

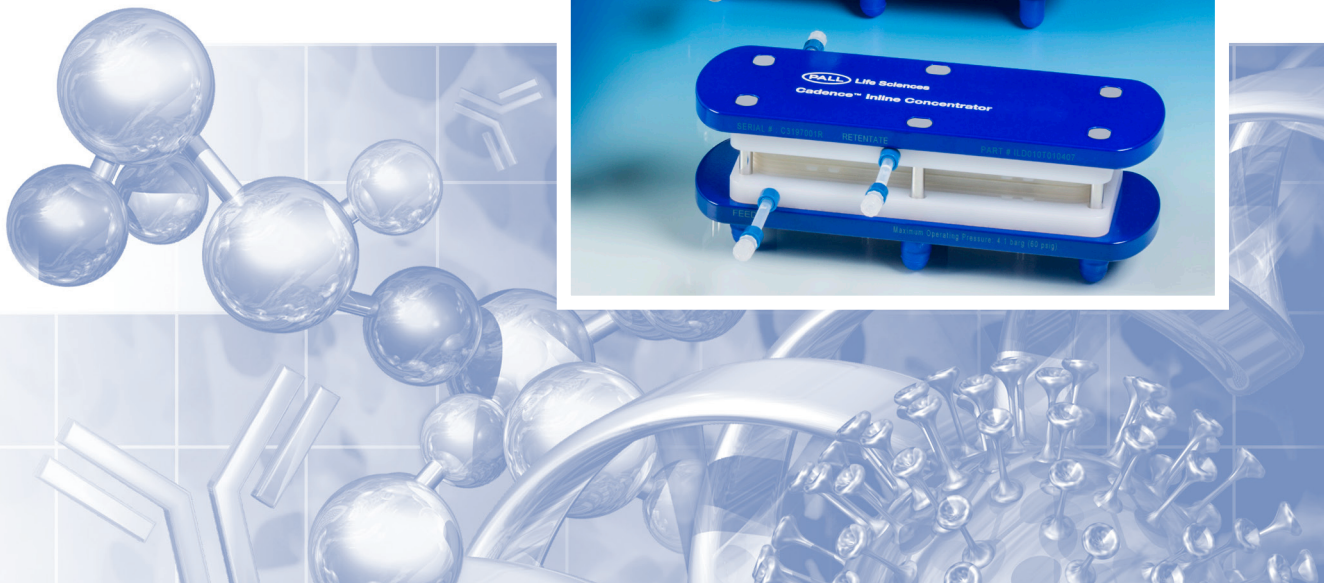


Biotech

## Application Note

USTR2913b

# Volume Reduction and Process Optimization with Cadence™ Inline Concentrator



## 1. Introduction

This patented single-pass technology is an opportunity to simplify current TFF processes. It eliminates the conventional TFF recirculation loop and allows product to be concentrated in a single pump pass by utilizing a proprietary flow path and flow ratio control<sup>1</sup>. The single-pass operation eliminates any mixing or foaming issues and exposes the product to low shear; thus, it is optimal for the processing of fragile and shear-sensitive molecules as well. The single-pass feed flow rates are lower which minimizes the hold-up volume and maximizes product recovery. It also allows higher final concentrations to be achieved because the processing limitations due to minimum working volumes are optimized<sup>2-4</sup>.

Pall's Cadence Inline Concentrator (ILC) utilizes the patented single-pass technology, while also offering a no-holder, single-use, and pre-assembled design (Figure 1). The Cadence ILC utilizes a built-in retentate resistor, which supplies a set amount of backpressure to the retentate side and allows a target VCF of 2 – 4X to be achieved. It is thus ideal for continuous operation and process coupling. It requires minimal hardware of a feed pressure source (i.e. pump or pressure can) and feed pressure measurement, minimizing any system and/or hardware requirements. Its single-use operation also eliminates any cleaning requirements or cross-contamination issues and offers many process economic advantages over re-use conventional TFF. These include up to 30% overall cost of goods savings per batch for a continuous operation, which is mainly attributed to the large savings in capital costs.

### Figure 1

*Pall's Cadence Inline Concentrator [a]. T01 Module - 0.065 m<sup>2</sup>, [b]. T02 Module 0.13 m<sup>2</sup> and T12 Module 0.7 m<sup>2</sup>*



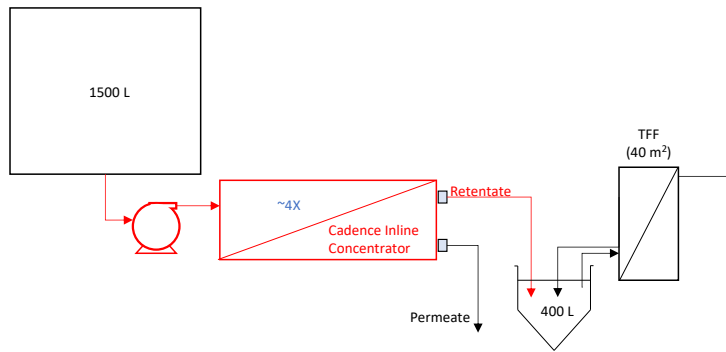
## 2. Inline Concentrator Customer Case Study

### 2.1 Case Study Overview

The Cadence ILC is an ideal technology for inline volume reduction, concentration prior to capture column, and processing of fragile biomolecules. The application that was leveraged for this testing was inline volume reduction of a highly viscous feed stream that consisted of a suspension of nanoparticles used in therapeutic drug delivery applications prior to a final UF/DF step that currently utilizes a membrane area of 10 m<sup>2</sup> to process a batch of 400 L.

Manufacturing floor space limitation is a major constraint at the target facility during future process scale-up considerations from 10 to 40 m<sup>2</sup> scale. Therefore, it is highly desirable not to increase the vessel size from current scale, which utilizes a 400 L stainless steel hold tank. A schematic depiction of the future scaled-up process is given in Figure 2. In order to meet the end-user's scalability goals, a cost-effective volume reduction step that will retrofit the existing tank capacity is the main motivation for this study. Therefore, the main objective was to test the feasibility of the Cadence ILC technology to achieve ~4X inline volume reduction prior to end user's final UF/DF unit operation and identify processing conditions that will maximize throughput.

**Figure 2**  
*Future scaled-up process*



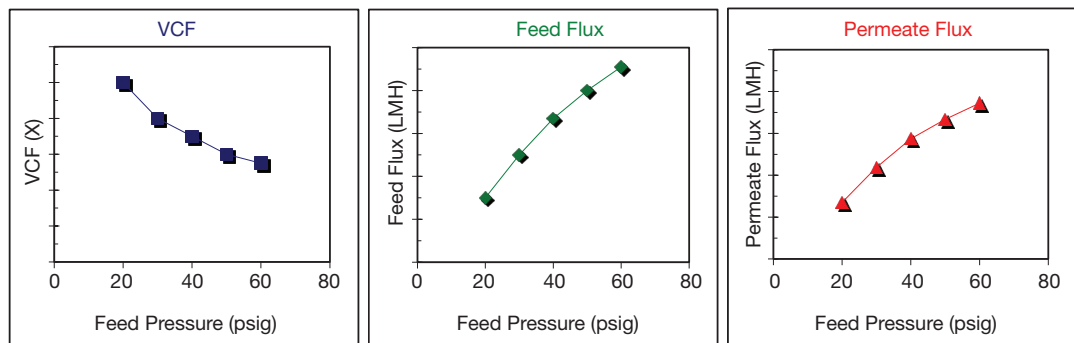
**2.2 Process Optimization with the Cadence ILC**

Cadence ILC pre- and post-conditioning steps are reduced because it is a pre-assembled, pre-flushed, and single-use product that shortens initial setup times, minimizes buffer consumption, and eliminates the need for cleaning and subsequent validation costs. The pre-conditioning steps are therefore limited to storage solution flushing, hold-up volume determination, integrity testing, and buffer conditioning. No post-use conditioning is required.

To find the optimal operating conditions and to evaluate the performance and the capacity of the device, the recommended Cadence ILC process optimization step consists of feed pressure excursions typically in the range of 20 – 60 psig (1.4 – 4.1 barg) that is performed in total recirculation mode. Similarly, feed flux excursions could also be performed as long as the recommended maximum operating feed pressure of 60 psig (4.1 barg) is not exceeded.

As depicted in Figure 3, higher feed pressures will result in higher permeate and feed fluxes but lower VCFs. Therefore, the end-user will need to evaluate the optimal feed pressure setting based upon the trade-off between flux and VCF. Upon the completion of process optimization step, the product can further be processed in single-pass to verify a stable process at the optimal condition.

**Figure 3**  
*VCF, feed flux, and permeate flux as function of feed pressure (y-axis with arbitrary units showing general process trends only)*

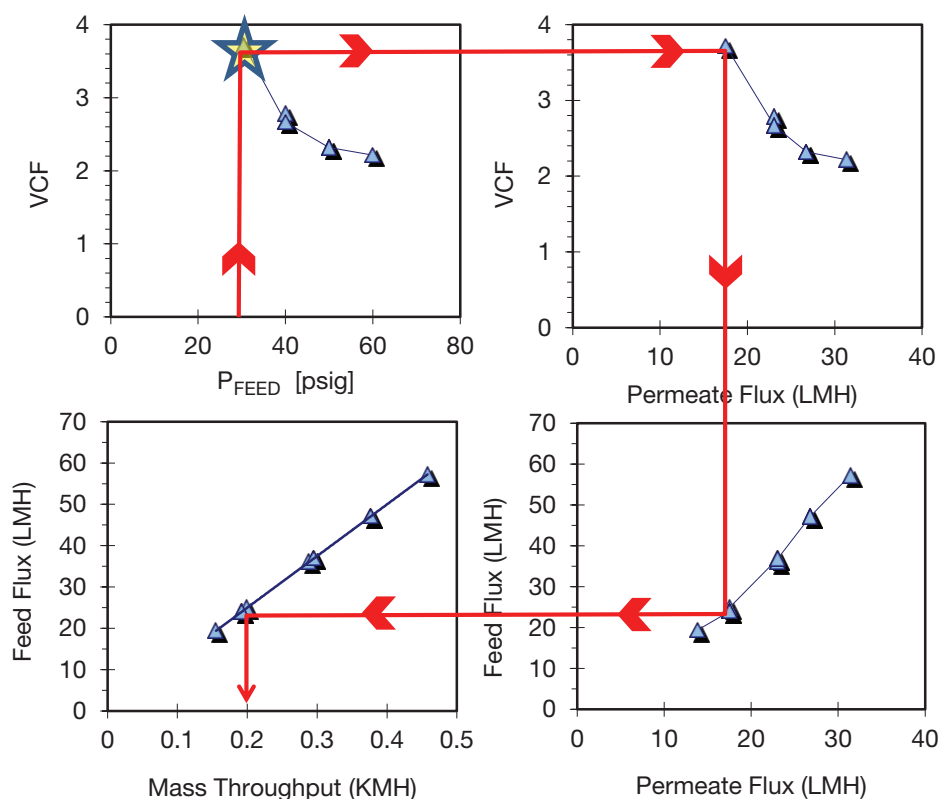


### 3. Results and Discussion

A small scale Cadence ILC T01 module (0.065 m<sup>2</sup>) with regenerated cellulose T-series Delta 30 kDa membrane was tested with a 2 L batch of feed. Aforementioned process optimization step was performed with the module in total recirculation mode to determine its operating range and capabilities. The optimization block in Figure 4 shows the VCF, permeate flux, feed flux, and mass throughput ranges during the feed pressure excursion between 30 – 60 psig (2.0 – 4.1 barg). As the feed pressure increased, the mass throughput and fluxes also increased. The feed fluxes ranged from 19-57 LMH while the permeate flux range was between 14 and 31 LMH. The fluxes were relatively low due to the highly viscous nature of the feedstock.

On the other hand, as the feed pressure decreased, the VCFs increased. This was simply due to the relatively longer residence times at lower feed pressures, which allowed more liquid to pass through the permeate and resulted in higher VCFs. The target VCF of 3.7X was achieved at a feed pressure of 30 psig (2.0 barg), which resulted in a permeate flux of 18 LMH, feed flux of 25 LMH, and mass throughput of 0.2 kg/m<sup>2</sup>/hr.

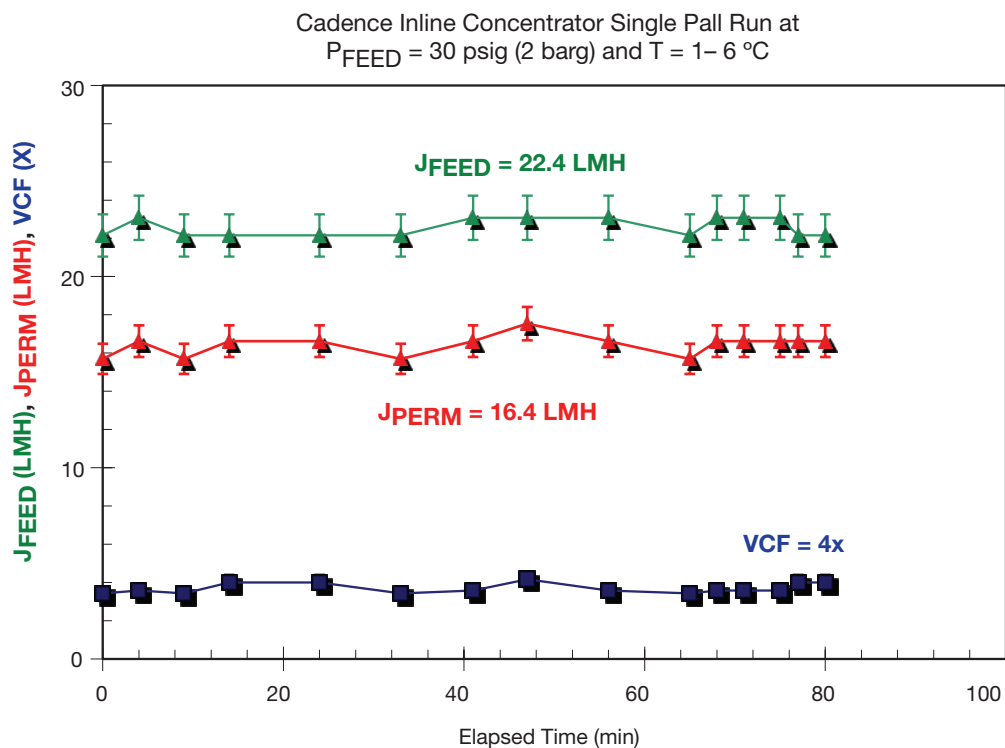
**Figure 4**  
Cadence ILC optimization block: VCF, permeate flux, feed flux, and mass throughput



Based upon the VCF data, a feed pressure of 30 psig (2.0 barg) was chosen for the single-pass run (Figure 5). The 2 L of feed was concentrated 3.7-fold. To confirm the VCF, retentate samples were taken throughout the run and further demonstrated a ~4X actual concentration factor. The process was very stable for the entire 80 minute run, during which average feed and permeate fluxes were 22 LMH and 16 LMH, respectively, as shown in Figure 5.

**Figure 5**

Single-pass run with 30 kDa Cadence ILC module at 30 psig (2.0 barg) feed pressure (Error bars represent 10% variability added to account for flow meter fluctuations)



#### 4. Conclusions

Pall's Cadence Inline Concentrator was tested with a highly viscous feed stream that consisted of a suspension of nanoparticles used in therapeutic drug delivery applications. The 30 kDa Cadence ILC module resulted in VCFs of 2.2 to 3.7X over the operating feed pressure range of 30 – 60 psig (2.0 – 4.1 barg), the higher of which would be a suitable volume reduction for the scaled-up process. The process target was identified during the process optimization run and the module was tested in single-pass at a feed pressure of 30 psig (2.0 barg), which resulted in a stable process with a feed flux of 22 LMH and a permeate flux of 16 LMH. The process produced both a 3.7X volumetric concentration factor and actual concentration factor of 4.1X (based upon solids content).

The Cadence ILC will thus enable a ~4X inline volume reduction of the product stream to be processed in continuous operation mode. The existing 400 L stainless steel product hold tank can be further utilized as the feed tank for the scaled-up process (40 m<sup>2</sup>) eliminating the need for a larger process tank. The Cadence ILC will therefore not only provide additional capital savings but will also resolve potential manufacturing floor space limitations.

## References

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