Viscosity/Injectability of Monoclonal Antibody Powder Suspension Formulations

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Some Proteins ONLY Show Efficacy at High Doses

Bolus injection?    IV infusion?

Figure source: Dr. T. Kararli, PharmaCircleDatabase, survey of 250+ MAbs, from phase 1 to launch Robin Hwang, 2011 AAPS-NBC, May, 2011, San Francisco, CA, USA
Formulation Approaches in SC Delivery of High Dose mAbs

• High dose of mAbs in small volume
  – Develop high concentration aqueous solution formulations
  – Develop highly concentrated suspension/dispersion formulations

• Low mAb concentration with large volume
  – Halozyme formulations with patch pump
Problems Observed at High Concentration Biologics Formulations

- Protein instability (soluble and insoluble aggregates) during formulation process and storage
- Very difficult to be processed and manufactured
  - High viscosity
  - Gelation (e.g. mAb > 200 mg/ml, clogged filter/gelation observed)
- High injection force during administration
Highly Concentrated Biologics Suspension Formulation Approach

Principle

Instead of being dissolved in a delivery vehicle, biologics are suspended as solids, allowing delivery of high dose biologics in small volume (<2 mL) while maintaining required stability.

Approaches

- Aqueous suspensions
- Nonaqueous suspensions
Challenges in Biologics Suspension Formulations

Examples

• Viscosity/Injectability
• Protein stability
• Biocompatibility
• Manufacturing (processability/scale up, sterility, etc.)
Case study

• mAb X, MW ~150kD
  – Difficult challenge in formulating mAb X in an aqueous solution at >150 mg/mL due to the protein stability/high viscosity

• Approach: Formulate mAb powders in non-aqueous vehicles to reduce the viscosity and improve protein stability
  – mAb powders were prepared by spray drying process and the suspensions prepared from lyo mAb powders were not injectable
  – Excipients: commonly used protein stabilizers, surfactants, etc.
  – Non-Aqueous vehicles: Examples include sesame oil, linoleic acid, ethyl oleate, propionic acid, triethyl citrate, isopropyl alcohol, ethanol, diethyl sebacate, or isopropyl myristate, etc
Preparation of Non-Aqueous Suspension Formulations

1. Particle engineering

2. Suspension mixing

3. Suspension filling

- Spray-dried mAb particles
- Nonaqueous vehicles
  Example: Sesame oil
- Homogenization
- Load to syringe
- Couple with Device for commercialization

Mix protein particles with vehicle

Nonaqueous suspension
Characterization of mAb Suspension Formulations: Viscosity and Injection Force

- **Viscosity**
  - Measured as a function of shear rate between 200 to 5000 s\(^{-1}\) at 25\(^{\circ}\)C by using AR2000 Rheometer (TA Instruments), and calculated by averaging the values between the measured shear rates.

- **Injection force**
  - Measured by loading prepared formulations into syringes equipped with a 0.5 inch 26 ½ gauge needle, setting the injection rate at 250 mm/minute and recording the piston travel force using a Zwick/Roell model, 2005.
Viscosity/Injection Force Increases with Spray-Dried mAb Particle Loadings in the Suspensions

- SD mAb particles 20wt% = 100mg mAb/mL and 40wt% = 200mg mAb/mL
- 8 µm SD mAb particles
How Can the Viscosity/Injection Force of mAb Suspension Formulations be Reduced?

Key Factors to be considered

- **Formulations**
  - Spray-Dried (SD) mAb Particle loadings
  - Vehicle viscosity
  - Particle properties (size and size distribution, morphology and porosity/density)

- **Syringes/needles** (barrel radius, material of plunger/barrel, needle radius, and length)

- **Injection rate**
  \[ F = \frac{8\eta LV}{4r_{\text{needle}}} R_{\text{barrel}}^2 + f \]
  - \( \eta \): Viscosity
  - \( L \): Needle length
  - \( V \): Injection rate
  - \( R_{\text{barrel}} \): Radius of barrel
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Suspension Viscosity Increases with Vehicle Viscosity

- Injection Force is proportional to viscosity for same syringes

- At high shear rate, for same particles and same weight fraction in different vehicle ratio, the dependence is reduced to $\eta_0$, **Vehicle viscosity**

\[
(F - f)_{vb1} = \frac{\eta_{0,vb1}}{\eta_{0,vb2}}
\]
Use of Low Viscosity Vehicles Reduce Injection Force of the Suspension Formulations

Sesame oil viscosity: ~50 cp, ethyl oleate viscosity ~10 cp
mAb Suspensions Exhibit Shear Thinning Behavior

- Shear thinning is significant in highly concentrated suspension formulations.
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Suspensions with Smaller SD mAb Particle size Have Higher Injection Force

Decrease in SD mAb particle size results in an increased number of particles for given wt% suspension, leading to high injection force, in particular at high mAb particle loadings.
Spray-Dried mAb Particles Have Different Morphologies

Spherical spray dried mAb

Donut like (partially collapsed) spray dried mAb
SD mAb Particle Size has a Greater Impact on Injection Force than Particle Morphology
Injection Force for Suspensions Increase as the Bulk Density of the mAb Particles is Reduced

- Bulk density/porosity impacts the volume fraction of particles in the suspension, further impacting viscosity/injectability

- 8 µm Porous particles have been obtained using blowing agent (ammonium carbonate) in the process

![Non-porous; Bulk density 0.3g/cc](image1)

![Porous; Bulk density 0.15g/cc](image2)

![Graph](graph.png)

- Bulk density 0.3 g/cc
- Bulk density 0.23 g/cc
- Bulk density 0.15 g/cc
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Needle Gauge Effect: Increasing Needle Diameter Reduces the Injection Force Significantly

\[ F = \frac{8\eta LV}{r_{needle}^4} R_{barrel}^2 + f \]
Syringe Configuration Affects Injection Force

Smaller barrel radius leads to low injection force

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Slow Injection Rate Leads to Low Injection Force of the Suspension Formulations

BD Syringe: (0.5ml volume)

- 250mm/min
- 125mm/min

Injection Force (N) vs. Viscosity (cp)
Summary

- Viscosity/injection forces of the suspension formulations increases with mAb particle loading in the suspensions. This can be reduced by using low viscosity formulation vehicles.

- Small-size mAb particles lead to an increase in the viscosity/injection force of the suspension formulations, and spherical particles are preferred in terms of injection force.

- Suspension viscosity/injection force increases as bulk density of mAb particles decreases.

- mAb suspension formulations exhibit shear thinning behavior.

- Injection force of the suspension formulations reduces significantly by increasing needle’s inner diameter and reducing barrel radius of the syringe.

- Injection force of the suspension formulations decreases with a slow injection rate.

- Non-aqueous mAb suspensions exhibit typical suspension viscosity behavior.
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