Purification of Nanoparticles by Hollow Fiber Diafiltration

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ABSTRACT

Hollow Fiber Diafiltration (Hollow Fiber Tangential Flow Filtration) is an efficient and rapid alternative to traditional methods of nanoparticle purification such as ultracentrifugation, stirred cell filtration, dialysis or chromatography. Hollow Fiber Diafiltration can be used to purify a wide range of nanoparticles including liposomes, colloids, magnetic particles and nanotubes.[1,2] Hollow Fiber Diafiltration is a membrane based method where pore size determines the retention or transmission 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 operating 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 100kD polysulfone hollow fiber module (Spectrum Labs MiniKros® Sampler Plus P/N M4AB-260-01P) was selected based upon the unreacted by-product molecular weight (<50kd) and the polymeric nanoparticle (250kD). The tubular geometry of the hollow fiber is beneficial to particle applications 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 $4000s^{-1}$. Figure 1 illustrates the relationship between flow/fiber and shear rate. Retentate backpressure 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.

$$TMP = \frac{P_{feed} + P_{retentate}}{2} - P_{permeate} \qquad (1)$$

Permeate collection began in a graduated cylinder to monitor process volumes and permeate flux. When the collected permeate volume was equal to the initial volume (1200mL), samples of the process were taken for analysis and the product was diluted twofold again to 4%. This dilution volume is referred as one diafiltration volume. This procedure was repeated nine times. The data acquisition program collected pressure and flow rate data results, critical to the direct scaling to larger volumes, throughout the process and provided a process chart in real time (Figures 2 and 3).

Figure 1
Correlation of Flow Per Fiber and Shear
for Three Standard Lumen ID fibers

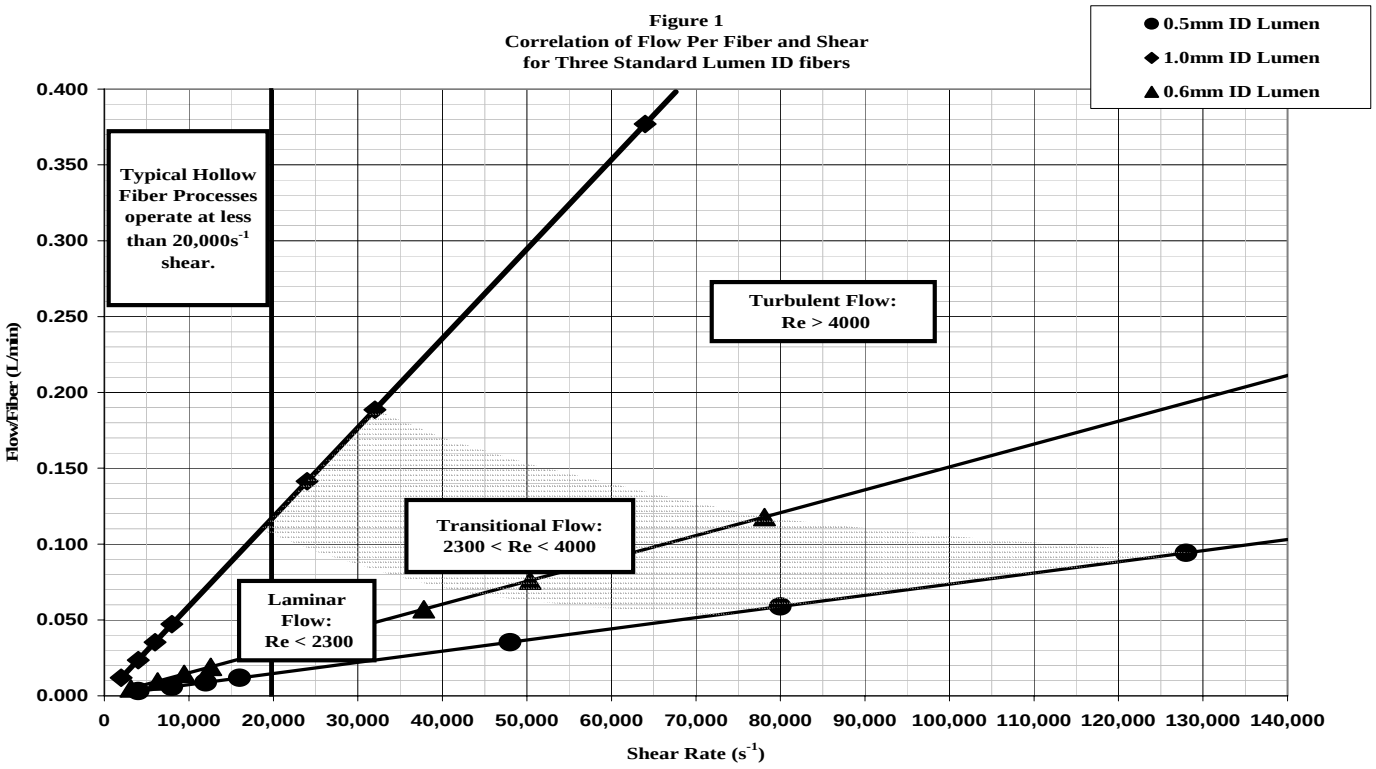
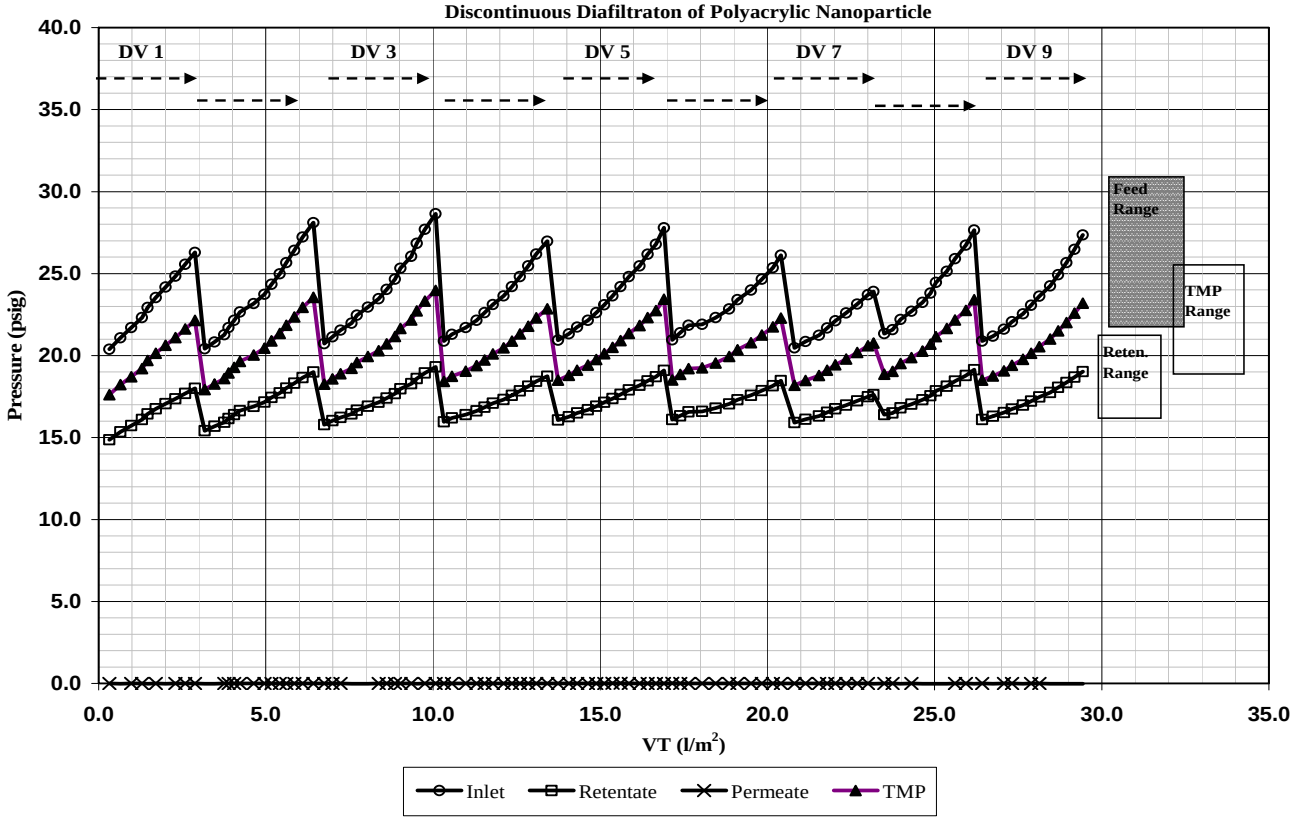
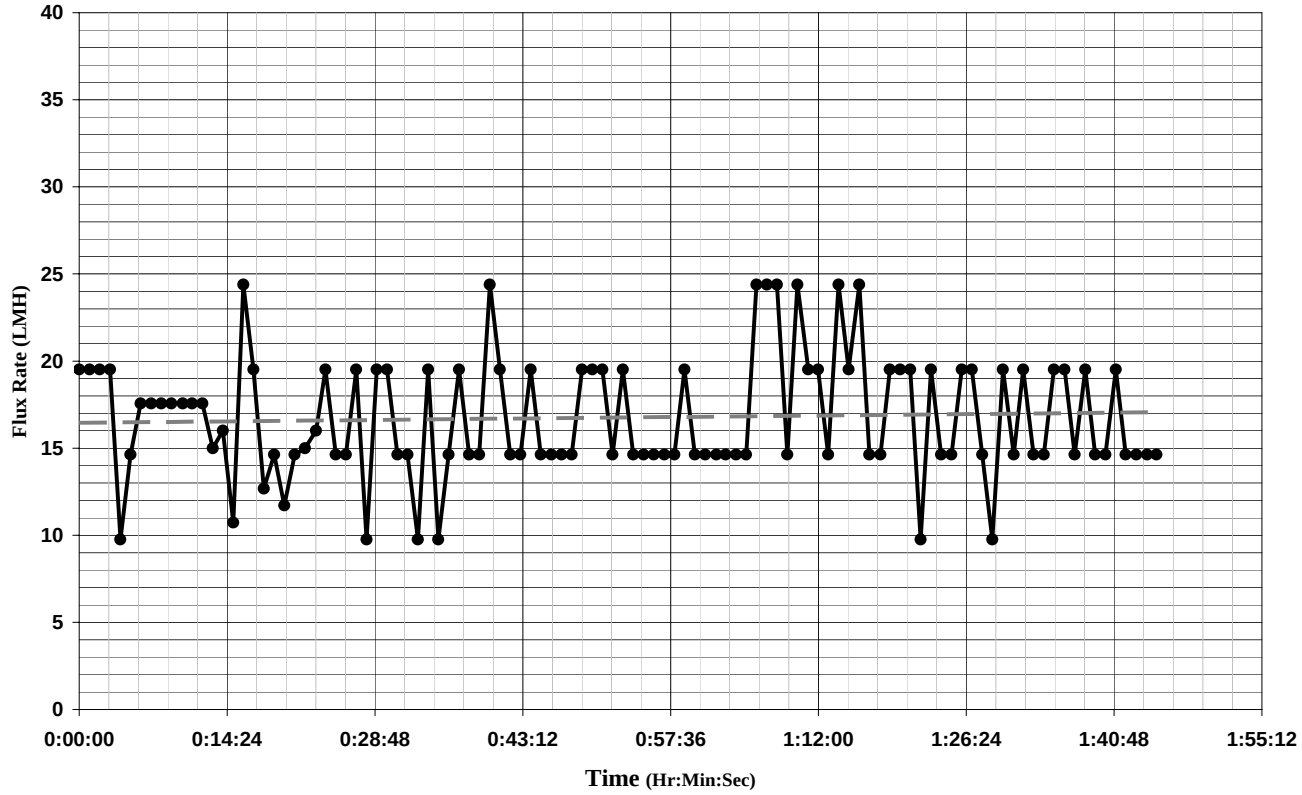


Figure 2
Pressure Profiles vs. Volumetric Throughput
Discontinuous Diafiltraton of Polyacrylic Nanoparticle



NSTI-Nanotech 2008, www.nsti.org, ISBN 978-1-4200-8505-1 Vol. 3

Figure 3
Flux Rate vs. Time
100kd, 0.5mm Lumen PS Hollow Fiber



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 15-20L/M^2/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:

$$Y = 1-(V_O / V_R)^{1+\, n(R-1)} \qquad (2)$$

Y= % Permeate Solute Removed
V_O / V_R =Volume Change Ratio
n=number of stages.
R=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.

$$\%T = \frac{conc_{PERM}}{conc_{FEED}} * 100\% \qquad (3)$$

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 12L 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 12L pilot scale volume, 100kD polysulfone hollow fiber module with 0.57M^2 of membrane (Spectrum Labs MiniKros® P/N K5AB-050-01P) was used. With a count of approximately 1800 fibers, and 20cm 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 12L process reproduced the bench scale measurements. The only anticipated difference was that slightly higher feed-to-retentate ΔP was measured at the pilot scale due to the longer fiber length (20cm vs 12cm at the R&D scale). The following table presents the scalability results.

Area	Shear (s^{-1})	ΔP @ 4% (psid)	DP@8% (psid)	Flux (LMH)
615cm^2 (bench)	4000	4	8	16
0.57M^2 (pilot)	4000	6	11	13

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