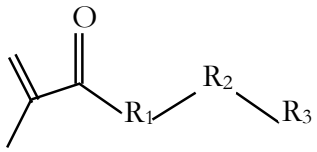
away from proteins as quickly as small molecule excipients upon dilution or *in vivo* administration.

SUMMARY

[005] The present disclosure describes, *inter alia*, polymers having higher molecular weights than traditional small molecule protein formulation stabilizers such as amino acids and sugars and sugar alcohols, for example, with greater than 10-fold higher molecular weights than such small molecule excipients. Such polymeric excipients, for example, may be used to stabilize high concentration protein formulations, such as by limiting viscosity and/or inhibiting precipitation. The disclosure includes multiple examples, including, but not limited to, the following examples.

[006] Example 1 is a random polymer library comprising a mixture of polymers, wherein the library comprises polymers comprising at least three monomers chosen from: (a) methyl methacrylate (MMA), (b) oligo(ethylene glycol) methyl ether methacrylate (OEGMA), (c) isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and (d) a compound of the Formula I,

Formula I:



wherein R_1 is O or NH, R_2 is methyl, ethyl, propyl, or butyl, and R_3 is NH_2 or $N(CH_3)_2$ or a guanidinium group, wherein the library comprises polymers of from 3 to 20 kDa.

[007] Example 2 is the random polymer library of example 1, wherein the library comprises polymers comprising a monomer of the Formula I, wherein the monomer is dimethyl amino methacrylate (DMAEMA), 2-aminoethyl methacrylate, arginine methacrylate, arginine methacrylamide, N-(3-aminopropyl) methacrylamide, N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), or N-3-(dimethylamino)propyl methacrylamide.

[008] Example 3 is the random polymer library of example 1 or 2, wherein at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the polymers in the library comprise at least three monomers, or wherein the random polymer library consists essentially of polymers comprising at least three monomers.

[009] Example 4 is the random polymer library of example 1 or 2, wherein at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the polymers in the library comprise at least four monomers, or wherein the random polymer library consists essentially of polymers comprising at least four monomers.

[0010] Example 5 is a random polymer library comprising a mixture of polymers, each polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and dimethyl amino methacrylate (DMAEMA), wherein the library comprises polymers of from 3 to 20 kDa.

[0011] Example 6 is a random polymer library comprising a mixture of polymers, each polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), wherein the library comprises polymers of from 3 to 20 kDa.

[0012] Example 7 is the random polymer library of any one of examples 1-6, wherein the library comprises polymers of from 3 to 15 kDa, from 5 to 20 kDa, from 5 to 15 kDa, from 5 to 10 kDa, from 10 to 20 kDa, from 7 to 10 kDa, or from 10 to 15 kDa.

[0013] Example 8 is the random polymer library of any one of examples 1-7, wherein the library comprises OEGMA with a molecular weight of from 300 to 1500 g/mol.

[0014] Example 9 is the random polymer library of example 8, wherein the OEGMA has a molecular weight of 300, 500, 750, 950, 1000, 1200, or 1500 g/mol.

[0015] Example 10 is the random polymer library of example 8, wherein the OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500).

[0016] Example 11 is the random polymer library of any one of examples 1-4 or 7-10, wherein library comprises polymers comprising three monomers.

[0017] Example 12 is the random polymer library of example 11, wherein at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the polymers in the library comprise three monomers, or wherein the random polymer library consists essentially of polymers comprising three monomers.

[0018] Example 13 is the random polymer library of example 11 or 12, wherein the three monomers are MMA, OEGMA, and either IBMA or BMA.

[0019] Example 14 is the random polymer library of example 13, wherein the three monomers are MMA, OEGMA, and IBMA.

[0020] Example 15 is the random polymer library of example 13, wherein the MMA, OEGMA, and IBMA or BMA are present in a ratio of: (a) 5 : 3 : 2, or (b) 3 : 5 : 2, or (c) 5 : 4 : 1.

[0021] Example 16 is the random polymer library of any one of examples 1-10, wherein the library comprises polymers comprising four monomers.

[0022] Example 17 is the random polymer library of example 16, wherein at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the polymers in the library comprise three monomers, or wherein the random polymer library consists essentially of polymers comprising three monomers.

[0023] Example 18 is the random polymer library of example 16 or 17, wherein the four monomers are MMA, OEGMA, IBMA, and DMAEMA.

[0024] Example 19 is the random polymer library of example 18, wherein the polymer library comprises polymers comprising 20-50% MMA, 20-50% OEGMA, 5-25% IBMA, and 5-25% DMAEMA by total weight of polymer.

[0025] Example 20 is the random polymer library of example 18, wherein the polymer library comprises polymers comprising MMA, OEGMA, IBMA, and DMAEMA in a molar ratio of: (a) 5 : 2.5 : 2 : 0.5, (b) 2 : 5 : 2 : 1, (c) 5 : 2.5 : 1 : 1.5, (d) 4 : 4 : 1 : 1; (e) 3 : 4 : 1 : 2; (f) 2 : 4 : 1 : 3; and/or (g) 2 : 3 : 1 : 4.

[0026] Example 21 is the random polymer library of example 18, wherein the MMA, OEGMA, IBMA, and DMAEMA are in a molar ratio of 5 : 2.5 : 2 : 0.5, wherein the OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500), wherein the library comprises polymers with a molecular weights of 3-15 kDa.

[0027] Example 22 is the random polymer library of example 16 or 17, wherein the four monomers are MMA, OEGMA, IBMA, and ArgMAm.

[0028] Example 23 is the random polymer library of example 22, wherein the polymer library comprises polymers comprising 20-50% MMA, 20-50% OEGMA, 5-25% IBMA, and 5-25% ArgMAm by total weight of polymer.

[0029] Example 24 is the random polymer library of example 22, wherein the polymer library comprises polymers comprising MMA, OEGMA, IBMA, and ArgMAm in a molar ratio of: (a) 5 : 2.5 : 2 : 0.5, (b) 2 : 5 : 2 : 1, (c) 5 : 2 : 1 : 2, (d) 4 : 4 : 1 : 1; (e) 3 : 4 : 1 : 2; (f) 2 : 4 : 1 : 3; and/or (g) 2 : 3 : 1 : 4.

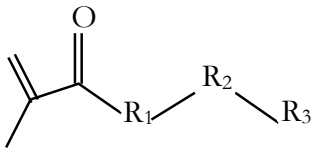
[0030] Example 25 is the random polymer library of example 22, wherein the MMA, OEGMA, IBMA, and ArgMAm are in a molar ratio of 5 : 2 : 1 : 2 or 4 : 4 : 1 : 1, wherein the

OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500), wherein the library comprises polymers with a molecular weights of 3-15 kDa.

[0031] Example 26 is a random polymer library comprising a mixture of polymers, wherein the library comprises polymers comprising at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and either isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and/or at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), optionally wherein the OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500), and optionally wherein the library comprises polymers with a molecular weights of 3-15 kDa.

[0032] Example 27 is a random polymer comprising a mixture of at least three monomers chosen from: (a) methyl methacrylate (MMA), (b) oligo(ethylene glycol) methyl ether methacrylate (OEGMA), (c) isobutyl methacrylate (IBMA), or (d) butyl methacrylate (BMA), and a compound of the Formula I,

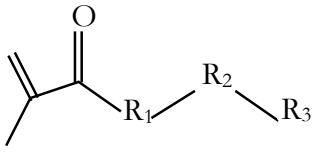
Formula I:



wherein R_1 is O or NH, R_2 is methyl, ethyl, propyl, or butyl, and R_3 is NH_2 or $N(CH_3)_2$ or a guanidinium group, wherein the polymer is from 3 to 20 kDa.

[0033] Example 28 is the random polymer of example 27, wherein the polymer comprises a monomer of the Formula I,

Formula I:



wherein the monomer is dimethyl amino methacrylate (DMAEMA), 2-aminoethyl methacrylate, arginine methacrylate, arginine methacrylamide, N-(3-aminopropyl) methacrylamide, N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), or N-3-(dimethylamino)propyl methacrylamide.

[0034] Example 29 is a random polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and dimethyl amino methacrylate (DMAEMA), wherein the polymer is from 3 to 20 kDa.

[0035] Example 30 is a random polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), wherein the polymer is from 3 to 20 kDa.

[0036] Example 31 is the random polymer of any one of examples 27-30, wherein the polymer is from 3 to 15 kDa, from 5 to 20 kDa, from 5 to 15 kDa, from 5 to 10 kDa, from 10 to 20 kDa, from 7 to 10 kDa, or from 10 to 15 kDa.

[0037] Example 32 is the random polymer of any one of examples 27-31, wherein the polymer comprises OEGMA with a molecular weight of from 300 to 1500 g/mol.

[0038] Example 33 is the random polymer of example 32, wherein the OEGMA has a molecular weight of 300, 500, 750, 950, 1000, 1200, or 1500 g/mol.

[0039] Example 34 is the random polymer of example 33, wherein the OEGMA has a molecular weight of 500 g/mol.

[0040] Example 35 is the random polymer of any one of examples 27-28 or 31-34, wherein the polymer comprises three monomers.

[0041] Example 36 is the random polymer of example 35, wherein the three monomers are MMA, OEGMA, and either IBMA or BMA.

[0042] Example 37 is the random polymer of example 36, wherein the three monomers are MMA, OEGMA, and IBMA.

[0043] Example 38 is the random polymer of example 37, wherein the MMA, OEGMA, and IBMA or BMA are present in a ratio of: (a) 5 : 3 : 2, or (b) 3 : 5 : 2, or (c) 5 : 4 : 1.

[0044] Example 39 is the random polymer of any one of examples 27-34, wherein the polymer comprises four monomers.

[0045] Example 40 is the random polymer of example 39, wherein the four monomers are MMA, OEGMA, IBMA, and DMAEMA.

[0046] Example 41 is the random polymer of example 40, wherein the polymer comprises 20-50% MMA, 20-50% OEGMA, 5-25% IBMA, and 5-25% DMAEMA by total weight of polymer.

[0047] Example 42 is the random polymer of example 40, wherein the polymer comprises MMA, OEGMA, IBMA, and DMAEMA in a molar ratio of: (a) 5 : 2.5 : 2 : 0.5, (b) 2 : 5 : 2 : 1, (c) 5 : 2.5 : 1 : 1.5, (d) 4 : 4 : 1 : 1; (e) 3 : 4 : 1 : 2; (f) 2 : 4 : 1 : 3; or (g) 2 : 3 : 1 : 4.

[0048] Example 43 is the random polymer of example 40, wherein the MMA, OEGMA, IBMA, and DMAEMA are in a molar ratio of 5 : 2.5 : 2 : 0.5, wherein the OEGMA is OEGMA 500, wherein the polymer has a molecular weight of from 3 to 15 kDa.

[0049] Example 44 is the random polymer of example 39, wherein the four monomers are MMA, OEGMA, IBMA, and ArgMAm.

[0050] Example 45 is the random polymer of example 44, wherein the polymer comprises 20-50% MMA, 20-50% OEGMA, 5-25% IBMA, and 5-25% ArgMAm by total weight of polymer.

[0051] Example 46 is the random polymer of example 44, wherein the polymer comprises MMA, OEGMA, IBMA, and ArgMAm in a molar ratio of: (a) 5 : 2.5 : 2 : 0.5, (b) 2 : 5 : 2 : 1, (c) 5 : 2.5 : 1 : 1.5, (d) 4 : 4 : 1 : 1; (e) 3 : 4 : 1 : 2; (f) 2 : 4 : 1 : 3; or (g) 2 : 3 : 1 : 4.

[0052] Example 47 is the random polymer of example 44, wherein the MMA, OEGMA, IBMA, and ArgMAm are in a molar ratio of 5 : 2 : 1 : 2 or 4 : 4 : 1 : 1, wherein the OEGMA is OEGMA 500, wherein the polymer has a molecular weight of from 3 to 15 kDa.

[0053] Example 48 is a random polymer comprising mixture of at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and either isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and/or at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), optionally wherein the OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500), and optionally wherein the polymer has a molecular weight of from 3 to 15 kDa.

[0054] Example 49 is the random polymer of any one of examples 27-48, wherein the polymer has a molecular weight of from 7 to 10 kDa.

[0055] Example 50 is a composition comprising a random polymer according to any one of examples 27-49 and at least one protein.

[0056] Example 51 is the composition of example 50, wherein the polymer is at a concentration of from 0.01 to 1% w/v, such as 0.01 to 0.1% w/v.

[0057] Example 52 is the composition of example 50 or 51, wherein the protein is an antibody.

[0058] Example 53 is the composition of example 52, wherein the antibody is an IgG antibody, such as a full-length IgG, a bi-specific IgG, or wherein the antibody is an antigen binding fragment, such as a Fab, Fab', (Fab')2, Fv, or scFv.

[0059] Example 54 is the composition of any one of examples 50-53, wherein the composition further comprises at least one buffer, such as histidine, phosphate, or citrate.

[0060] Example 55 is the composition of any one of examples 50-54, wherein the composition further comprises at least one surfactant, such as a polysorbate, for example polysorbate 20 or polysorbate 80.

[0061] Example 56 is the composition of any one of examples 50-55, wherein the antibody is at a concentration of 10 mg/mL to 150 mg/mL, such as 10-100 mg/mL, 20-100 mg/mL, 20-80 mg/mL, 10-50 mg/mL, 10-25 mg/mL, 25-50 mg/mL, 50-80 mg/mL, 50-100 mg/mL, or 70-100 mg/mL.

[0062] Example 57 is a method of reducing the viscosity and/or inhibiting precipitation of a protein-containing composition, comprising adding a random polymer of any one of examples 27-49 to the composition, optionally wherein the composition comprises the protein and/or excipients of any one of examples 50-56.

[0063] Example 58 is a method of preparing a random polymer library according to any one of examples 1-26 or a random polymer according to any one of examples 27-49, wherein the method comprises reverse addition/fragmentation chain transfer (RAFT), free radical polymerization (FRP), or atom transfer radical polymerization (ATRP).

[0064] Example 59 is a method of preparing a random polymer library according to any one of examples 1-26 or a random polymer according to any one of examples 27-49, the method comprising: exposing the monomers to LED light and/or heat in the presence of a zinc tetraphenyl porphyrin catalyst (ZnTPP) and a chain transfer agent.

[0065] Example 60 is the method of example 59, wherein the chain transfer agent is 2-cyano-2-propyl benzodithioate, 2-cyano-2-propyldodecyl trithiocarbonate, 4-((((2-carboxyethyl)thio)carbonothioyl)thio)-4-cyanopentanoic acid, 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid, or 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl] pentanoic acid (CDTPA).

[0066] Example 61 is the method of example 59 or 60, wherein the monomers are exposed to LED light in the presence of the ZnTPP and chain transfer agent for 3 to 18 hours.

[0067] Example 62 is the method of any one of examples 59-61, wherein polymerization is ended by removing the LED light.

[0068] Example 63 is the method of any one of examples 58-62, further comprising performing at least one filtration, buffer exchange, or dialysis step to isolate the polymers.

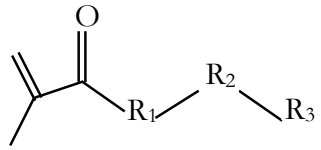
[0069] Example is a kit comprising the random polymer library of any one of examples 1-26, for use in testing polymers comprised within the library for their effect on precipitation, viscosity, and/or turbidity of a solution comprising a protein, the kit optionally further comprising instructions for use.

[0070] Example 65 is the kit of example 64, wherein the library comprises at least 10, at least 20, at least 50, or at least 80 different individual random polymers.

[0071] Example 66 is a method of identifying a random polymer excipient for a protein solution, comprising exposing the protein solution to a random polymer library of any one of examples 1-26 or the kit of example 64 or 65 and determining one or more of the viscosity, turbidity, or precipitation of the solution.

[0071a] In one aspect, the disclosure provides a random polymer library comprising a mixture of polymers, wherein the library comprises polymers comprising at least three monomers chosen from: a. methyl methacrylate (MMA), b. oligo(ethylene glycol) methyl ether methacrylate (OEGMA), c. isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and d. a compound of the Formula I,

Formula I:



wherein R_1 is O or NH, R_2 is methyl, ethyl, propyl, or butyl, and R_3 is NH_2 or $N(CH_3)_2$ or a guanidinium group, wherein the library comprises polymers of from 3 to 20 kDa.

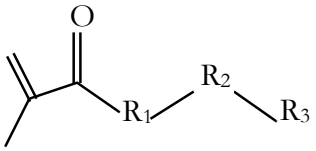
[0071b] In one aspect, the disclosure provides a random polymer library comprising a mixture of polymers, each polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and dimethyl amino methacrylate (DMAEMA), wherein the library comprises polymers of from 3 to 20 kDa.

[0071c] In one aspect, the disclosure provides a random polymer library comprising a mixture of polymers, each polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), wherein the library comprises polymers of from 3 to 20 kDa.

[0071d] In one aspect, the disclosure provides a random polymer library comprising a mixture of polymers, wherein the library comprises polymers comprising at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and either isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and/or at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), optionally wherein the OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500), and optionally wherein the library comprises polymers with a molecular weights of 3-15 kDa.

[0071e] In one aspect, the disclosure provides a random polymer comprising a mixture of at least three monomers chosen from: a. methyl methacrylate (MMA), b. oligo(ethylene glycol) methyl ether methacrylate (OEGMA), c. isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and d. a compound of the Formula I,

Formula I:



wherein R_1 is O or NH, R_2 is methyl, ethyl, propyl, or butyl, and R_3 is NH_2 or $N(CH_3)_2$ or a guanidinium group, wherein the polymer is from 3 to 20 kDa.

[0071f] In one aspect, the disclosure provides a random polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and dimethyl amino methacrylate (DMAEMA), wherein the polymer is from 3 to 20 kDa.

[0071g] In one aspect, the disclosure provides a random polymer comprising a mixture of at least three of monomers: methyl methacrylate (MMA), oligo(ethylene glycol) methyl ether methacrylate (OEGMA), isobutyl methacrylate (IBMA), and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), wherein the polymer is from 3 to 20 kDa.

[0071h] In one aspect, the disclosure provides a random polymer comprising mixture of at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and either isobutyl methacrylate (IBMA) or butyl methacrylate (BMA), and/or at least two monomers chosen from oligo(ethylene glycol) methyl ether methacrylate (OEGMA) and N-(3-methacrylamidopropyl) guanidinium chloride (ArgMAm), optionally wherein the OEGMA has a molecular weight of 500 g/mol (i.e., is OEGMA 500), and optionally wherein the polymer has a molecular weight of from 3 to 15 kDa.

[0071i] In one aspect, the disclosure provides a composition comprising a random polymer as disclosed herein and at least one protein.

[0071j] In one aspect, the disclosure provides a method of reducing the viscosity and/or inhibiting precipitation of a protein-containing composition, comprising adding a random polymer as disclosed herein to the composition, optionally wherein the composition comprises the protein and/or excipients as disclosed herein.

[0071k] In one aspect, the disclosure provides a method of preparing a random polymer library as disclosed herein or a random polymer as disclosed herein, wherein the method comprises reverse addition/fragmentation chain transfer (RAFT), free radical polymerization (FRP), or atom transfer radical polymerization (ATRP).

[0071l] In one aspect, the disclosure provides a method of preparing a random polymer library as disclosed herein or a random polymer as disclosed herein, the method comprising: exposing the monomers to LED light and/or heat in the presence of a zinc tetraphenyl porphyrin catalyst (ZnTPP) and a chain transfer agent.

[0071m] In one aspect, the disclosure provides a kit comprising the random polymer library as disclosed herein, for use in testing polymers comprised within the library for their effect on precipitation, viscosity, and/or turbidity of a solution comprising a protein, the kit optionally further comprising instructions for use, optionally the library comprises at least 10, at least 20, at least 50, or at least 80 different individual random polymers.

[0071n] In one aspect, the disclosure provides a method of identifying a random polymer excipient for a protein solution, comprising exposing the protein solution to a random polymer library as disclosed herein or the kit as disclosed herein and determining one or more of the viscosity, turbidity, or precipitation of the solution.

[0072] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claims.

[0073] References cited herein are incorporated herein by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] Figure 1 shows an exemplary method of evaluating a polymer library for each polymer's effect on monoclonal antibody (mAb, such as mAb G) precipitation.

[0075] Figures 2A-B show turbidity measurements (absorbance at 600 nm) of mAb G (80 mg/mL) after incubation overnight in 15 mM phosphate buffer pH 7.4 with 100 mM NaCl (Figure 2A) or with 150 mM NaCl (Figure 2B) with selected polymer excipients at 1.6, 6.6, and 33 μM polymer (~0.0014, 0.006, 0.03% polymer).

[0076] Figure 3 shows precipitation kinetics of mAb G (80 mg/mL) in 15 mM phosphate buffer pH 7.4 + 150 mM NaCl with polymer excipients. Turbidity was measured using absorbance at 600 nM.

[0077] Figure 4 shows precipitation kinetics of mAb G (80 mg/mL) in 15 mM phosphate buffer pH 7.4 + 150 mM NaCl with polysorbate 20 (PS20). Turbidity was measured using absorbance at 600 nM.

[0078] Figures 5A-B show changes in viscosity of mAb G solutions (194 mg/mL in 30 mM histidine chloride (HisCl) pH 5.5) with excipients Poly1D ("Poly1"), polysorbate 20 (PS20), and Poly1D in combination with PS20, at different excipient concentrations. Figure 5A shows a graph of change in viscosity with increasing concentrations of either Poly1D or PS20. Figure 5B