Best practices for high concentration Ultrafiltration Applications

Subhasis Banerjee, Ph.D.
Group Manager, BSN, Merck Millipore

Biowavers, Biologics & Biosimilar Conference; Hyderabad, Oct 2014
Overview

■ Driver for high protein concentration (HPC) in Biologics.
■ Challenges in processing HPC using UF.
■ New UF cassette development for HPC applications.
High Concentration Drivers for Biologics

- High patient doses required for biological products (mAbs):
  - ~1-3mg/kG (→ upto 10 mg/kg)

- Intravenous (IV) infusion – traditional delivery method
  - Issues: Infusion side effects, cost, quality of life, patient compliance
High Concentration Drivers for Biologics

- High patient doses required for biological products (mAbs):
  - ~1-3mg/kG (→ upto 10 mg/kg)
- Intravenous (IV) infusion – traditional delivery method
  - Issues: Infusion side effects, cost, quality of life, patient compliance
- Subcutaneous administration (Sub-Q) preferred by patients

<table>
<thead>
<tr>
<th>Table 1 Selected drugs in development using alternative delivery a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Company (location)</strong></td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Abbott</td>
</tr>
<tr>
<td>Novartis</td>
</tr>
<tr>
<td>Biogen Idec/Genentech/Roche</td>
</tr>
<tr>
<td>GlaxoSmithKline/Genmab (Copenhagen)</td>
</tr>
<tr>
<td>Roche</td>
</tr>
<tr>
<td>Roche</td>
</tr>
</tbody>
</table>

SubQ, subcutaneous
aComplete table available online. bFDA approved for other delivery modes and/or indications.
High Concentration Drivers for Biologics

- Subcutaneous injection Issues/Requirements
  - Needle phobia and pain of injection
Subcutaneous injection Issues/Requirements

- Needle phobia and pain of injection
  
  - Studies show that increasing injection vol from 0.5 ml to 1 ml increases pain significantly
  
  - Target injection vol < 1 ml
    
    - For a 2-3 mg/kg dose, for a 70 kg person → 140-210 mg dose; if injection vol. needs to be less than 1 ml, we are talking about a protein concentration of > 140-210 g/L

Sub-Q injections require **high conc.** protein formulations
Challenges with High Concentration of Proteins

- Potentially significant changes in solution properties
  - Viscosity → mechanical processing, drug delivery
  - Osmotic Pressure → max conc in a TFF process
  - Thermodynamic properties (excluded volume, donnan) → impurity clearance in diafiltration
Challenges with High Concentration of Proteins

- Viscosity and Osmotic effects may combine to limit the ‘Max’ achievable concentration in a TFF process
- Let’s see how?
- Viscosity increases non-linearly with concentration

Burckbuhler, V., European Journal of Pharmaceutics 2010
Viscosity Effects

- Viscosity increases non-linearly with concentration
  - Varies widely with mAb type for a given concentration
Viscosity Effects – TFF Processing

- Pressure drop in a TFF system

\[ \text{TMP} = \frac{\Delta P_M}{2} + \Delta P_{\text{Valve}} + \Delta P_{\text{System}} - P_P \]
Pressure drop in a TFF system \( \uparrow \) as viscosity \( \uparrow \)

- Cassette resistance dominates for a given flow geometry
Viscosity Effects – TFF Processing

- For a given flow, viscosity, cassette resistance determined by geometry:
  - Channel size, screen type

  ![Diagram showing different screen types: Open, Suspended, Coarse, Fine]

  - **A** screen “fine” - High pressure drop
  - **C** screen “coarse” - Medium pressure drop
  - **V** screen “suspended” - Very Low pressure drop

Screen variables
- Weave pattern, wire diameter, mesh count, mesh opening, overmolding, orientation, etc.

DaCosta, A., JMS 1994
Viscosity Effects – TFF Processing

- For a given flow, viscosity, cassette resistance determined by geometry:
  - Channel size, screen type

![Diagram showing different types of screens: Open, Suspended, Coarse, Fine.]

![Graph showing differential pressure vs. bovine serum concentration at constant retentate flow. Legend includes V-Screen, A-Screen, C-Screen, and V-Screen @ 15L/min/m².](image-url)
Osmotic Pressure Effects – TFF Processing

- Osmotic pressure resulting from concentration difference between membrane wall (Cw) and permeate (Cf≈0)

\[
\Delta \Pi = \frac{R T}{V_m} \ln \left( \frac{C_w}{C_f} \right)
\]

- Applied TMP must be > osmotic pressure to force permeate flow
  - Modules and equipment limit maximum TMP

\[
J = L_p (\text{TMP} - \Delta \Pi)
\]

... Osmotic Pressure Model
How do high viscosity & osmotic pressure affect TFF processing?

- Permeate flux through a TFF membrane:
  - Is determined by excess TMP over osmotic pressure
  - Depends on mass transfer coeff (flow, geom) and solute conc.

\[ J = L_p (\text{TMP} - \Delta \Pi) \]
\[ J = k \ln \left( \frac{C_{gel}}{C_{bulk}} \right) \]
Example – Permeate flux vs Concentration for Tight and Open screens

- We notice that V-screen $C_{gel}^{open} > C$-Screen $C_{gel}^{tight}$.

\[
J = 19.3 \ln \left( \frac{242}{C} \right)
\]

---

<table>
<thead>
<tr>
<th></th>
<th>IVIG Concentration (g/L)</th>
<th>Permeate Flux (LMH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>398</td>
<td>C 5LMM</td>
</tr>
<tr>
<td>Tight</td>
<td>242</td>
<td>V 9LMM</td>
</tr>
</tbody>
</table>

\[
J = 9.2 \ln \left( \frac{398}{C} \right) \quad R^2 = 0.895
\]

\[
J = 19.3 \ln \left( \frac{242}{C} \right) \quad R^2 = 0.9593
\]
High final concentrations achievable at lower feed flows and more open feed channel!

- **Develop** a more optimum feed channel for high conc (high viscosity) apps
  - Existing C-Screen too tight, V-Screen possibly too open → optimum probably in-between

- Trade-off: lower permeate flux, larger membrane area
■ Product need:
  – What is the right screen size? What viscosity do we target?
Viscosity Target – Estimation

- High viscosity impacts the ability to load and deliver drug from the syringe

\[ F = \frac{8Q\eta L}{R_{\text{needle}}^4 A_{\text{syringe}}} \]

- At a given force, flow (Q) is proportional to
  - fourth power of needle radius
  - Inversely to viscosity
- If needle is too narrow
  - Require High force or Slow flow
  - Unreasonable time for patient to hold PFS during injection
    - >20 sec
High viscosity impacts the ability to load and deliver drug from the syringe.

Fig A: Viscosity (solid line, open circles) and syringe (27 gauge) loading time (dashed line, solid triangles) of a monoclonal antibody as a function of concentration.

Shire et al, J. of Pharm Sci, V93, NO. 6, JUNE 2004
Viscosity Target – Estimation

- High viscosity impacts the ability to load and deliver drug from the syringe
  - Manual injection force limited to 10-30 N
  - Typical sub-Q needle size range between 25-27 gauge*

![Viscosity Chart]

**SC delivery limited by**
- Viscosity ~30cp
- Needle Size
- Injection Flowrate

*Burckbuchler, V., European Journal of Pharmaceutics 2010

*http://en.wikipedia.org/wiki/Needle_gauge_comparison_chart*

*http://www.bccdc.ca/NR/rdonlyres/24C36473-261A-4FB8-8A41-444B3520DB64/0/SectionIV_AdministrationofBiologicalProducts_June2012_.pdf*
Other Viscosity Reduction Techniques

- Viscosity may be reduced by appropriate excipients
  - Ex. Addition of salt may reduce viscosity

Fig: Viscosity (solid line, open circles) and syringe (25 gauge) loading time of a monoclonal antibody at 125 mg/mL as a function of NaCl concentration.

Shire et al, J. of Pharm Sci, V93, NO. 6, JUNE 2004
High Viscosity (Protein Conc) TFF Cassette

Too Open for HC Apps

Too tight for HC Apps

Develop the ‘Just Right’ Size
Pressure drop vs Concentration & Xflow:

At 8 L/min/m² cross flow rate

HV Cassette screen (‘D’ Screen) \( \Delta P \sim 50\% \) of C screen \( \Delta P \)

\[ \Delta P = K \mu J_F \]
The HV TFF Cassette – “Preview”

Flux vs. Concentration & Xflow:

At 8 L/min/m² cross flow rate

HV TFF Cassette –Cross Flow Effects

HV Cassette (D) screen J~ 80% of C screen J
do you think talking about D-screen is OK and people may ask about the launch time
M176127, 20-09-2013
<table>
<thead>
<tr>
<th>Product Attribute</th>
<th>Performance Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final viscosity</td>
<td>&gt; 25 cP</td>
</tr>
<tr>
<td>Feed channel ΔP-water</td>
<td>2-6 psi</td>
</tr>
<tr>
<td>Feed channel ΔP-mAb</td>
<td>50% of C screen at ≥ 25 cP</td>
</tr>
<tr>
<td>Mass transfer k*</td>
<td>≥ 150% of V-screen ≥ 80% of C-screen</td>
</tr>
<tr>
<td>Membrane Area</td>
<td>≈ 0.5 X of V-Screen</td>
</tr>
<tr>
<td></td>
<td>≈ 1.2 X of C-Screen</td>
</tr>
</tbody>
</table>

*Mass transfer coefficient is compared at the same cross flow rate.

†At 8 L/min/m² cross flow rate

- Enables the TFF process to optimally get to high protein concentrations required for Subcutaneous drug delivery
Thank You!

Acknowledgements
Herb Lutz
Joseph Parrella
Bala Raghunath