EXAMPLES

Example 1

Different pharmaceutical formulations of epratuzumab at a concentration of 300 mg/mL were prepared. The concentration of sodium acetate (NaOAc) and sodium chloride (NaCl) was varied in order to investigate the effect of these salts on the viscosity of the formulation.

Materials were concentrated and buffer exchanged using viva flow cassettes and spin tubes. Formulation concentrations were confirmed using a Solo-VPE high concentration variable path length UV/Vis spectrophotometer (C Technologies, Inc., Bridgewater, NJ, USA) and viscosity determined using a RVDV-II viscometer (Brookfield Engineering Laboratories, Inc., Massachusetts, USA).

Ten separate formulations were generated (from an initial protein stock of 6 mg/mL) from a combination of replicates and Design of Experiments (DoE) to investigate the relationships between antibody, glycine, NaCl, NaOAc, and Polysorbate 80 (PS80) concentration all at pH 5.0.

Table 1: Table of formulation based on 200 mg/mL epratuzumab, 220 mM, pH 5.0 based formulation

Formulation	NaOAc (mM)	Polysorbate 80 (%)	NaCl	Viscosity/ cP
1	30	0.01	0	190.75
2	40	0	0	181.99
3	40	0.01	0	140.57
4	40	0.03	0	139.76
5	60	0.01	0	105.08
6	60	0	0	103.03
7	80	0	0	91.56
8	30	0	0	164.76
9	60	0.01	50	51.80
10	60	0.01	100	48.29

Based on the results of the experiments it was concluded that surprisingly NaOAc has a greater effect on reducing the viscosity of high concentration formulations of antibodies than NaCl. Figure 2 shows the reduction in the viscosity of the 273 mg/mL, 220 mM glycine, 60 mM NaOAc formulation observed with varying NaCl concentrations (0, 50, and 100 mM), with 100 mM NaCl the viscosity reduced from 61.7 cP (0 mM) to 48.3 cP(100 mM) a 21.7% reduction. Figure 3 shows the reduction in viscosity observed

due to an increase of NaOAc. Reduction in viscosity of 300 mg/mL material with 220 mM glycine and NaOAc between 30-60 mM, with a reduction in viscosity from 164.8 cP (30 mM) to 103.03 cP (60 mM) a 37.3% reduction with a 30 mM increase.

Example 2

Further experiments were performed in order to investigate the effect of NaOAc on the viscosity of high concentration antibody formulations.

Materials were concentrated and buffer exchanged using viva flow cassettes and spin tubes. Formulation concentrations were confirmed using a Solo-VPE high concentration variable path length UV/Vis spectrophotometer (C Technologies, Inc., Bridgewater, NJ, USA) and viscosity determined using a RVDV-II viscometer (Brookfield Engineering Laboratories, Inc., Massachusetts, USA). Osmolality of the pharmaceutical formulations was determined using a vapor pressure osmometer (Vapro® 5520, Wescor, Inc., Utah, USA).

Formulations in Table 2 (30 formulations) and Table 3 (12 formulation in duplicate/triplicate) were prepared and analyzed in triplicate, where there was insufficient material, formulations were tested in duplicate.

CLAIMS

1. A liquid pharmaceutical formulation comprising an antibody as active ingredient at a concentration of 220 to 400 mg/ml and acetate.

2. The liquid pharmaceutical formulation of claim 1 comprising acetate at a concentration of 20 to 150 mM.

3. The liquid pharmaceutical formulation of claim 1 or 2 comprising glycine at a concentration of 100 to 500 mM.

4. The liquid pharmaceutical formulation of claims 1, 2 or 3 having an osmolality of 250 to 550 mOsm/kg.

5. The liquid pharmaceutical formulation of any one of claims 1 to 4 having a viscosity of equal or less than 110 mPa s.

6. The liquid pharmaceutical formulation of any one of claims 1 to 5 having a pH of 4.0 to 7.0.

7. The liquid pharmaceutical formulation of any one of claims 1 to 6 comprising NaCl at a concentration of 0 to 100 mM.

8. The liquid pharmaceutical formulation of any one of claims 1 to 7 comprising a surfactant, preferably Polysorbate 80.

9. The liquid pharmaceutical formulation of claim 7 wherein the surfactant is polysorbate 80 at a concentration of 0.001 to 0.03% w/v.

10. The liquid pharmaceutical formulation of any one of claims 1 to 9 characterized in that it does not comprise $MgCl_2$ or $CaCl_2$.

11. The liquid pharmaceutical formulation of any one of claims 1 to 10 wherein the antibody is epratuzumab.

12. A container containing the liquid pharmaceutical formulation according to any one of claims 1 to 11.

13. A kit containing the container of claim 12 and instructions for use.

14. A method for reducing the viscosity of a liquid pharmaceutical formulation containing a protein or an antibody at a concentration of 220 to 400 mg/ml, the method comprising

    a) providing the liquid pharmaceutical formulation, and

    b) adding acetate to a final concentration of 20 to 150 mM,

    wherein the viscosity of the liquid pharmaceutical formulation is reduced as compared to the same liquid pharmaceutical formulation without acetate.

EXAMPLES

Example 1

Different pharmaceutical formulations of epratuzumab at a concentration of 300 mg/mL were prepared. The concentration of sodium acetate (NaOAc) and sodium chloride (NaCl) was varied in order to investigate the effect of these salts on the viscosity of the formulation.

Materials were concentrated and buffer exchanged using viva flow cassettes and spin tubes. Formulation concentrations were confirmed using a Solo-VPE high concentration variable path length UV/Vis spectrophotometer (C Technologies, Inc., Bridgewater, NJ, USA) and viscosity determined using a RVDV-II viscometer (Brookfield Engineering Laboratories, Inc., Massachusetts, USA).

Ten separate formulations were generated (from an initial protein stock of 6 mg/mL) from a combination of replicates and Design of Experiments (DoE) to investigate the relationships between antibody, glycine, NaCl, NaOAc, and Polysorbate 80 (PS80) concentration all at pH 5.0.

Table 1: Table of formulation based on 300 mg/mL epratuzumab, 220 mM, pH 5.0 based formulation

Formulation	NaOAc (mM)	Polysorbate 80 (%)	NaCl	Viscosity/ cP
1	30	0.01	0	190.75
2	40	0	0	181.99
3	40	0.01	0	140.57
4	40	0.03	0	139.76
5	60	0.01	0	105.08
6	60	0	0	103.03
7	80	0	0	91.56
8	30	0	0	164.76
9	60	0.01	50	51.80
10	60	0.01	100	48.29

Based on the results of the experiments it was concluded that surprisingly NaOAc has a greater effect on reducing the viscosity of high concentration formulations of antibodies than NaCl. Figure 3 shows the reduction in viscosity observed

due to an increase of NaOAc. Reduction in viscosity of 300 mg/mL material with 220 mM glycine and NaOAc between 30-60 mM, with a reduction in viscosity from 190.75 cP (30 mM) to 105.08 cP (60 mM), a 44.9% reduction with a 30 mM increase.

Example 2

Further experiments were performed in order to investigate the effect of NaOAc on the viscosity of high concentration antibody formulations.

Materials were concentrated and buffer exchanged using viva flow cassettes and spin tubes. Formulation concentrations were confirmed using a Solo-VPE high concentration variable path length UV/Vis spectrophotometer (C Technologies, Inc., Bridgewater, NJ, USA) and viscosity determined using a RVDV-II viscometer (Brookfield Engineering Laboratories, Inc., Massachusetts, USA). Osmolality of the pharmaceutical formulations was determined using a vapor pressure osmometer (Vapro® 5520, Wescor, Inc., Utah, USA).

Formulations in Table 2 (30 formulations) and Table 3 (12 formulation in duplicate/triplicate) were prepared and analyzed in triplicate, where there was insufficient material, formulations were tested in duplicate.

CLAIMS

1. A liquid pharmaceutical formulation comprising an antibody as active ingredient at a concentration of 220 to 400 mg/ml and acetate at a concentration of 20 to 150 mM.

2. The liquid pharmaceutical formulation of claim 1 comprising glycine at a concentration of 100 to 500 mM.

3. The liquid pharmaceutical formulation of claims 1 or 2 having an osmolality of 250 to 550 mOsm/kg.

4. The liquid pharmaceutical formulation of any one of claims 1 to 3 having a viscosity of equal or less than 110 mPa s.

5. The liquid pharmaceutical formulation of any one of claims 1 to 4 having a pH of 4.0 to 7.0.

6. The liquid pharmaceutical formulation of any one of claims 1 to 5 comprising NaCl at a concentration of 0 to 100 mM.

7. The liquid pharmaceutical formulation of any one of claims 1 to 6 comprising a surfactant, preferably Polysorbate 80.

8. The liquid pharmaceutical formulation of claim 7 wherein the surfactant is polysorbate 80 at a concentration of 0.001 to 0.03% w/v.

9. The liquid pharmaceutical formulation of any one of claims 1 to 8 characterized in that it does not comprise $MgCl_2$ or $CaCl_2$.

10. The liquid pharmaceutical formulation of any one of claims 1 to 9 wherein the antibody is epratuzumab.

11. A container containing the liquid pharmaceutical formulation according to any one of claims 1 to 10.

12. A kit containing the container of claim 11 and instructions for use.

13. A method for reducing the viscosity of a liquid pharmaceutical formulation containing a protein or an antibody at a concentration of 220 to 400 mg/ml, the method comprising

    a) providing the liquid pharmaceutical formulation, and

    b) adding acetate to a final concentration of 20 to 150 mM,

    wherein the viscosity of the liquid pharmaceutical formulation is reduced as compared to the same liquid pharmaceutical formulation without acetate.