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Impact of formulation viscosity on delivery of biotherapies

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Over the past 10 to 15 years, interest in the development of bio-therapeutic agents targeting a wide array of autoimmune disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease has increased dramatically. Most recently, immunotherapy using specific types of antibodies has also shown significant promise in the treatment of cancer. Biologics are typically injected parenterally, due to poor oral bioavailability, and for many indications, subcutaneous delivery is preferred over intravenous infusion based on increased patient convenience and reduced treatment cost. However, subcutaneous dosing can present special challenges for formulation and delivery of bio-therapeutics, particularly at high doses, as dose volumes for subcutaneous injection are limited. The viscosity of highly concentrated protein formulations can have substantial impact on injectability, and this is further compounded by the fine needle gauges generally used to minimize injection discomfort for subcutaneous products. In order to develop a successful product, it is, therefore, important to understand the contributions that the active molecule and other formulation components make to overall solution viscosity and syringe ability. The present work describes studies conducted to investigate and model the effect of protein type and concentration, as well as added excipients, on formulation viscosity, and the impact of viscosity on drug delivery through a syringe and needle system. Results of these studies showed that viscosity increased nonlinearly with protein concentration, and different proteins contributed differently to formulation viscosity, with PEGylated proteins having a high PEG to protein ratio showing 10 to 100 fold higher viscosity than monoclonal antibodies (mAbs) in a concentration range of 10 to 50 mg/mL protein. For the proteins PEGylated with 20 to 40 kD PEGs, viscosity increased with PEG chain length and was also impacted by degree of chain branching. Unlike mAbs, the minimum viscosity of formulations containing PEGylated proteins was controlled by the intrinsic viscosity of the PEG and could, therefore, not be likely reduced by addition of excipients such as sugars or amino acids. Rather, addition of excipients tended to increase formulation viscosity. The impact of viscosity on injectability (required injection force) of proteins depended on multiple factors including the dose to be delivered, syringe size, needle gauge, and injection time. A case study is presented for modeling these factors to facilitate an assessment of the develop ability of protein-based therapeutics.

Biography

William Ying received his MS graduate training in Chemical and Environmental Engineering from Illinois Institute of Technology. He is currently a senior scientist in Drug Product Science and Technology of Bristol Myer Squibb, a large global biopharmaceutical company in many therapeutic areas, including cancer, HIV/AIDS, cardiovascular disease, diabetes, hepatitis, rheumatoid arthritis and psychiatric disorders. He has 20 years of industrial experience in formulation and delivery of small molecules, peptides and proteins as drugs used in the areas of immunology, virology, cardiology, oncology, and immuno-oncology.

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