Application Note

Cadence™ Systems Employ New Single-Pass TFF Technology to Simplify Processes and Lower Costs

Understanding the New Technology

Introduction

The commercialization of a revolutionary TFF technology by Pall Life Sciences presents opportunities to simplify biopharmaceutical process design and lower capital and operational costs. The new technology, single-pass TFF, is brought to life through Pall's Cadence systems and modules. This Application Note introduces the design innovations of Cadence single-pass TFF systems to biopharmaceutical researchers and manufacturers.

Figure 1
Example of a Cadence Single-pass TFF System

How Cadence Single-pass TFF Systems Work

Single-pass TFF simplifies the concentration process by eliminating the need for a recirculation loop. It allows continuous operation at high conversion. For example, in a Cadence single-pass TFF system designed for concentration, the feed is pumped into the feed port of a Cadence single-pass TFF module. Separation takes place in the module, and the concentrated product (retentate) exits the retentate port (Figure 2). The elimination of the recirculation loop and its associated equipment is made possible by two elements that characterize single-pass TFF:

1. The staged design of the Cadence single-pass TFF module
2. The use of flow ratio control

Figure 2
Process Flow in a Cadence Single-pass TFF System
Flow Ratio Control Determines the Concentration Factor

Flow ratio control brings predictability and precision to the continuous concentration of a feed stream. Flow ratio control means regulating the feed and retentate flow rates to known values to achieve the desired concentration factor. This applies for those applications where the molecule of interest is fully retained by the membrane, which is the case in most biopharmaceutical applications.

Applying flow ratio control in a Cadence single-pass TFF system enables operators to achieve concentrations of up to 250 g/L IgG/MAb and concentration factors up to 30X.

For a given module, the concentration factor can be adjusted resulting in control of the outlet concentration. Flow ratio control is accomplished by controlling the speed of two positive displacement pumps or by using flow controllers.

The Staged Design of Cadence Single-Pass TFF Modules

While Cadence single-pass TFF modules use the same membranes and flow channels as those used in Pall’s conventional TFF cassettes, it is the proprietary configuration of the cassettes that enables single-pass TFF to work (Figure 3).

Physically, Cadence single-pass TFF modules consist of a specific configuration of cassettes held between two flow manifolds. The flow manifolds channel fluids into and out of the stack of membrane cassettes (Figure 3).

A proprietary stainless steel holder supports the Cadence single-pass TFF modules in use (Figure 4).

Because the materials of construction and separation capability are equivalent to conventional TFF cassettes, users of existing TFF systems can transition to the new technology quite easily. Many biopharmaceutical separation processes that researchers and manufacturers accomplish with conventional TFF can be accomplished with single-pass TFF in a more efficient manner.

Comparing Single-Pass TFF Technology to Conventional TFF

Incremental improvements in TFF membranes over the last several years have not changed these defining characteristics of conventional TFF:

- Short flow path
- High velocity recirculation of the feed
- Low pressure drop along the length of the channel
- Constant channel dimension

In contrast, Cadence single-pass TFF modules have much longer flow paths, are driven with lower flow velocities and higher pressures, and have cross-sectional changes along the flow channel (Table 1).

The new single-pass approach is based on two important characteristics of pressure-driven membrane processes:

1. The flux is only a weak function of flow velocity, whereas the pressure drop is a strong function of flow velocity.
2. The use of a lower velocity results in a small reduction in flux but a large reduction in pressure drop which enables a much longer flow path, giving up a small amount of flux in return for process simplification (Table 1).
Table 1

Comparison of Typical Process Parameters for Cadence Single-pass TFF Systems and Conventional TFF Systems

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cadence Single-pass TFF</th>
<th>Conventional TFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel Length (cm)</td>
<td>100 ~ 200</td>
<td>16 ~ 20</td>
</tr>
<tr>
<td>Flow Velocity (cm/s)</td>
<td>4 ~ 10</td>
<td>6 ~ 18</td>
</tr>
<tr>
<td>Change in Channel Cross Section</td>
<td>2:1 ~ 4:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Feed Pressure (psi)</td>
<td>50 ~ 80</td>
<td>40 ~ 50</td>
</tr>
<tr>
<td>Retentate Pressure (psi)</td>
<td>5 ~ 10</td>
<td>20 ~ 30</td>
</tr>
<tr>
<td>Pressure Drop (psi)</td>
<td>40 ~ 60</td>
<td>10 ~ 30</td>
</tr>
<tr>
<td>Specific Feed Rate (lmh)</td>
<td>50 ~ 100</td>
<td>250 ~ 500</td>
</tr>
<tr>
<td>Feed to Permeate Conversion per Pass (%)</td>
<td>80 ~ 97</td>
<td>5 ~ 15</td>
</tr>
<tr>
<td>Exposure Time</td>
<td>1 ~ 3 min</td>
<td>3 ~ 4 hr</td>
</tr>
</tbody>
</table>

Performance Advantages

Because the fluid stream is concentrated within the module (not the feed tank) and the highest concentration of product is toward the retentate (product) end, recovery is simple and virtually complete, requiring small volumes of buffer to recover the product.

Because a Cadence single-pass TFF system does not have recirculation process lines, it can process product streams continuously and allow the coupling of process steps.

In a Cadence single-pass TFF system process, the entire separation occurs in a single pass along the flow path of the module over a period of a few minutes and under steady-state conditions (Figure 5). In contrast, in a TFF process the separation occurs gradually over the 3 to 4 hours of processing time, requiring multiple passes through the TFF cassette.

Figure 5

Concentration in Single-pass TFF is Measured in the Module Flow Path, Not in Time

The elimination of a recirculation line and feed tank means a smaller pump or no pump is required. For example, the single-pass process can use a pressurized feed container (Figure 6). This system configuration is specifically recommended when processing shear-sensitive molecules.

A smaller pump or no pump minimizes capital and operating costs.

Figure 6

Cadence Single-pass TFF System Process Using Pressurized Feed Container

Process Development and Module Selection

Selecting the right configuration for the target bioprocess application is relatively straight-forward with single-pass TFF. Based on simple, conventional TFF data such as flux and viscosity as a function of concentration, design curves can be developed that will simplify module selection and help identify the optimum operating conditions.

What follows is an example of an IgG design curve for a 9-in-series Cadence module. As shown in Figure 7, the design curve, consisting of lines of constant concentration and feed pressure, depicts the operating space for the target application. Here is a step-wise procedure to better understand the operating space:

- Select the starting concentration, \( C_{\text{Feed}} \) (i.e., 10 g/L)
- Locate the \( C_{\text{Feed}} \) operating line
- Select the desired volumetric concentration factor, VCF (i.e., 6X)
- Match the operating point on the concentration line to get the nominal operating pressures and permeate flux (i.e., \( P_{\text{Feed}} = 60 \) psig, \( P_{\text{Ret}} = 10 \) psig, and \( J = \sim 64 \) LMH)

Also note that at a feed concentration of 5 g/L and a target VCF of 10X, the nominal operating pressures and the subsequent permeate flux would be \( P_{\text{Feed}} = 50 \) psig, \( P_{\text{Ret}} = 10 \) psig, and \( J = \sim 72 \) LMH, respectively.

The design curves also allow the estimation of effects and variations in operating pressures or starting concentrations on performance. Operating feed flux, \( J_F \), can also be determined based on \( J_F = \text{VCF} \times J / (\text{VCF}-1) \), knowing the VCF and permeate flux, \( J \).
Benefits Summary of Cadence Single-Pass TFF Systems Technology

Single-pass TFF technology brings practical and economic advances to TFF by simplifying the process and creating new capabilities including:

- Increased yield of product due to improved recovery capability and lower hold-up volume.
- Increased final product concentration due to high concentration factor capability.
- Elimination of product damage or aggregation due to reduced residence time and shear exposure.
- Elimination of capital cost, operating cost, process complexity, and footprint of a feed tank and circulation loop.
- Shortened production time by allowing continuous operation and the coupling of process steps.
- Option of single-use systems that are smaller and that have no risk of cross contamination.
- Linearly scalable in ranges from 0.1 m² (1–2 liters) to 9.0 m² (>1000 liters).

Applications and Implementation

With volume capacities ranging from a few liters to thousands of liters, single-pass TFF is capable of performing various steps in a wide range of applications in the biopharmaceutical industry, including:

- In-process volume reduction
- Desalting protein solutions
- High concentration formulations
- Processing fragile biomolecules

The implementation of single-pass TFF starts with a characterization of your fluid stream. Subsequently, the appropriate configuration can be determined, and Cadence single-pass TFF modules can be supplied for your testing and validation.

Contact your Pall representative or email biopharm@pall.com if you’d like to know more about how single-pass TFF technology can simplify and improve the performance of your downstream process.

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