PHARMACEUTICS, PREFORMULATION AND DRUG DELIVERY

High Concentration Formulation Feasibility of Human Immunoglubulin G for Subcutaneous Administration

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ABSTRACT: The delivery of monoclonal antibodies (mAbs) as subcutaneous (sc) injections hinges on the high dose requirement of these usually low potency molecules. This necessitates their formulation as high concentration solutions or suspensions, which presents a formidable formulation challenge due to the concentration-driven protein aggregation and high solution viscosity generated at these conditions. The objective of this study was to evaluate the feasibility of spray-drying in preparing stable, high concentration formulations of mAbs. A model polyclonal antibody, human immunoglobulin G (IgG) was formulated as dry powder using Nektar's glass stabilization technology. Formulation in sugar glasses stabilized IgG during spray-drying and maintained the protein's secondary structure. Further, in contrast to the bulk material, the glass-stabilized powders successfully reconstituted at 200 mg/mL IgG without loss of the protein monomer. Spectroscopic analysis confirmed that upon high concentration reconstitution, spray-dried glass-stabilized IgG retained both its secondary and tertiary structure. Further, the spray-dried powder reconstituted within a few minutes yielding clear, low viscosity solutions that syringed easily through narrow (28 G) needles. The results of this study suggest that formulation in spray-dried, glass-stabilized powders may enable the development of products suitable for sc administration of mAbs and other low potency protein therapeutics. J Pharm Sci 96:1504–1517, 2007

Keywords: high concentration protein delivery; monoclonal antibodies; human immunoglobulin G; spray-drying; protein formulation; stabilization; injectables; FTIR; circular dichroism

INTRODUCTION

Since the 1980s, antibodies have been considered as possibly powerful therapeutic agents, due to their exquisite specificity towards a variety of disease hosts, their possibly limited side effects, and their potential to move more rapidly from discovery to the clinic than other classes of drugs

Abbreviations: IgG, immunoglobulin G; mAb, monoclonal antibody; rhDNase, recombinant human deoxyribonuclease; PTH, parathyroid hormone; BSA, bovine serum albumin; SEC, size exclusion chromatography; HPLC, high performance liquid chromatography; USP, United States Pharmacopoeia; WFI, water for injection; RH, relative humidity; UV–Vis, ultraviolet–visible; FTIR, Fourier transform infrared; ATR, attenuated total reflectance; CD, circular dichroism; OD, optical density; FDA, Food and Drug Administration; sc, subcutaneous.

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(both small and macromolecules). However, it was not until the past decade that they came to fruition, primarily fueled by significant innovations in the development of human or humanized antibodies, better target identification and validation technologies, and feasible large scale manufacturing processes. Today, monoclonal antibodies hold a significant promise in the development of new, safe, and effective medicines treating a range of diseases. Cancer, cardiovascular diseases, and inflammation, are the areas where antibody-based treatments show the most promise, by virtue of their specific binding and subsequent neutralization of the cellular targets, which are involved in disease states. Currently, there are 14 approved mAb products,[1] with ~480 launched and developmental antibody programs worldwide, which represent more than 20% of all biotech drugs in late stage development. They represent the second fastest growing therapeutic protein class, with sales increasing by 38% in 2002 to $4150M and are expected to triple in value by 2008.

The majority of marketed mAb products, some of which are summarized in Table 1, are administered by intravenous infusion due to the high administered doses. Although in certain treatments this route of administration may be acceptable, it may present significant patient compliance, acceptability, and cost of treatment issues that render it undesirable. The limitations in the injection volumes required for subcutaneous (sc) administration (poor tolerance of volumes in excess of 1.5 mL) and the large dose requirements of antibody treatments (in excess of 100 mg, typically 100–400 mg) necessitate their formulation as high concentration solutions or suspensions. However, development of high concentration protein formulations poses significant challenges, primarily due to their susceptibility towards concentration-dependent aggregation and their tendency to form viscous solutions due to their high potential of inter-molecular interactions and macromolecular crowding in solution.

These issues have motivated antibody innovators and drug delivery providers to evaluate strategies to enable sc delivery of mAbs. Some of these rely on improving solution stability and reducing the viscosity of the high concentration protein formulations. Liu and Shire[2] have proposed that manipulation of the solution conditions, such as ionic strength, buffer species, and pH lead to a significant viscosity reduction of high concentration solutions of recombinant anti-IgE mAb (rhuMAb E25 and E26). However, it is anticipated that due to the high reactivity of proteins in the solution state, formulation in liquid dosage forms would be very challenging due to stability problems during both formulation development and long-term storage at room temperature.

Table 1. List of Marketed and Approved Monoclonal Antibody (mAb) Therapeutics (2005)

Brand Name	Indication	Antibody Type	Dose	Route of Administration	Dosage Form
Orthoclone-OKT3	Transplant rejection	Murine	5 mg	iv infusion	Solution
ReoPro	Blood clots, unstable angina	Chimeric	7.2 mg	iv infusion	Solution
Rituxan	Non-Hodgkin's lymphoma	Chimeric	375 mg/m^2	iv infusion	Solution
Zenapax	Transplant rejection	CDR-grafted	80 mg	iv infusion	Solution
Simulect	Transplant rejection	Chimeric	20 mg	iv infusion	Powder
Synagis	RSV[a]	CDR-grafted	15 mg/kg	im injection	Powder
Remicade	Crohn's disease, rheumatoid arthritis	Chimeric	3–10 mg/kg	iv infusion	Powder
Herceptin	Breast cancer	CDR-grafted	160 mg	iv infusion	Powder
Mylotarg	Myeloid leukemia	CDR-grafted	9 mg/m^2	iv infusion	Powder
Campath	CD52-positive chronic lymphocyte leukemia	CDR-grafted	30 mg	iv infusion	Solution
Zevalin	Spleen disease, non-Hodgkin's lymphoma	Antibody-conjugate	1.6 mg	iv injection	Solution
Humira	Rheumatoid arthritis	Fully human	40 mg	sc injection	Solution
Bexxar	Non-Hodgkin's lymphoma	Murine	450 mg	iv infusion	Solution
Xolair	Asthma	Fully human	150–375 mg	sc injection	Powder

[a]Respiratory syncytial virus.