# Injectability /Viscosity Analysis for High-Concentration Monoclonal Antibody Formulations

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## PURPOSE

Developing high-concentration mAb formulations (≥ 150 mg/mL) for subcutaneous delivery is now in great demand. The mAbs with high concentrations usually exhibit high viscosity and physical instability of the protein due to changes in colloidal properties resulting in aggregation, making administration by injection a challenge. Therefore, strategies for developing high-concentration antibody formulations require several considerations, such as the selection of excipients- stabilizers, buffer, pH to create a suitable environment for the antibodies/proteins to remain in solution and to also have attributes like lower viscosity to allow for administration by injection. Viscosity, syringeability, and injectability, therefore is an essential and important part of the strategy to develop high-concentration antibody formulation for subcutaneous administration. In this study, the injectability of antibody formulations is discussed.

## OBJECTIVE(S)

The objectives are to evaluate the injectability of high-concentration antibody formulations at about 150-210 mg/mL, using Stability FingerPrinting ®. The correlation of concentration and viscosity with respect to injectability is presented.

## METHOD(S)

To obtain concentrated antibody formulations, suitable buffer, pH, and excipients were evaluated by an iterative process utilizing Stability Fingerprinting®. The viscosity of formulations was measured using an EMS-1000s viscometer. The injectability was determined using a Texture analyzer where initial break-loose force, dynamic glide force, and maximum force were measured using 25, 27, and 30G BD needles with 2.2 mL fill. The force measurement consisted of a displacement rate of the formulation filled in a syringe that related to an injection rate.

## RESULT(S)

Three antibody formulations (≥150 mg/mL) for subcutaneous delivery were developed through an iterative process of selecting suitable buffer, pH, stabilizers, and surfactants. The lead formulations for the three antibodies evaluated are presented below. The formulations for three antibodies used to understand the viscosity and injectability are listed in Table 1.

Table 1: List of High concentration mAbs with viscosity ≤20 cP

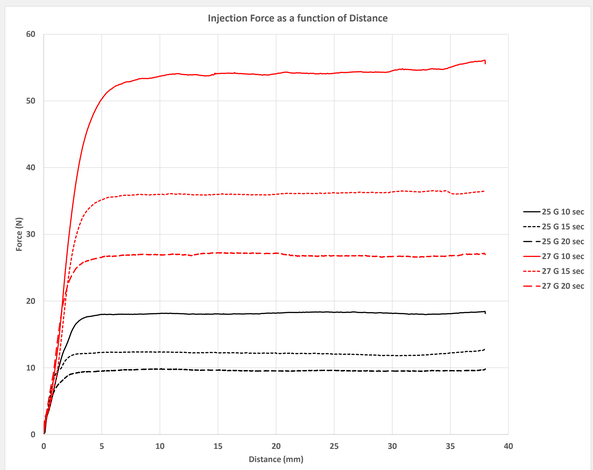
| Antibody | pH | Excipients | Concentrations (mg/mL) | Viscosity (cP) |
|---|---|---|---|---|
| mAb1 (IgG1) | 5.5 | Histidine, Trehalose, Methionine, Polysorbates 20 | 150 | 14 |
| mAb2 (IgG2) | 5.3 | Acetate, Proline, Sorbitol, Mannitol, Poloxamer | 210 | 18 |
| mAb3 (IgG2) | 6.2 | Histidine, Arginine, Glutamic acid, Sorbitol, Polysorbates 80 | 200 | 20 |

The key parameters for injectability assessed are break-loose force, dynamic glide force, and maximum force. The break-loose force is the force required to initiate the movement of the plunger. The dynamic glide force is the force required to sustain the movement of the plunger. The maximum force is the highest force measured before the plunger finishes its course. Each antibody was tested at three injection rates and three-needle gauges; the results for 15-sec injections are listed in Table 2. An aqueous glycerol solution with a viscosity of 21.5 cP was also studied for injectability as a control. A representative profile of injectability for the antibody at 150 mg/ml, using 25G and 27G needles, is presented in Figure 1. The data also indicates there is a good correlation of viscosity vs injection force with polynomial order 2 with a correlation of 1.0 (Figure 2)

Table 2: Dynamic Glide Force (N), Initial breakthrough force (N), and Maximum force (N) for 15-sec injections.

| Formulation | Viscosity (cP) | 25 G 5/8" needle | 27 G 1/2" needle |
|---|---|---|---|
| | | Dynamic Glide Force (N) | |
| mAb1 (IgG1) | 14 | 12.28 | 36.19 |
| mAb2 (IgG 2) | 18 | 15.91 | 41.81 |
| mAb3 (IgG 2) | 20 | 20.67 | 41.62 |
| 72 % w/w Glycerol | 21.5 | 18.97 | 51.80 |
| | | Initial Break Through Force (N) | |
| mAb1 (IgG1) | 14 | 12.42 | 35.75 |
| mAb2 (IgG 2) | 18 | 15.95 | 41.19 |
| mAb3 (IgG 2) | 20 | 20.74 | 40.89 |
| 72% w/w Glycerol | 21.5 | 19.22 | 52.26 |
| | | Maximum Force (N) | |
| mAb1 (IgG1) | 14 | 12.52 | 36.93 |
| mAb2 (IgG 2) | 18 | 16.16 | 42.17 |
| mAb3 (IgG 2) | 20 | 21.01 | 42.39 |
| 72 % w/w Glycerol | 21.5 | 19.28 | 53.01 |

Figure 1: Injectability of mAb1 (150 mg/mL) using 25G and 27G needles



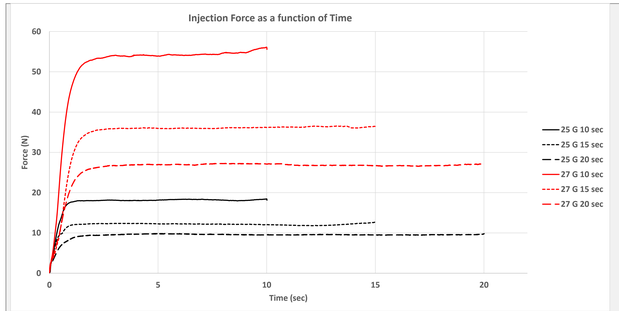
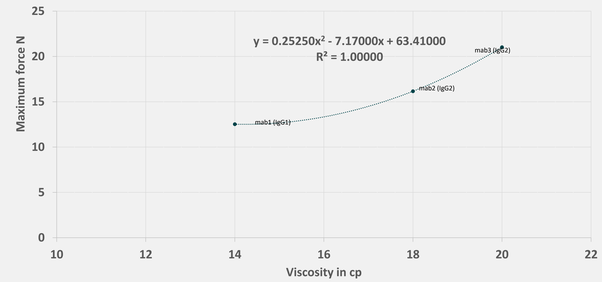




Figure 2: Correlation between viscosity and injection force N




## CONCLUSION(S)

The high-concentration antibody formulations were obtained by an iterative process through Stability Fingerprinting®. Injectability tests allowed for the characterization of high concentration antibody formulations with respect to initial breakthrough force, dynamic glide force, and maximum force. The data for 25G and 27G needles obtained helped in the selection of delivery rate based on formulation viscosity and suitable injection force. Although the dynamic glide force for 27G needles at lower viscosity was 2-3 times the force measured for 25G needles in the 15-sec injection, it is within the acceptable range for injectability of Injection Force < 20 N and maximum injection force of 40 N.