

comprising an antibody, such as an anti-VEGF antibody and an anti-CD20 antibody, which mitigates formation of dimers, soluble aggregates, and particulates.

SUMMARY

[0006] Disclosed is a stable aqueous pharmaceutical formulation, the formulation comprising a monoclonal antibody, trehalose and a buffer, wherein the weight ratio of the monoclonal antibody to the trehalose in the formulation is greater than or equal to 0.41 and less than 1.65, and wherein the formulation has a pH of about 5.5 to about 7.0. In one aspect, the present disclosure refers to a stable aqueous pharmaceutical formulation, the formulation comprising a monoclonal antibody, trehalose, and a buffer, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has a pH of 5.5 to 7.0, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF. In some examples, the weight ratio of the monoclonal antibody to the trehalose is 0.49 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose is about 0.41 to 0.73. In some examples, the weight ratio of the monoclonal antibody to the trehalose is about 0.73 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose is any of 0.41, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, and 1.64, including every value in between these numbers. In some examples, the monoclonal antibody in the formulation is about 25 mg/mL to about 100 mg/mL. In some examples, the monoclonal antibody in the formulation is about 45 mg/mL to about 55 mg/mL. In some examples, the monoclonal antibody in the formulation is about 35 mg/mL to about 75 mg/mL. In some examples, the trehalose in the formulation is about 45 mM to about 634 mM. In some examples, the trehalose in the formulation is about 50 mM to about 600 mM. In some examples, the trehalose in the formulation is about 150 mM to about 400 mM. In some examples, the trehalose in the formulation is about 45 mM to about 135 mM. In some examples, the trehalose in the formulation is about 180 mM to about 634 mM. In some examples, the buffer is an amount of about 15 mM to about 100 mM. In some examples, the buffer is an amount of greater than 35 mM to about 100 mM. In some examples, the buffer comprises histidine (e.g., histidine acetate, histidine hydrochloride) or phosphate (e.g., sodium phosphate).

[0007] Disclosed is a stable aqueous pharmaceutical formulations comprising (a) a monoclonal antibody in an amount of about 25 mg/mL to about 100 mg/mL; (b) trehalose in an amount of about 45 mM to about 634 mM; and (c) sodium phosphate in an amount of greater than 35 mM to about 100 mM, wherein said formulation has a pH of about 5.5 to about 7.0, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.65, and an optional surfactant. In one aspect, the present disclosure refers to a stable aqueous pharmaceutical formulation, the formulation comprising (a) a monoclonal antibody in an amount of 25 mg/mL to 100 mg/mL; (b) trehalose in an amount of 45 mM to 634 mM; and (c) sodium phosphate in an amount of greater than 35 mM to 100 mM, wherein said formulation has a pH of 5.5 to 7.0, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF. In some examples, the weight ratio of the monoclonal antibody to the trehalose in the formulation is 0.41 to 0.73. In some examples, the weight ratio of the monoclonal antibody to the trehalose is 0.73 to 1.47. In some examples, the weight ratio of the monoclonal

antibody to the trehalose is 0.49 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose is any of 0.41, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, and 1.64, including every value in between these numbers.

[0008] Disclosed is a stable aqueous pharmaceutical formulation, the formulation comprising (a) an antibody (e.g., a monoclonal antibody) in an amount of less than or equal to about 100 mg/mL; and (b) trehalose in an amount of about 150 mM to about 400 mM, wherein said formulation has a pH of about 5.5 to about 7.0, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.65. In some examples, the formulation is for subcutaneous administration. In some examples, the formulation is for intraocular administration. In some examples, the formulation is isotonic. In some examples, the formulation has an osmolality of greater than about 240 mOsm/kg.

[0008a] In one aspect, the present disclosure refers to a stable aqueous pharmaceutical formulation for subcutaneous or intraocular administration, the formulation comprising (a) a monoclonal antibody in an amount of less than or equal to about 100 mg/mL, wherein the monoclonal antibody binds VEGF; and (b) trehalose in an amount of 150 mM to 400 mM, wherein said formulation has a pH of 5.5 to 7.0, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months.

[0009] Disclosed is a stable aqueous pharmaceutical formulation, the formulation comprising (a) an antibody (e.g., a monoclonal antibody) in an amount of less than or equal to about 100 mg/mL; and (b) trehalose in an amount of 50 mM to 600 mM, wherein said formulation has a pH of 5.5 to 7.0, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.65. In some examples, the formulation is for intravenous administration.

[0009a] In one aspect, the present disclosure refers to a stable aqueous pharmaceutical formulation for intravenous administration, the formulation comprising (a) a monoclonal antibody in an amount of less than or equal to about 100 mg/mL, wherein the monoclonal antibody binds VEGF; and (b) trehalose in an amount of about 50 mM to about 600 mM, wherein said formulation has a pH of 5.5 to 7.0, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months.

[0010] In some examples, the monoclonal antibody in the formulation described herein is in an amount of about 30 mg/mL to about 90 mg/mL, about 35 mg/mL to about 85 mg/mL, about 35 mg/mL to 75 mg/mL, about 40 mg/mL to about 80 mg/mL, about 45 mg/mL to about 70 mg/mL, or about 45 mg/mL to about 55 mg/mL. In some examples, the monoclonal antibody in the formulation is about 25 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, or about 100 mg/mL, including every value in between these numbers. In some examples, the monoclonal antibody in the formulation is about 45 mg/mL, about 50 mg/mL, or about 55 mg/mL.

[0011] In some examples, the formulation described herein comprises the trehalose in about 45 mM to about 600 mM, about 45 mM to about 550 mM, about 45 mM to about 500 mM, about 45 mM to about 450 mM, about 45 mM to about 400 mM, about 45 mM to about 350 mM, about 45 mM to about 300 mM, about 45 mM to about 250 mM, about 45 mM to about 200 mM, about 45 mM to about 180 mM, about 45 mM to about 150 mM, about 45 mM to about 140 mM, about 45 mM to about 135 mM, about 45 mM to about 130 mM, about 45

mM to about 120 mM, about 45 mM to about 110 mM, about 45 mM to about 100 mM, about 180 mM to about 634 mM, about 50 mM to about 600 mM, or about 150 mM to about 400 mM. In some examples, the trehalose in the formulation is about 45 mM, about 50 mM, about 60 mM, about 70 mM, about 80 mM, about 90 mM, about 100 mM, about 110 mM, about 120 mM, about 130 mM, about 135 mM, about 140 mM, about 150 mM, about 180 mM, about 200 mM, about 250 mM, about 300 mM, about 350 mM, about 400 mM, about 450 mM, about 500 mM, about 550 mM, about 600 mM, about 610 mM, about 620 mM, about 630 mM, or about 634 mM, including every value in between these numbers. In some examples, the formulation comprises phosphate (e.g., sodium phosphate) as a buffer. In some examples, the phosphate buffer (e.g., sodium phosphate) in the formulation is about 15 mM to about 30 mM, about 20 mM to 30 mM, about 22 mM to about 28 mM, greater than 35 mM to about 100 mM, about 40 mM to about 100 mM, about 45 mM to about 90 mM, about 50 mM to about 75 mM, or about 15 mM to about 100 mM. In some examples, the phosphate (e.g., sodium phosphate) in the formulation is about 15 mM, about 20 mM, about 22 mM, about 25 mM, about 28 mM, about 30 mM, about 35 mM, about 36 mM, about 40 mM, about 45 mM, about 50 mM, about 51 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM, including every value in between these numbers. In some examples, the formulation comprises histidine (such as L-histidine) as a buffer. In some examples, the histidine in the formulation is about 15 mM to about 30 mM, about 20 mM to 30 mM, about 22 mM to about 28 mM, greater than 35 mM to about 100 mM, about 40 mM to about 100 mM, about 45 mM to about 90 mM, about 50 mM to about 75 mM, or about 15 mM to about 100 mM. In some examples, the histidine in the formulation is about 15 mM, about 20 mM, about 22 mM, about 25 mM, about 28 mM, about 30 mM, about 35 mM, about 36 mM, about 40 mM, about 45 mM, about 50 mM, about 51 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM, including every value in between these numbers.

[0012] In some examples, the formulation described herein further comprises a surfactant. In some examples, surfactant is polysorbate (such as polysorbate 20) or poloxamer (such as poloxamer 188). In some examples, surfactant concentration is about 0.01% to about 0.1%, about 0.01% to about 0.05%, or about 0.02% to about 0.04%. In some examples, the surfactant concentration is about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, or about 0.1%, including every value in between these numbers.

[0013] In some examples, the formulation described herein has a pH about 5.5 to about 6.5, about 5.8 to about 6.8, about 5.9 to about 6.5, about 6.0 to about 6.5, about 6.0 to about 6.4, or about 6.0 to about 6.2. In some examples, the formulation has a pH about 5.6, about 5.8,

about 5.9, about 6.0, about 6.2, about 6.4, about 6.5, about 6.8, or about 7.0, including every value in between these numbers.

[0014] In some examples, the monoclonal antibody in the formulation described herein is not subject to prior lyophilization. In some examples, the monoclonal antibody is a full length antibody. In some examples, the monoclonal antibody is an IgG1, IgG2, or IgG4 antibody. In some examples, the monoclonal antibody is a humanized antibody, a chimeric antibody or a human antibody. In some examples, the monoclonal antibody is an antibody fragment comprising an antigen-binding region. In some examples, the antibody fragment is a Fab or F(ab')₂ fragment. In some examples, the monoclonal antibody binds VEGF. In some examples, the antibody is bevacizumab. In some examples, the monoclonal antibody is susceptible to aggregation.

[0015] In some examples, the monoclonal antibody in the formulation described herein is not subject to prior lyophilization. In some examples, the monoclonal antibody is a full length antibody. In some examples, the monoclonal antibody is an IgG1, IgG2, or IgG4 antibody. In some examples, the monoclonal antibody is a humanized antibody, a chimeric antibody or a human antibody. In some examples, the monoclonal antibody is an antibody fragment comprising an antigen-binding region. In some examples, the antibody fragment is a Fab or F(ab')₂ fragment. In some examples, the monoclonal antibody binds CD20. In some examples, the antibody that binds CD20 is a humanized B-Ly1 antibody described herein. In some examples, the antibody that binds CD20 is an antibody comprising a heavy chain variable region amino acid sequence selected from SEQ ID NO:3 to SEQ ID NO:19 and a light chain variable region amino acid sequence of SEQ ID NO:20. In some examples, the antibody is obinutuzumab. In some examples, the monoclonal antibody is susceptible to aggregation.

[0016] In some examples, the formulation described herein is stable at -20°C for at least about 6 months, at least about 12 months, at least about 15 months, at least about 18 months, at least about 19 months, at least about 20 months, or at least about 2 years. In some examples, the formulation is sterile. In some examples, the formulation is for administration to a subject. In some examples, the formulation is for intravenous (IV), subcutaneous (SQ), intraocular (IO), or intramuscular (IM) administration.

[0017] In another aspect, the disclosure refers to articles of manufacture comprising a container holding a stable aqueous pharmaceutical formulation described herein. In some examples, the formulation comprises a monoclonal antibody, trehalose, and a buffer, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.65, and wherein the formulation has a pH of about

5.5 to about 7.0. In some examples, the formulation comprises (a) a monoclonal antibody in an amount of about 25 to about 100 mg/mL; (b) trehalose in an amount of about 45 mM to about 634 mM; and (c) sodium phosphate in an amount of greater than 35 mM to about 100 mM, wherein said formulation has a pH of about 5.5 to about 7.0, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.6, and an optional surfactant. In some examples, the weight ratio of the monoclonal antibody to the trehalose in the formulation is 0.41 to 0.73. In some examples, the weight ratio of the monoclonal antibody to the trehalose is 0.73 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose is 0.49 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose in the formulation is any of 0.41, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, and 1.64, including every value in between these numbers.

[0018] In some examples, the monoclonal antibody in the formulation is in an amount of about 30 mg/mL to about 90 mg/mL, about 35 mg/mL to about 85 mg/mL, about 35 mg/mL to about 75 mg/mL, about 40 mg/mL to about 80 mg/mL, about 45 mg/mL to about 70 mg/mL, or about 45 mg/mL to about 55 mg/mL. In some examples, the monoclonal antibody in the formulation is about 25 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, or about 100 mg/mL, including every value in between these numbers. In some examples, the monoclonal antibody in the formulation is about 45 mg/mL, about 50 mg/mL, or about 55 mg/mL.

[0019] In some examples, the formulation comprises the trehalose in about 45 mM to about 600 mM, about 45 mM to about 550 mM, about 45 mM to about 500 mM, about 45 mM to about 450 mM, about 45 mM to about 400 mM, about 45 mM to about 350 mM, about 45 mM to about 300 mM, about 45 mM to about 250 mM, about 45 mM to about 200 mM, about 45 mM to about 180 mM, about 45 mM to about 150 mM, about 45 mM to about 140 mM, about 45 mM to about 135 mM, about 45 mM to about 130 mM, about 45 mM to about 120 mM, about 45 mM to about 110 mM, about 45 mM to about 100 mM, about 180 mM to about 634 mM, about 50 mM to about 600 mM, or about 150 mM to about 400 mM. In some examples, the trehalose in the formulation is about 45 mM, about 50 mM, about 60 mM, about 70 mM, about 80 mM, about 90 mM, about 100 mM, about 110 mM, about 120 mM, about 130 mM, about 135 mM, about 140 mM, about 150 mM, about 180 mM, about 200 mM, about 250 mM, about 300 mM, about 350 mM, about 400 mM, about 450 mM, about 500 mM,

about 550 mM, about 600 mM, about 610 mM, about 620 mM, about 630 mM, or about 634 mM, including every value in between these numbers. In some examples, the formulation comprises sodium phosphate as a buffer. In some examples, the sodium phosphate in the formulation is about 15 mM to about 30 mM, about 20 mM to 30 mM, about 22 mM to about 28 mM, greater than 35 mM to about 100 mM, about 40 mM to about 100 mM, about 45 mM to about 90 mM, about 50 mM to about 75 mM, or about 15 mM to about 100 mM. In some examples, the sodium phosphate in the formulation is about 15 mM, about 20 mM, about 22 mM, about 25 mM, about 28 mM, about 30 mM, about 35 mM, about 36 mM, about 40 mM, about 45 mM, about 50 mM, about 51 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM, including every value in between these numbers. In some examples, the formulation comprises histidine (such as L-histidine) as a buffer. In some examples, the histidine in the formulation is about 15 mM to about 30 mM, about 20 mM to 30 mM, about 22 mM to about 28 mM, greater than 35 mM to about 100 mM, about 40 mM to about 100 mM, about 45 mM to about 90 mM, about 50 mM to about 75 mM, or about 15 mM to about 100 mM. In some examples, the histidine in the formulation is about 15 mM, about 20 mM, about 22 mM, about 25 mM, about 28 mM, about 30 mM, about 35 mM, about 36 mM, about 40 mM, about 45 mM, about 50 mM, about 51 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM, including every value in between these numbers.

[0020] In some examples, the formulation further comprises a surfactant. In some examples, surfactant is polysorbate (such as polysorbate 20) or poloxamer (such as poloxamer 188). In some examples, the surfactant concentration is about 0.01% to about 0.1%, about 0.01% to about 0.05%, or about 0.02% to about 0.04%. In some examples, the surfactant concentration is about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, or about 0.1%, including every value in between these numbers.

[0021] In some examples, the formulation has a pH about 5.5 to about 6.5, about 5.8 to about 6.8, about 5.9 to about 6.5, about 6.0 to about 6.5, about 6.0 to about 6.4, or about 6.0 to about 6.2. In some examples, the formulation has a pH about 5.6, about 5.8, about 5.9, about 6.0, about 6.2, about 6.4, about 6.5, about 6.8, or about 7.0, including every value in between these numbers.

[0022] In some examples, the monoclonal antibody is not subject to prior lyophilization. In some examples, the monoclonal antibody is a full length antibody. In some examples, the monoclonal antibody is an IgG1, IgG2, or IgG4 antibody. In some examples, the monoclonal antibody is a humanized antibody, a chimeric antibody or a human antibody. In

some examples, the monoclonal antibody is an antibody fragment comprising an antigen-binding region. In some examples, the antibody fragment is a Fab or F(ab')₂ fragment. In some examples, the monoclonal antibody binds VEGF. In some examples, the antibody is bevacizumab. In some examples, the monoclonal antibody is susceptible to aggregation.

[0023] In some examples, the monoclonal antibody is not subject to prior lyophilization. In some examples, the monoclonal antibody is a full length antibody. In some examples, the monoclonal antibody is an IgG1, IgG2, or IgG4 antibody. In some examples, the monoclonal antibody is a humanized antibody, a chimeric antibody or a human antibody. In some examples, the monoclonal antibody is an antibody fragment comprising an antigen-binding region. In some examples, the antibody fragment is a Fab or F(ab')₂ fragment. In some examples, the monoclonal antibody binds CD20. In some examples, the antibody that binds CD20 is a humanized B-Ly1 antibody described herein. In some examples, the antibody that binds CD20 is an antibody comprising a heavy chain variable region amino acid sequence selected from SEQ ID NO:3 to SEQ ID NO:19 and a light chain variable region amino acid sequence of SEQ ID NO:20. In some examples, the antibody is obinutuzumab. In some examples, the monoclonal antibody is susceptible to aggregation.

[0024] In some examples, the formulation is stable at -20°C for at least about 6 months, at least about 12 months, at least about 15 months, at least about 18 months, at least about 19 months, at least about 20 months, or at least about 2 years. In some examples, the formulation is sterile. In some examples, the formulation is for administration to a subject. In some examples, the formulation is for intravenous (IV), subcutaneous (SQ), intraocular (IO), or intramuscular (IM) administration.

[0025] In some examples, the container is a vial with a stopper pierceable by a syringe, wherein the vial comprises any one of the formulations described herein. In some examples, the vial is stored at about 2-8°C. In some examples, the vial is stored at about -20°C. In some examples, the vial is a 3 cc, 20 cc or 50 cc vial.

[0026] Disclosed are stainless steel tanks comprising any one of the formulations described herein inside the tank. In some examples, the formulation is frozen.

[0027] Also disclosed are methods of reducing aggregation of a therapeutic monoclonal antibody. In some examples, the method comprises formulating the monoclonal antibody in a formulation comprising trehalose and a buffer, wherein the weight ratio of the monoclonal antibody to the trehalose in the formulation is greater than or equal to 0.41 and less than 1.65, and wherein the formulation has a pH of about 5.5 to about 7.0. In one aspect, the present disclosure refers to a method of reducing aggregation of a therapeutic monoclonal antibody, comprising formulating said antibody in a formulation comprising trehalose and a buffer, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has a pH of 5.5 to 7.0, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF. In some examples, the method comprises formulating the antibody in a formulation comprising trehalose in an amount of about 45 mM to about 634 mM, about 50 mM to about 600 mM, or

about 150 mM to about 400 mM and sodium phosphate in an amount of greater than 35 mM to about 100 mM, and said formulation having a pH of about 5.5 to about 7.0, wherein said monoclonal antibody is formulated in an amount of about 25 mg/mL to about 100 mg/mL in the formulation, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.65. In one aspect, the present disclosure refers to a method of reducing aggregation of a therapeutic monoclonal antibody, comprising formulating said antibody in a formulation comprising trehalose in an amount of 45 mM to 634 mM and sodium phosphate in an amount of greater than 35 mM to 100 mM, and said formulation having a pH of 5.5 to 7.0, wherein said monoclonal antibody is formulated in an amount of 25 mg/mL to 100 mg/mL in the formulation, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF.

[0028] In some examples of the method described herein, the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.41 and less than 1.65. In some examples of the methods described herein, the weight ratio of the monoclonal antibody to the trehalose is 0.73 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose is 0.49 to 1.47. In some examples, the weight ratio of the monoclonal antibody to the trehalose is any of 0.41, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, and 1.64, including every value in between these numbers.

[0029] In some examples, the monoclonal antibody in the formulation is in an amount of about 30 mg/mL to about 90 mg/mL, about 35 mg/mL to about 85 mg/mL, about 35 mg/mL to about 75 mg/mL, about 40 mg/mL to about 80 mg/mL, about 45 mg/mL to about 70 mg/mL, or about 45 mg/mL to about 55 mg/mL. In some examples, the monoclonal antibody in the formulation is about 25 mg/mL, about 30 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, about 60 mg/mL, about 65 mg/mL, about 70 mg/mL, about 75 mg/mL, about 80 mg/mL, about 85 mg/mL, about 90 mg/mL, about 95 mg/mL, or about 100 mg/mL, including every value in between these numbers. In some examples, the monoclonal antibody in the formulation is about 45 mg/mL, about 50 mg/mL, or about 55 mg/mL.

[0030] In some examples, the formulation comprises the trehalose in about 45 mM to about 600 mM, about 45 mM to about 550 mM, about 45 mM to about 500 mM, about 45 mM to about 450 mM, about 45 mM to about 400 mM, about 45 mM to about 350 mM, about 45 mM to about 300 mM, about 45 mM to about 250 mM, about 45 mM to about 200 mM, about 45 mM to about 180 mM, about 45 mM to about 150 mM, about 45 mM to about 140 mM, about 45 mM to about 135 mM, about 45 mM to about 130 mM, about 45 mM to about 120 mM, about 45 mM to about 110 mM, about 45 mM to about 100 mM, about 180 mM to about 634 mM, about 50 mM to about 600 mM, or about 150 mM to about 400 mM. In some examples, the trehalose in the formulation is about 45 mM, about 50 mM, about 60 mM, about 70 mM, about 80 mM, about 90 mM, about 100 mM, about 110 mM, about 120 mM, about 130 mM, about 135 mM, about 140 mM, about 150 mM, about 180 mM, about 200 mM, about 250 mM, about 300 mM, about 350 mM, about 400 mM, about 450 mM, about 500 mM,

about 550 mM, about 600 mM, about 610 mM, about 620 mM, about 630 mM, or about 634 mM. In some examples, the formulation comprises sodium phosphate as a buffer. In some examples, the sodium phosphate in the formulation is about 15 mM to about 30 mM, about 20 mM to 30 mM, about 22 mM to about 28 mM, greater than 35 mM to about 100 mM, about 40 mM to about 100 mM, about 45 mM to about 90 mM, about 50 mM to about 75 mM, or about 15 mM to about 100 mM. In some examples, the sodium phosphate in the formulation is about 15 mM, about 20 mM, about 22 mM, about 25 mM, about 28 mM, about 30 mM, about 35 mM, about 36 mM, about 40 mM, about 45 mM, about 50 mM, about 51 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM, including every value in between these numbers. In some examples, the formulation comprises histidine (such as L-histidine) as a buffer. In some examples, the histidine in the formulation is about 15 mM to about 30 mM, about 20 mM to 30 mM, about 22 mM to about 28 mM, greater than 35 mM to about 100 mM, about 40 mM to about 100 mM, about 45 mM to about 90 mM, about 50 mM to about 75 mM, or about 15 mM to about 100 mM. In some examples, the histidine in the formulation is about 15 mM, about 20 mM, about 22 mM, about 25 mM, about 28 mM, about 30 mM, about 35 mM, about 36 mM, about 40 mM, about 45 mM, about 50 mM, about 51 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM, including every value in between these numbers.

[0031] In some examples, the formulation further comprises a surfactant. In some examples, surfactant is polysorbate (such as polysorbate 20) or poloxamer (such as poloxamer 188). In some examples, surfactant concentration is about 0.01% to about 0.1%, about 0.01% to about 0.05%, or about 0.02% to about 0.04%. In some examples, the surfactant concentration is about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, or about 0.1%, including every value in between these numbers.

[0032] In some examples, the formulation has a pH about 5.5 to about 6.5, about 5.8 to about 6.8, about 5.9 to about 6.5, about 6.0 to about 6.5, about 6.0 to about 6.4, or about 6.0 to about 6.2. In some examples, the formulation has a pH about 5.6, about 5.8, about 5.9, about 6.0, about 6.2, about 6.4, about 6.5, about 6.8, or about 7.0, including every value in between these numbers.

[0033] In some examples, the monoclonal antibody is not subject to prior lyophilization. In some examples, the monoclonal antibody is a full length antibody. In some examples, the monoclonal antibody is an IgG1, IgG2, or IgG4 antibody. In some examples, the monoclonal antibody is a humanized antibody, a chimeric antibody or a human antibody. In some examples, the monoclonal antibody is an antibody fragment comprising an antigen-

binding region. In some examples, the antibody fragment is a Fab or F(ab')₂ fragment. In some examples, the monoclonal antibody binds VEGF. In some examples, the antibody is bevacizumab. In some examples, the monoclonal antibody is susceptible to aggregation.

[0034] In some examples, the monoclonal antibody is not subject to prior lyophilization. In some examples, the monoclonal antibody is a full length antibody. In some examples, the monoclonal antibody is an IgG1, IgG2, or IgG4 antibody. In some examples, the monoclonal antibody is a humanized antibody, a chimeric antibody or a human antibody. In some examples, the monoclonal antibody is an antibody fragment comprising an antigen-binding region. In some examples, the antibody fragment is a Fab or F(ab')₂ fragment. In some examples, the monoclonal antibody binds CD20. In some examples, the antibody that binds CD20 is a humanized B-Ly1 antibody described herein. In some examples, the antibody that binds CD20 is an antibody comprising a heavy chain variable region amino acid sequence selected from SEQ ID NO:3 to SEQ ID NO:19 and a light chain variable region amino acid sequence of SEQ ID NO:20. In some examples, the antibody is obinutuzumab. In some examples, the monoclonal antibody is susceptible to aggregation.

[0035] In some examples, the formulation is stable at -20°C for at least about 6 months, at least about 12 months, at least about 15 months, at least about 18 months, at least about 19 months, at least about 20 months, or at least about 2 years. In some examples, the formulation is sterile. In some examples, the formulation is for administration to a subject. In some examples, the formulation is for intravenous (IV), subcutaneous (SQ), intraocular (IO), or intramuscular (IM) administration.

[0036] In another aspect, the present disclosure refers to methods of making a pharmaceutical formulation comprising: (a) preparing any one of the formulations described herein, (b) storing the formulation at -20°C or -40°C for at least about 6 months, and (c) evaluating physical stability, chemical stability, or biological activity of the antibody in the formulation. In some examples, the physical stability, chemical stability, or biological activity of the antibody in the formulation is evaluated at about 6 months, about 12 months, about 18 months, or about 24 months after the formulation is stored (e.g., at -20°C or -40°C).

[0036a] In one aspect, the present disclosure refers to use of any one of the formulations described herein in the manufacture of a medicament for treating a disease or disorder in a subject.

[0037] Disclosed are methods of treating a disease or disorder in a subject comprising administering any one of the formulations described herein to a subject in an amount effective to treat the disease or disorder. In some examples, the formulation comprises an antibody that binds to VEGF. In some examples, the antibody is bevacizumab. In some examples, the disease is cancer. In some examples, the cancer is selected from colorectal cancer, lung cancer, breast cancer, renal cancer, and glioblastoma.

[0038] Also disclosed are methods of treating a disease or disorder in a subject comprising administering any one of the formulations described herein to a subject in an

amount effective to treat the disease or disorder. In some examples, the formulation comprises an antibody that binds to CD20. In some examples, the antibody is obinutuzumab. In some examples, the disease is cancer. In some examples, the cancer is a CD20 expression cancer, for example, lymphoma, lymphocytic leukemia, and multiple myeloma.

[0039] It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure. These and other aspects of the disclosure will become apparent to one of skill in the art. These and other examples of the disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIGS. 1A, 1B, 1C and 1D show visual trehalose crystallization after induced nucleation on the surface of frozen samples with pharmaceutically relevant concentrations of trehalose of (**FIG. 1A**) 0.0% (wt/v) trehalose, (**FIG. 1B**) 2.0% (wt/v) trehalose, (**FIG. 1C**) 4.0% (wt/v) trehalose, and (**FIG. 1D**) 8.0% (wt/v) trehalose.

[0041] FIG. 2A shows the solubility of sucrose (**1**), trehalose (**2**), and mannitol (**3**) as a function of temperature, as labeled. **FIG. 2B** depicts the percent high molecular weight species of bevacizumab in various cryoprotectant formulations before and after freezing and induced nucleation for 28 days at -20 °C as determined by HP-SEC, as labeled.

[0042] FIGS. 3A, 3B and 3C show the time dependent increase in aggregation of mAb1 (**FIG. 3A**), bevacizumab (**FIG. 3B**), and mAb3 (**FIG. 3C**) fast freeze samples stored frozen at -20 °C (**1**), -14 °C (**2**), and -8 °C (**3**), as labeled.

[0043] FIGS. 4A and 4B show representative size exclusion chromatography (SEC) chromatograms of mAb3 monomer, dimer, and high molecular weight species (HMWS). (**FIG. 4A**) Effect of Freeze Rate. mAb3 samples frozen at the slow (**1**), normal (**2**), and fast (**3**) freeze rates (as labeled) and stored at -20°C for 12 months. Study control (stored at -70 °C) shown for comparison. (**FIG. 4B**) Effect of Storage Temperature. mAb3 samples frozen at the fast freeze rate and stored at -20 °C (**3**), -14 °C (**2**), and -8 °C (**1**) for 12 months, as labeled. Study control (stored at -70 °C) shown for comparison.

[0044] FIG. 5 shows normalized NIR spectra of the three trehalose forms discussed in this study: amorphous trehalose (**1**), trehalose anhydrate (crystalline) (**2**), and trehalose dihydrate (crystalline) (**3**), as labeled.

[0045] FIGS. 6A1-FIG. 6C3 show normalized NIR spectra of the (**FIGS. 6A1, 6A2 and 6A3**) mAb1, (**FIGS. 6B1, 6B2, and 6B3**) bevacizumab, and (**FIGS. 6C1, 6C2, and 6C3**) mAb3

CLAIMS

WHAT IS CLAIMED IS:

1. A stable aqueous pharmaceutical formulation, the formulation comprising a monoclonal antibody, trehalose, and a buffer, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has a pH of 5.5 to 7.0, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF.
2. The formulation of claim 1, wherein the weight ratio of said monoclonal antibody to said trehalose is 0.49 to 0.73.
3. The formulation of claim 1, wherein the weight ratio of said monoclonal antibody to said trehalose is 0.73 to 1.47.
4. The formulation of any one of claims 1-3, wherein said monoclonal antibody in the formulation is 25 mg/mL to 100 mg/mL.
5. The formulation of any one of claims 1-4, wherein said monoclonal antibody in the formulation is 35 mg/mL to 75 mg/mL.
6. The formulation of any one of claims 1-5, wherein said monoclonal antibody in the formulation is 45 mg/mL to 55 mg/mL.
7. The formulation of any one of claims 1-6, wherein said trehalose in the formulation is 45 mM to 634 mM, 50 mM to 600 mM, or 150 mM to 400 mM.
8. The formulation of any one of claims 1-7, wherein said trehalose in the formulation is 45 mM to 135 mM.
9. The formulation of any one of claims 1-7, wherein said trehalose in the formulation is 180 mM to 634 mM.
10. The formulation of any one of claims 1-9, wherein said buffer is in an amount of greater than 35 mM to 100 mM.

11. The formulation of claim 10, wherein said buffer comprises histidine.
12. The formulation of claim 10, wherein said buffer comprises sodium phosphate.
13. A stable aqueous pharmaceutical formulation, the formulation comprising (a) a monoclonal antibody in an amount of 25 mg/mL to 100 mg/mL; (b) trehalose in an amount of 45 mM to 634 mM; and (c) sodium phosphate in an amount of greater than 35 mM to 100 mM, wherein said formulation has a pH of 5.5 to 7.0, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF.
14. The formulation of claim 13, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is 0.49 to 0.73.
15. The formulation of claim 13, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is 0.73 to 1.47.
16. The formulation of any one of claims 13-15, wherein said monoclonal antibody is in an amount of 35 mg/mL to 85 mg/mL.
17. The formulation of any one of claims 13-16, wherein said monoclonal antibody is in an amount of 45 mg/mL to 55 mg/mL.
18. The formulation of any one of claims 13-17, wherein said monoclonal antibody is in an amount of about 50 mg/mL.
19. The formulation of any one of claims 13-18, wherein said trehalose is in an amount of 45 mM to 135 mM.
20. The formulation of any one of claims 13-18, wherein said trehalose is in an amount of 180 mM to 634 mM.
21. The formulation of any one of claims 13-19, wherein said trehalose is in an amount of about 60 mM.
22. The formulation of any one of claims 13-21, wherein said sodium phosphate is in an amount of 45 mM to 90 mM.

23. The formulation of any one of claims 13-22, wherein said sodium phosphate is in an amount of 50 mM to 75 mM.
24. The formulation of any one of claims 13-23, wherein said sodium phosphate is in an amount of about 51 mM.
25. The formulation of any one of claims 1-24, further comprising a surfactant.
26. The formulation of claim 25, wherein said surfactant is polysorbate or poloxamer.
27. The formulation of claim 26, wherein said polysorbate is polysorbate 20.
28. The formulation of claim 26, wherein said poloxamer is poloxamer 188.
29. The formulation of any one of claims 25-28, wherein said surfactant concentration is 0.01% to 0.1%.
30. The formulation of any one of claims 25-29, wherein said surfactant concentration is 0.01% to 0.05%.
31. The formulation of any one of claims 25-30, wherein said surfactant concentration is about 0.04%.
32. The formulation of any one of claims 1-31, wherein said formulation has a pH of 5.9 to 6.5.
33. The formulation of any one of claims 1-32, wherein said formulation has a pH of about 6.2 or about 6.0.
34. The formulation of any one of claims 1-33, wherein said monoclonal antibody is not subject to prior lyophilization.
35. The formulation of any one of claims 1-34, wherein said monoclonal antibody is a full length antibody.
36. The formulation of any one of claims 1-35, wherein said monoclonal antibody is an IgG1 antibody.
37. The formulation of any one of claims 1-36, wherein said monoclonal antibody is a humanized antibody.

38. The formulation of any one of claims 1-34 and 37, wherein said monoclonal antibody is an antibody fragment comprising an antigen-binding region.
39. The formulation of claim 38, wherein the antibody fragment is a Fab or F(ab')₂ fragment.
40. The formulation of any one of claims 1-39, wherein said antibody is bevacizumab.
41. The formulation of any one of claims 1-40, wherein said monoclonal antibody is susceptible to aggregation.
42. The formulation of any one of claims 1-41, wherein the formulation is stable at -20°C for at least 12 months, at least 18 months, or at least 24 months.
43. The formulation of any one of claims 1-42, which is sterile.
44. The formulation of any one of claims 1-43, wherein said formulation is for administration to a subject.
45. The formulation of any one of claims 1-44, which is for intravenous (IV), subcutaneous (SQ), intraocular (IO), or intramuscular (IM) administration.
46. An article of manufacture comprising a container holding the stable aqueous pharmaceutical formulation of any one of claims 1-45.
47. A method of reducing aggregation of a therapeutic monoclonal antibody, comprising formulating said antibody in a formulation comprising trehalose in an amount of 45 mM to 634 mM and sodium phosphate in an amount of greater than 35 mM to 100 mM, and said formulation having a pH of 5.5 to 7.0, wherein said monoclonal antibody is formulated in an amount of 25 mg/mL to 100 mg/mL in the formulation, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF.

48. The method of claim 47, wherein said sodium phosphate is in an amount of 50 mM to 75 mM.
49. The method of claim 47 or 48, wherein said sodium phosphate is in an amount of about 51 mM.
50. A method of reducing aggregation of a therapeutic monoclonal antibody, comprising formulating said antibody in a formulation comprising trehalose and a buffer, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has a pH of 5.5 to 7.0, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months, and wherein the monoclonal antibody binds VEGF.
51. The method of any one of claims 47-50, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is any of 0.49, 0.58, 0.65, 0.73, 0.74, 0.83, 0.97, 1.16, and 1.47.
52. The method of any one of claims 47-50, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is 0.49 to 0.73.
53. The method of any one of claims 47-50, wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is 0.73 to 1.47.
54. The method of any one of claims 47-53, wherein said monoclonal antibody is in an amount of 35 mg/mL to 75 mg/mL.
55. The method of any one of claims 47-54, wherein said monoclonal antibody is in an amount of 45 mg/mL to 55 mg/mL.
56. The method of any one of claims 47-55, wherein said monoclonal antibody is in an amount of about 50 mg/mL.
57. The method of any one of claims 47-56, wherein said trehalose is in an amount of 45 mM to 135 mM.
58. The method of any one of claims 47-57, wherein said trehalose is in an amount of about 60 mM.

59. The method of any one of claims 47-56, wherein said trehalose is in an amount of 180 mM to 634 mM.
60. The method of any one of claims 47-59, wherein said formulation further comprises a surfactant.
61. The method of claim 60, wherein said surfactant is polysorbate or poloxamer.
62. The method of claim 61, wherein said polysorbate is polysorbate 20.
63. The method of claim 61, wherein said poloxamer is poloxamer 188.
64. The method of any one of claims 60-63, wherein said surfactant concentration is 0.01% to 0.1%.
65. The method of any one of claims 60-64, wherein said surfactant concentration is 0.01% to 0.05%.
66. The method of any one of claims 60-65, wherein said surfactant concentration is about 0.04%.
67. The method of any one of claims 47-66, wherein said formulation has a pH of 5.9 to 6.5.
68. The method of any one of claims 47-67, wherein said formulation has a pH of about 6.2 or about 6.0.
69. The method of any one of claims 50-68, wherein said buffer comprises sodium phosphate in an amount of greater than 35 mM to 100 mM.
70. The method of any one of claims 47-69, wherein said antibody is bevacizumab.
71. A method of making a pharmaceutical formulation comprising:
 - (a) preparing the formulation of any one of claims 1- 45,
 - (b) storing the formulation at -20°C or -40°C for at least about 6 months, and
 - (c) evaluating physical stability, chemical stability, or biological activity of the antibody in the formulation.
72. Use of the formulation of any one of claims 1-45 in the manufacture of a medicament for treating a disease or disorder in a subject.

73. A stable aqueous pharmaceutical formulation for intravenous administration, the formulation comprising (a) a monoclonal antibody in an amount of less than or equal to about 100 mg/mL, wherein the monoclonal antibody binds VEGF; and (b) trehalose in an amount of 50 mM to 600 mM, wherein said formulation has a pH of 5.5 to 7.0, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months.
74. A stable aqueous pharmaceutical formulation for subcutaneous or intraocular administration, the formulation comprising (a) a monoclonal antibody in an amount of less than or equal to about 100 mg/mL, wherein the monoclonal antibody binds VEGF; and (b) trehalose in an amount of 150 mM to 400 mM, wherein said formulation has a pH of 5.5 to 7.0, and wherein the weight ratio of said monoclonal antibody to said trehalose in the formulation is greater than or equal to 0.49 and less than or equal to 1.47, wherein the formulation has been stored at -20°C or -40°C for at least about 6 months.