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Bulky Polar Additives That Greatly Reduce the Viscosity of Concentrated Solutions of Therapeutic Monoclonal Antibodies

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ABSTRACT

The viscosity of concentrated aqueous solutions of 3 clinical monoclonal antibodies (mAbs), Erbitux®, Herceptin®, and Rituxan®, has been reduced up to over 10-fold by adding certain bulky polar additives instead of saline at isotonic levels. Because these additives are also found not to compromise mAbs' stability against aggregation induced by stresses, a drug-delivery modality switch from intravenous infusions to more convenient and inexpensive parenteral options like subcutaneous injections may become possible.

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Introduction

Although pharmaceutical use of monoclonal antibodies (mAbs) has become ubiquitous due to their exquisite target specificity and efficacy, there are major formulation challenges associated with this class of human drugs. Despite their specificity, the potency of mAbs is typically low; therefore, large doses—often as high as 3-8 mg/kg[1,2]—are required to achieve the desired therapeutic effect, which for an average adult could require upward of 500 mg of a mAb in a single dose. If a subcutaneous (SC) injection is contemplated, this dose in a <1.5-mL injection volume (the volume limit for SC injections)[3] results in a very concentrated (hundreds of mg/mL) and thick aqueous solution that is difficult to expel though standard 27- to 31-gauge needles.

The highly viscous texture of these solutions is due to multiple noncovalent intermolecular interactions, primarily hydrophobic and electrostatic ones, among mAb molecules that result in large transient networks of associated protein molecules that resist flow and hence exhibit great solution viscosities (Fig. 1a).[4,5] Consequently, many commercial therapeutic mAbs (e.g., the blockbuster drugs Erbitux®, Remicade®, Herceptin®, and Rituxan®) are administered intravenously (IV) because of the daunting challenges of developing and using their concentrated aqueous solutions. However, IV infusions require lengthy and inconvenient administration by health care professionals, generally in a doctor's office or clinical setting.[6] Also, in the United States, financial reimbursements for physicians to administer IV infusions are declining with the evolving health care landscape.[7,8]

Due to the foregoing and patients' preference for SC administration, as opposed to IV, there is a need for concentrated (>100 mg/mL) but still relatively nonviscous formulations of therapeutic mAbs.[6,9,10] An alternative approach toward this challenging goal is to circumvent the viscosity issues of concentrated solutions and focus on volume limitations of solutions injected into the SC space.[6,11] Such therapeutic mAbs as Herceptin® (trastuzumab) and Rituxan® (rituximab) have been coadministered with the enzyme hyaluronidase, which breaks down hyaluronan in the SC space, thus allowing injections of larger volumes; this approach still requires a skilled health care practitioner for administration.[6,10-12] In contrast, including the research reported in this paper, concentrated but low-viscosity SC aqueous formulations of mAbs can be created through the addition of viscosity-reducing additives.[13,14] These formulations could allow for at-home self-administration using a prefilled syringe.

In the present study, we have identified a library of commercially available additives that drastically reduce the viscosities of

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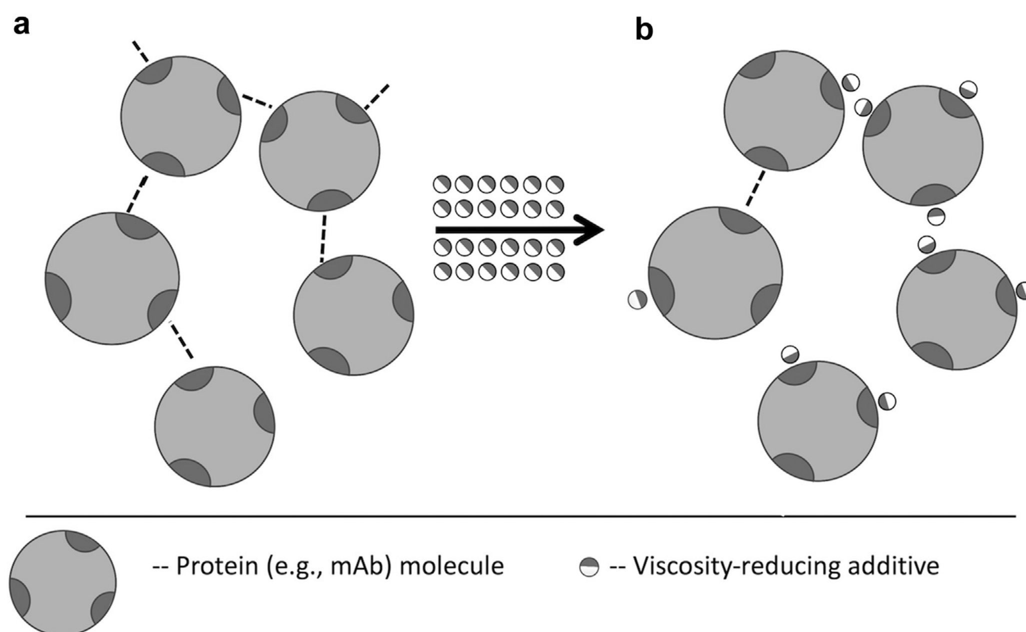

Figure 1. Schematic depiction of intermolecular interactions in a concentrated aqueous protein solution in the absence (a) and presence (b) of bulky cationic viscosity-reducing additives. On the left, the protein molecules, being in close proximity to each other due to a high concentration in solution, participate in multiple intermolecular interactions (such as electrostatic and hydrophobic) with the dark spots representing the sites of complementarity. These interactions generate transient extended networks of protein molecules, which resist flow and thus contribute to a high solution viscosity. When a molar excess of a viscosity-reducing additive is added to a solution (b), they outcompete the protein molecules for intermolecular interactions, thereby breaking up the transient protein networks responsible for high viscosity and allowing a freer flow of protein molecules (and hence yielding a less viscous solution).

concentrated aqueous solutions of the anticancer therapeutic mAbs Erbitux®, Herceptin®, and Rituxan® without compromising their stability during storage and freezing-thawing. Although the liquid mAb formulations described herein are at least 150 mg/mL, they still exhibit modest viscosities that would be unattainable without the use of our additives, thus permitting a SC dosing regimen.

Materials and Methods

Materials

Branded commercial mAbs (Erbitux®, Herceptin®, and Rituxan®) were purchased from Pharmaceutical Buyers International (New Hyde Park, NY) and biosimilar rituximab from Alpha mAb (Suzhou, China). Formulation additives were purchased from Sigma-Aldrich (St. Louis, MO) and Chembridge (San Diego, CA). Chemicals for buffer solutions were also from Sigma-Aldrich. All cationic additives were in the form of either their chloride or bromide salts, except for 1-butyl-3-methylimidazolium (BMI) which was the mesylate salt and chloroquine which was the phosphate salt. It should be noted that some of the additives used herein are also recognized as active pharmaceutical ingredients appearing in the Food and Drug Administration's Orange Book.

Preparation of mAbs for Viscosity Assessment

Herceptin® was reconstituted according to the manufacturer's instructions.[2] Briefly, for a 150-mg vial, 7.4 mL of sterile water was added to the lyophilized cake and the vial was gently swirled until complete dissolution. The other mAbs examined by us were in their commercially available liquid formulations. If present, polysorbate was removed with DetergentOUT™ Medi columns (G-Biosciences, St. Louis, MO) according to the manufacturer's instructions. The resultant protein solutions were then concentrated using Amicon® Ultra 15-mL centrifugal filters with a 30-kDa molecular weight cutoff at 5°C (EMD Millipore, Billerica, MA) until an intermediate concentration of approximately 100 mg/mL was reached. Alternatively, mAb samples were preconcentrated by tangential flow filtration (TFF) with a Minimate™ TFF System using the Minimate TFF Capsule (30 kDa, polyethersulfone membrane) (Pall, Port Washington, NY). After concentration, samples were discontinuously buffer-exchanged twice into the desired buffer condition using the aforementioned Amicon® Ultra 15-mL centrifugal filters.

For additive screening studies, following initial concentration, Erbitux® samples were buffer-exchanged into 10 mM phosphate buffer at pH 7.0 and then concentrated to above 200 mg/mL. Concentrated stock solutions (1.0 M) of a viscosity-lowering additive or NaCl (control) in 10 mM phosphate buffer at pH 7.0 were added to aliquots of the concentrated mAb solutions to generate samples of approximately 175 mg/mL protein and 0.15 M additive. When preparing additive stock solutions, pH adjustment with NaOH or HCl was often necessary to achieve desired pH values.

For pH-dependence studies, following initial concentration of Erbitux®, samples were buffer-exchanged into 10 mM phosphate/citrate buffer at pH 5.0, 6.0, or 7.0 and then subsequently concentrated to above 200 mg/mL. Concentrated solutions (1.0 M) of a viscosity-lowering additive or NaCl (control) in a 10 mM phosphate/citrate buffer at the same pH values were added to aliquots of the concentrated mAb solutions to generate samples of approximately 190 mg/mL protein and 0.15 M additive at the desired pH.

To obtain viscosity versus protein concentration curves, mAb samples were buffer-exchanged into a 10 mM phosphate buffer at pH 6.0 formulated with 0.15-M appropriate viscosity-lowering additive or NaCl (control). Samples were produced by concentrating the protein to above 220 mg/mL and then adding the necessary amount of 0.15 M additive or NaCl (control) solution (prepared in 10 mM phosphate buffer at pH 6.0) to achieve several intermediate protein concentrations. Measured viscosity values

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