Purification of Nanoparticles by Hollow Fiber Diafiltration
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Abstract

Hollow Fiber Diafiltration (Hollow Fiber Tangential Flow Filtra-
tion) is an efficient and rapid alternative to traditional meth-
ods of nanoparticle purification such as ultracentrifugation,
stirred cell filtration, dialysis or chromatography. Hollow Fiber
Diafiltration can be used to purify a wide range of nanopar-
ticles including liposomes, colloids, magnetic particles and
nanotubes.1,2 Hollow Fiber Diafiltration is a membrane based
method where pore size determines the retention or trans-
mission of solution components. It is a flow process where
the sample is gently circulated through a tubular membrane.
With controlled replacement of the permeate or (dialysate),
pure nanoparticles can be attained. Hollow Fiber Diafiltration
can be directly scaled up from R&D volumes to production.
By adding more membrane fibers and maintaining the oper-
ating parameters, large volumes can be processed in the
same time with the same pressure, and flow dynamics as
bench-scale volumes.

Keywords: hollow fiber, diafiltration, filtration, purification, tangential flow filtration

Materials and Methods

A 100 kD polysulfone hollow fiber module (Spectrum Labs
MiniKros® Sampler Plus P/N M4AB-260-01P) was selected
based upon the unreacted by-product molecular weight (<50
kD) and the polymeric nanoparticle (250kD). The tubular
geometry of the hollow fiber is beneficial to particle applica-
tions due to the phenomenon known as tubular pinch effect
where particles migrate to the center of the hollow fiber where
flow velocity is the highest.3 1200 mL of an 8% polymeric
nanoparticle solution was used in a bench scale diafiltration.
Discontinuous diafiltration was selected for the application
due to the high viscosity, 500 cps. Initial dilution of the product
would provide the best performance for permeate flow rate
and process pressures and achieve better mixing of the
diafiltration buffer with the polymeric solution. A bench scale
Tangential Flow Filtration development system with data
acquisition software and pressure indicator (Spectrum Labs
KrosFlo® Research II P/N SYR2-S21-01N) was used for the
process.

Results

1200 mL of the solution was poured into a 4 L TFF process
reservoir (Spectrum Labs P/N ACTO-4PP-01N) and diluted
to 2400 mL with DI water. The feed pump was set to a feed
flow rate of 950 mL/min to begin the process. This feed flow
rate was selected to provide an even laminar flow process
with a shear rate of 4000 s⁻¹. Figure 1 illustrates the relation-
ship between flow/fiber and shear rate. Retentate backpres-
sure was applied using a gauge down tubing diameter
approach to reach a transmembrane pressure (TMP) of 20
psig with a feed-to-retentate pressure drop of 7 psig.
Discussion

As expected, the process pressures cycled with each dilution, climbing during the concentration from 4% to 8% and then falling back to their initial values with each dilution. This increase in pressure is caused by the increase in viscosity and polymer concentration at the membrane surface during the concentration and is typical for Tangential Flow Filtration processes. The permeate flow rate per unit of membrane area, also referred to as the process flux, ranged from 15-20 L/M²/hr following the concentration of the polymeric nanoparticle. As indicated by the sample analysis, the removal efficiency of the by-product (rejection coefficient) was nearly 50% higher due to the shift in concentration factor based on the viscosity of the process material therefore impacting the permeability of the solute removed as expressed below:

\[ Y = 1 - \left( \frac{V_O}{V_R} \right)^{1/n} \]  \hspace{1cm} (2)

\( Y = \% \ Permeate \ Solute \ Removed \)
\( \frac{V_O}{V_R} = \text{Volume Change Ratio} \)
\( n = \text{number of stages} \)
\( R = \text{Rejection Coefficient} \)

The removal efficiency of diafiltration is dependent upon how easily the small molecular weight by product passes through the membrane. The concentration of the retained material at the membrane surface during the TFF (Tangential Flow Filtration Process) plays a significant role in the transmission of the smaller molecules. Transmission is calculated by measuring the concentration of the byproduct in the permeate stream and dividing it by the concentration of the byproduct in the retentate stream.

\[ \%T = \frac{\text{conc}_{PERM}}{\text{conc}_{FEED}} \times 100\% \]  \hspace{1cm} (3)

Analysis by HPLC and functional assays showed that the transmission of the by-product in this experiment started at 59% and decreased with each diafiltration volume to 43%. Many diafiltration processes with less viscous starting solutions exhibit transmission of 90 to 100% and require only 4-5 diafiltration volumes to reduce small MW molecules to minimum levels.

The results of several R&D scale tangential flow filtration diafiltration experiments prompted the rapid scale-up of the process to a 12 L pilot scale batch volume. To determine the membrane area required for the scale-up, assuming product concentrations were to be identical at both scales, a linear factor of process volume/membrane area was used.

Therefore, for the 12 L pilot scale volume, 100 kD polysulfone hollow fiber module with 0.57 M² of membrane (Spectrum Labs MiniKros® P/N K5AB-050-01P) was used. With a count of approximately 1800 fibers, and 20 cm fiber length a shear of 4000 sec⁻¹ was again utilized at a feed flow rate of 5.2 LPM.

Permeate flux, process time and final product yield of the 12 L process reproduced the bench scale measurements. The only anticipated difference was that slightly higher feed-to-retentate P was measured at the pilot scale due to the longer fiber length (20 cm vs 12 cm at the R&D scale). The following table presents the scalability results.

<table>
<thead>
<tr>
<th>Area</th>
<th>Shear (psid)</th>
<th>( \Delta P @ 4% ) (psid)</th>
<th>( \Delta P @ 8% ) (psid)</th>
<th>Flux (LMH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>615 cm²</td>
<td>4000</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>(bench)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.57 M²</td>
<td>4000</td>
<td>6</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>(pilot)</td>
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References

