at 25ºC, 50 cP at 25ºC and 35 cP at 37ºC, respectively. In addition, Pena *et al.* determined the suspension performance of spray dried powder was inferior to lyophilized counterpart.

Publications describing monoclonal antibody formulations include: US Patent 6,284,282 (Maa *et al.*); US Patent Nos. 6,267,958 and 6,685,940 (Andya *et al.*); US Patent No. 6,171,586 (Lam *et al.*); US Patent Nos. 6,875,432 and 7,666,413 (Liu *et al.*); WO2006/044908 (Andya *et al.*); US-2011-0076273-A1 (Adler *et al.*); US 2011/0044977 and WO 2011/012637 (Adler *et al.*); US 2009/0226530A1 (Lassner *et al.*); US-A 2003/0190316 (Kakuta *et al*.); US-A 2005/0214278 and US-A 2005/0118163 (Mizushima *et al*.); US-A 2009/0291076 (Morichika *et al*.); and US-A 2010/0285011 (Imaeda *et al*.)

Summary

The objectives of the present study were to: (1) identify process parameters that dictate suspension performance; (2) assess the feasibility of establishing monoclonal antibody powder suspensions (i.e. ≥ 250 mg monoclonal antibody/mL) with acceptable injectability (i.e. injection force ≤ 20 N through 27-guage thin-walled (TW) needle) and physical suspension stability; and/or (3) understand the mechanism of suspension performance. To prepare monoclonal antibody powders, spray drying was used. Spray drying is a mature, scalable, and efficient manufacturing process. The short-term effect of spray drying on monoclonal antibody was studied at accelerated temperature. An important criterion for suspension vehicle selection was that the viscosity of the suspension vehicle be below 10 centipoise (cP). The three model suspension vehicles, propylene glycol dicaprylate/dicaprate, benzyl benzoate, and ethyl lactate, tested in this study have low viscosity and met this requirement.

Inverse gas chromatography (IGC) has been used for surface energy analysis (SEA) (Newell *et al., Pharm Res* 18:662-666 (2001); Grimsey *et al., J Pharm Sci* 91:571-583 (2002); Newell and Buckton, *Pharm Res* 21:1440-1444 (2004); Saleem and Smyth, *Drug Devel & Ind Pharm* 34:1002-1010 (2008); Panzer and Schreiber, *Macromolecules* 25:3633-3637 (1992)). In IGC, a probe is injected into a column packed with the powder of interest (stationary phase) and the time required for the probe to pass through the column (t_r) is a measure of the magnitude of the interaction between the probe and the stationary phase. Surface energy can normally be divided into polar and dispersive (non-polar) components. Thus, the use of non-polar (alkanes) and polar (electron acceptor-donor or acid-base solvents) probes allowed these two surface energy components to be quantified. Surface energies of

the spray-dried particles may serve as a more direct and relevant indicator to suspension performance than other particle characteristics. Another parameter is heat of sorption which is a direct measure of the strength of the interactions between a solid and gas molecules adsorbed on the surface (Thielmann F., "Inverse gas chromatography: Characterization of alumina and related surfaces," In "*Encyclopedia of Surface and Colloid Science* Volume 4 (edit by P. Somasundaran). CRC Press, Boca Raton, FL., p3009-3031 (2006); Thielmann and Butler, "Heat of sorption on microcrystalline cellulose by pulse inverse gas chromatography at infinite dilution," Surface Measurement Services Application Note 203 (http://www.thesorptionsolution.com/Information_Application_Notes_IGC.php#Aps) (2007)). The IGC method was employed to measure the heat of sorption between spray dried particles and the suspension vehicle in this study.

The experimental data herein demonstrate that the objectives were achieved, and high-concentration monoclonal antibody suspension formulations suitable for subcutaneous administration were developed.

Thus, in a first example, the disclosure concerns a suspension formulation comprising a spray dried monoclonal antibody at a concentration of about 200 mg/mL or more suspended in a non-aqueous suspension vehicle, wherein the viscocity of the suspension vehicle is less than about 20 centipoise. In one aspect, the present disclosure refers to a suspension formulation comprising a spray dried monoclonal antibody at a concentration of about 200 mg/mL or more suspended in a non-aqueous suspension vehicle with a viscocity of less than about 20 centipoise at about 25 °C, wherein the non-aqueous suspension vehicle comprises propylene glycol dicaprylate/dicaprate.

In another example, the disclosure concerns a suspension formulation comprising a spray dried full length human IgG1 monoclonal antibody at a concentration from about 200 mg/mL to about 400 mg/mL suspended in a non-aqueous suspension vehicle with a viscocity less than about 20 centipoise, wherein the formulation has an average particle size from about 2 microns to about 10 microns, and injection glide force less than about 15 newton. In one aspect, the present disclosure refers to a suspension formulation comprising a spray dried full length human IgG1 monoclonal antibody at a concentration from about 200 mg/mL to about 400 mg/mL suspended in a non-aqueous suspension vehicle with a viscocity less than about 20 centipoise at 25 °C, wherein the formulation has an average particle size from about 2 microns to about 10 microns, and injection glide force less than about 15 newton; and wherein the non-aqueous suspension vehicle comprises propylene glycol dicaprylate/dicaprate.

The disclosure further concerns a subcutaneous administration device (e.g. a pre-filled syringe) with the formulation therein. In another aspect, the present disclosure refers to a subcutaneous administration device with the formulation as described herein.

In another example, the disclosure concerns a method of making a suspension formulation comprising suspending a spray dried monoclonal antibody in a non-aqueous suspension vehicle with a viscosity less than about 20 centipoise, wherein the antibody concentration in the suspension formulation is about 200 mg/mL or more. In one aspect, the present disclosure refers to a method of making a suspension formulation comprising suspending a spray dried monoclonal antibody in a non-aqueous suspension vehicle with a viscosity less than about 20 centipoise at 25 °C, wherein the monoclonal antibody concentration in the suspension formulation is about 200 mg/mL or more and wherein the non-aqueous suspension vehicle comprises propylene glycol dicaprylate/dicaprate.

Additionally, the disclosure provides a method of making an article of manufacture comprising filling a subcutaneous administration device with the formulation herein. In one aspect, the present disclosure refers to a method of making an article of manufacture comprising filling a subcutaneous administration device with the formulation as described herein.

In related examples, the disclosure concerns use of the formulation in the preparation of a medicament for treating a patient in need of treatment with the monoclonal antibody in the formulation, as well as a method of treating a patient comprising administering the formulation to a patient in need of treatment with the monoclonal antibody in the formulation. In one aspect, the present disclosure refers to use of the formulation as described herein in the preparation of a medicament for treating a patient in need of treatment with the monoclonal antibody in the formulation.

Brief Description of the Drawings

Figure 1: Antibody stability (as size exclusion chromatography (SEC) % monomer change from right after spry drying) as a function of storage time at 40 ºC for bevacizumab/trehalose formulation spray-dried (●) and freeze dried (○) as well as for trastuzumab/trehalose formulation spray dried (■) and freeze dried (□).

Figure 2: The viscosity-powder concentration profiles for propylene glycol dicaprylate/dicaprate suspensions with three monoclonal antibody (mAb) powders spray dried with a pilot-scale or a bench-top spray dryer: bevacizumab by pilot-scale (◊), bevacizumab by bench-top (♦), trastuzumab by pilot-scale (□), trastuzumab by bench-top (■), rituximab by pilot-scale (Δ), rituximab by bench-top (▲), empirical fitting (solid line), and theoretical fitting from Equation 4 (dash line).

Figure 3: The glide force-mAb concentration profiles for rituximab powder suspension in propylene glycol dicaprylate/dicaprate (Δ), ethyl lactate (◊), benzyl benzoate (○) and predicted glide force for mAb liquid solution extracted from Figure 4 in Overcashier et al. *Am. Pharm Rev.* 9(6): 77-83 (2006) (■).

Figure 4: The profiles of viscosity-mAb concentration for rituximab powder suspension in propylene glycol dicaprylate/dicaprate (Δ), in benzyl benzoate (◊), and in ethyl lactate (○).

Figure 5: Particle size distribution of rituximab suspensions in propylene glycol dicaprylate/dicaprate (◊), in benzyl benzoate (□), and in ethyl lactate (Δ).

Figures 6A-C: Photographs of rituximab suspension at 150 mg/mL in ethyl lactate after 2-week storage (6A), in ethyl lactate vortexed after 1-day storage (6B), and in propylene glycol dicaprylate/dicaprate after 2 weeks storage (6C). (Note: the tape is not part of the suspension but used for optical focusing during photo taking.)

Figures 7A and 7B: Rituximab suspensions. Figure 7A: Particle size distribution of rituximab suspensions in mixtures of propylene glycol dicaprylate/dicaprate and ethyl lactate at 100/0 (◊), 75/25 (■), 50/50 (□), 25/75 (♦), and 0/100 (Δ). Figure 7B: Photograph of rituximab suspension in 75/25 propylene glycol dicaprylate/dicaprate/ethyl lactate mixture

WHAT IS CLAIMED IS:

1. A suspension formulation comprising a spray dried monoclonal antibody at a concentration of about 200 mg/mL or more suspended in a non-aqueous suspension vehicle with a viscocity of less than about 20 centipoise at about 25 °C, wherein the non-aqueous suspension vehicle comprises propylene glycol dicaprylate/dicaprate.

2. The formulation of claim 1 wherein the viscosity of the suspension vehicle is less than about 10 centipoise at about 25 °C.

3. The formulation of claim 2 wherein the viscosity of the suspension vehicle is less than about 5 centipoise at about 25 °C.

4. The formulation of any one of the preceding claims wherein the injection glide force of the formulation is about 20 newton or less.

5. The formulation of claim 4 wherein the injection glide force of the formulation is about 15 newton or less.

6. The formulation of any one of the preceding claims wherein the average particle size in the formulation is from about 2 microns to about 30 microns.

7. The formulation of claim 6 wherein the average particle size in the formulation is from about 2 microns to about 10 microns.

8. The formulation of any one of the preceding claims wherein the antibody concentration in the formulation is from about 200 mg/mL to about 500 mg/mL.

9. The formulation of claim 8 wherein the antibody concentration in the formulation is from about 200 mg/mL to about 350 mg/mL.

10. The formulation of any one of the preceding claims further comprising a sachharide.

11. The formulation of claim 10 wherein the saccharide is trehalose or sucrose.

12. The formulation of claim 10 or 11 wherein the molar ratio of saccharide: monoclonal antibody is from about 50 to about 400:1.

13. The formulation of claim 12 wherein the molar ratio of saccharide: monoclonal antibody is from about 100 to about 250: 1.

14. The formulation of any one of the preceding claims further comprising a surfactant.

15. The formulation of claim 14 wherein the surfactant is polysorbate 20 or polysorbate 80.

16. The formulation of any one of the preceding claims which is suitable for subcutaneous administration.

17. The formulation of any one of the preceding claims wherein the monoclonal antibody is a full length monoclonal antibody.

18. The formulation of claim 17 wherein the monoclonal antibody is a human IgG1.

19. The formulation of any one of the preceding claims wherein the monoclonal antibody is a chimeric, humanized, or human antibody.

20. The formulation of any one of the preceding claims wherein the monoclonal antibody binds an antigen selected from the group consisting of: CD20, HER2, VEGF, IL6R, beta7, Abeta, HER3, EGFR, and M1'.

21. The formulation of claim 20 wherein the antibody is rituximab, trastuzumab, or bevacizumab.

22. A subcutaneous administration device with the formulation of any one of the preceding claims therein.

23. The device of claim 22, which comprises a pre-filled syringe.

24. A method of making a suspension formulation comprising suspending a spray dried monoclonal antibody in a non-aqueous suspension vehicle with a viscosity less than about 20 centipoise at 25 °C, wherein the monoclonal antibody concentration in the suspension formulation is about 200 mg/mL or more and wherein the non-aqueous suspension vehicle comprises propylene glycol dicaprylate/dicaprate.

25. A method of making an article of manufacture comprising filling a subcutaneous administration device with the formulation of any one of claims 1 to 21.

26. A suspension formulation comprising a spray dried full length human IgG1 monoclonal antibody at a concentration from about 200 mg/mL to about 400 mg/mL suspended in a non-aqueous suspension vehicle with a viscocity less than about 20 centipoise at 25 °C, wherein the formulation has an average particle size from about 2 microns to about 10 microns, and injection glide force less than about 15 newton; and wherein the non-aqueous suspension vehicle comprises propylene glycol dicaprylate/dicaprate.

27. The formulation of claim 26 which further comprises saccharide wherein the molar ratio of saccharide: monoclonal antibody is from about 100 to about 250:1.

28. The formulation of claim 26 or claim 27 wherein the antibody is rituximab, trastuzumab, or bevacizumab.

29. Use of the formulation of any one of claims 1 to 21 in the preparation of a medicament for treating a patient in need of treatment with the monoclonal antibody in the formulation.

30. The use of claim 29 wherein the formulation is for administration to the patient subcutaneously.

31. The use of claim 29 or 30 wherein the formulation is for administration using a pre-filled syringe containing the formulation therein.