffer. In some examples, the histidine buffer is in the formulation at a concentration of about 5 mM to about 20 mM. In some examples, the histidine buffer is in the formulation at a concentration of about 10 mM. In some examples, the formulation further comprises a polysorbate. In some examples, the polysorbate is polysorbate 20. In some examples, the polysorbate in the formulation at a concentration of about 0.005% (w/v) to about 0.5% (w/v). In some examples, the polysorbate is in the formulation at a concentration of about 0.01% (w/v). In some examples, the pH of the formulation is about 5.5 to about 7.0. In some examples, the pH of the formulation is about 6.5.

[0009] In some examples if the disclosure, the polypeptide in the formulation is an antibody. In some examples, the polypeptide is a monoclonal antibody. In some examples, the polypeptide is a human antibody, a chimeric antibody or a humanized antibody. In some examples, the antibody is an antibody fragment selected from a Fab, Fab'-SH, Fv, scFv, and (Fab')2 fragment. In some examples, the antibody fragment is a (Fab')2 fragment. In some examples, the polypeptide is in the formulation at a concentration of about 5 mg/mL to about 100 mg/mL, or about 10 mg/mL to about 80 mg/mL In some examples, the polypeptide is in the formulation at a concentration of about 10 mg/mL.

[0010] In some examples, the disclosure provides a formulation comprising an antibody at a concentration of about 5 mg/mL to about 50 mg/mL, an HPMCAS-LF, wherein the ratio of the HPMCAS-LF to antibody in the formulation is about 1:1 (mg/mg), a histidine-HCl buffer at a concentration of about 5 mM to about 20 mM, polysorbate 20 at a concentration of about 0.005% (w/v) to about 0.5% (w/v), and wherein the pH of the formulation is about 5.5 to about 7.0. In one aspect, the disclosure provides a formulation comprising: an antibody at a concentration of 5 mg/mL to 50 mg/mL, an HPMCAS-LF, wherein the ratio of the HPMCAS-LF to antibody in the formulation is about 4:1 (mg/mg), about 1:1 (mg/mg), or about 1:4 (mg/mg), a histidine-HCl buffer at a concentration of 5 mM to 20 mM, polysorbate 20 at a concentration of 0.005% (w/v) to 0.5% (w/v), and wherein the pH of the formulation is 5.5 to 7.0. In some examples, the disclosure provides a formulation comprising an antibody at a concentration of about 10 mg/mL, an HPMCAS-LF, wherein the ratio of the HPMCAS-LF to antibody in the formulation is about 1:1 (mg/mg), a histidine-HCl buffer at a concentration of about 10 mM, polysorbate 20 at a concentration of about 0.01% (w/v), and wherein the pH of the formulation is about 6.5. In one aspect, the disclosure provides a formulation comprising: an antibody at a concentration of about 10 mg/mL, an HPMCAS-LF, wherein the ratio of the HPMCAS-LF to antibody in the formulation is about 4:1 (mg/mg), about 1:1 (mg/mg), or about 1:4 (mg/mg), a histidine-HCl buffer at a concentration of about 10 mM, polysorbate 20 at a concentration of about 0.01% (w/v), and wherein the pH of the formulation is about 6.5. In some examples, the disclosure provides a formulation comprising an antibody at a concentration of about 5 mg/mL to about 50 mg/mL, an HPMCAS-HF, wherein the ratio of the HPMCAS-HF to antibody in the formulation is about 1:1 (mg/mg), a histidine-HCl buffer at a concentration of about 5 mM to about 20 mM, polysorbate 20 at a concentration of about 0.005% (w/v) to about 0.5% (w/v), and wherein the pH of the formulation is about 5.5 to about 7.0. In one aspect, the disclosure provides a formulation comprising: an antibody at a concentration of 5 mg/mL to 50 mg/mL, an HPMCAS-HF, wherein the ratio of the HPMCAS-HF to antibody in the formulation is about 4:1 (mg/mg), about 1:1 (mg/mg), or about 1:4 (mg/mg), a histidine-HCl buffer at a concentration of 5 mM to 20 mM, polysorbate 20 at a concentration of 0.005% (w/v) to 0.5% (w/v), and wherein the pH of the formulation is 5.5 to 7.0. In some examples, the disclosure provides a formulation comprising an antibody at a concentration of about 10 mg/mL, an HPMCAS-HF, wherein the ratio of the HPMCAS-HF to antibody in the formulation is about 1:1 (mg/mg), a histidine-HCl buffer at a concentration of about 10 mM, polysorbate 20 at a concentration of about 0.01% (w/v), and wherein the pH of the formulation is about 6.5. In one aspect, the disclosure provides a formulation comprising: an antibody at a concentration of about 10 mg/mL, an HPMCAS-HF, wherein the ratio of the HPMCAS-HF to antibody in the formulation is about 4:1 (mg/mg), about 1:1 (mg/mg), or about 1:4 (mg/mg), a histidine-HCl buffer at a concentration of about 10 mM, polysorbate 20 at a concentration of about 0.01% (w/v), and wherein the pH of the formulation is about 6.5.

[0011] In some examples of the disclosures, the formulation is spray dried to form a spray dried formulation of a polypeptide or antibody. In some examples, the polypeptide (*e.g*, an antibody) in the formulation is stable at about 90°C for at least about 5 hours and/or is stable at about 37°C for at least about 4 weeks. In some examples, the polypeptide in the formulation shows reduced aggregation and/or reduced chemical degradation. In some examples, the reduced chemical degradation comprises reduced formation of succinimide

variants of the polypeptide and/or reduced formation of pyroglutamate variants of the polypeptide. In some examples, the formulation is an amorphous glassy formulation.

[0012] In some examples of the disclosure, the spray dried formulation of a polypeptide (*e.g.*, an antibody) is encapsulated in a polymer system that produces acidic microclimate. In some examples, the spray dried formulation of a polypeptide is encapsulated in lactic acid/glycolic acid polymer system. In some examples, the spray dried formulation of a polypeptide is encapsulated in poly(lactic-co-glycolic acid) (PLGA). In some examples, the spray dried formulation of a polypeptide is encapsulated in a PLGA rod.

[0013] In some examples, the disclosure provides a composition comprising any of the formulations described herein; for example, a composition comprising a spray dried formulation of a polypeptide (*e.g.*, an antibody) as described herein. In one aspect, the disclosure provides a composition comprising the formulation as disclosed herein. In one aspect, the disclosure provides a composition comprising the spray dried formulation of a polypeptide or antibody as disclosed herein. In some examples, the disclosure provides a composition comprising a lactic acid/glycolic acid polymer particle comprising any of the formulations described herein. In one aspect, the disclosure provides a composition comprising a lactic acid/glycolic acid polymer particle comprising the formulation as disclosed herein. In some examples, the disclosure provides a composition comprising a lactic acid/glycolic acid polymer particle comprising any of the spray dried formulations described herein. In one aspect, the disclosure provides a composition comprising a lactic acid/glycolic acid polymer particle comprising the spray dried formulation as disclosed herein. In some examples, the lactic acid/glycolic acid polymer particle is a PLGA particle. In some examples, the lactic acid/glycolic acid polymer particle is a PLGA rod.

[0014] In some examples, the disclosure provides methods of preparing a spray dried polypeptide, the method comprising preparing a formulation as described herein, and subjecting the formulation to spray drying. In one aspect, the disclosure provides a method of preparing a spray dried polypeptide, the method comprising preparing a formulation as disclosed herein, and subjecting the formulation to spray drying. In some examples, the disclosure provides methods of preparing a spray dried antibody, the method comprising preparing a formulation as described herein, and subjecting the formulation to spray drying. In one aspect, the disclosure provides a method of preparing a spray dried antibody, the method comprising preparing a formulation as disclosed herein, and subjecting the formulation to spray drying. In some examples, the spray drying is performed using a spray dryer comprising an inlet and an outlet. In some examples, the inlet has a temperature of about 90°C to about 120°C, about 100°C, or about 110°C. In some examples, the outlet has a temperature of about 60°C.

[0015] In some examples, the disclosure provides methods of preparing a lactic acid/glycolic acid polymer particle comprising a polypeptide, the method comprising encapsulating the formulation as described herein in a lactic acid/glycolic acid polymer system. In one aspect, the disclosure provides a method of preparing a lactic acid/glycolic acid polymer particle comprising a polypeptide, the method comprising encapsulating the formulation as disclosed herein in a lactic acid/glycolic acid polymer system. In some examples, the disclosure provides methods of preparing a lactic acid/glycolic acid polymer particle comprising a polypeptide, the method comprising encapsulating the spray dried formulation as described herein in a lactic acid/glycolic acid polymer system. In one aspect, the disclosure provides a method of preparing a lactic acid/glycolic acid polymer particle comprising a polypeptide, the method comprising encapsulating the spray dried formulation as disclosed herein in a lactic acid/glycolic acid polymer system. In some examples, the lactic acid/glycolic acid polymer particle is a PLGA particle.

[0016] In some examples, the disclosure provides articles of manufacture comprising any of the formulations (*e.g.*, spray dried formulations) or compositions as described herein. In one aspect, the disclosure provides an article of manufacture comprising the formulation as disclosed herein, the spray dried formulation as disclosed herein, or the composition as disclosed herein. In one aspect, the disclosure provides an article of manufacture comprising spray dried formulation prepared by the method as disclosed herein. In one aspect, the disclosure provides an article of manufacture comprising lactic acid/glycolic acid polymer particle encapsulated polypeptide prepared by the method as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** shows the structures of trehalose and a generic structure of cellulose. The bottom panel shows the nature of R groups that define Metolose, AS-LF and AS-HF and the molecular weight and glass transition temperature of polymeric excipients along with Trehalose

[0018] **FIG. 2** shows the formulation glass transition temperature as represented by differential scanning calorimetry (DSC) thermograms of all five, spray dried Fab2 formulations

[0019] **FIG. 3** is a schematic showing the preparation of spray dried AS-LF and AS-HF formulations. AS-HF or AS-LF polymers were dissolved in water, titrated with histidine base to pH 6.5 and then mixed with Fab2 solution in pH 5.5 buffer. The cloudy polymer and protein mixed solution was spray dried to yield a solid formulation.

[0020] **FIGs. 4A** and **4B** show characterization of spray dried formulations. **FIG. 4A** shows size distribution of spray dried Fab2 formulation measured using laser diffraction. **FIG. 4B** shows SEM images of spray dried formulations. Scale bar in each image corresponds to 10 μm.

[0021] **FIGs. 5A** and **5B** show Fab2 aggregation in spray dried formulations. The change in monomer content as a function of time for Fab2 in spray dried formulations after exposure to 90ºC for 5 hours (**FIG. 5A**) and 37ºC for 4 weeks (**FIG. 5B**).

[0022] **FIGs. 6A-6D** show chemical degradation of Fab2 in spray dried formulations. Ion-exchange chromatogram of Fab2 in different formulations after 5 hours at 90ºC and (**FIG. 6A**) 4 weeks at 37ºC (**FIG. 6B**). Pyroglutamate formation, measured as ratio of PyroE and main peak areas, with time at 90ºC (**FIG. 6C**) and 37ºC (**FIG. 6D**).

[0023] **FIGs. 7A** and **7B** show the buffer capacity of AS excipients. HPMCAS excipients resist change in pH (**FIG. 7A**) upon titration with a strong base (0.5 N NaOH) in raw material form (**FIG. 7B**) and during titration with a strong acid (0.1 N HCl) in spray dried Fab2 formulations.

[0024] **FIG. 8** shows Fab2 stability within the PLGA rod. The change in extracted Fab2 monomer content upon recovery after 3 weeks within a PLGA rod at 37 ºC for all four formulations.