Continuous processing of biotherapeutics through application of a novel coiled flow inversion reactor (CFIR)

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Abstract

Despite the technological advances, affordability and accessibility of biotherapeutics continues to be a daunting challenge, particularly in developing countries like India. This requires advancements in manufacturing that can offer higher productivity and better economics without sacrificing product quality. In this regard, continuous bioprocessing holds great promise. Biotherapeutics industry presently is undergoing a transition from batch to continuous processing by investing in novel continuous processing technologies. In this study, we propose the use of a novel coiled flow inversion reactor (CFIR) for continuously performing biotech unit operations that require reaction and mixing. Coiled flow inversion reactor (CFIR) has been proposed as a configuration consisting of helical coils bent at equidistant right angles to cause flow inversion for improved cross-sectional mixing in the tube. The configuration can be appropriately utilized to provide a sharper residence time distribution along with good cross-sectional mixing. The novel reactor has been explored for continuously performing protein refolding and precipitation in two different case studies. The refolding and precipitation conditions were optimized in the continuous mode in CFIR using a design of experiments (DOE) study and compared to optimized batch protocols. It has been demonstrated that during refolding, enhanced mixing in CFIR allows for operation at two times higher protein concentration and reduction in overall process time. In case of continuous precipitation, improved clearance of host cell proteins (HCP) and DNA was obtained compared to batch. Being a modular unit, a successful integration of CFIR with the downstream train for the creation of end-to-end continuous manufacturing process for GCSF has also been demonstrated. In all the case studies, the continuous configuration demonstrated a 10-20X increase in productivity and a 30-70% decrease in the manufacturing cost with no adverse effects on product quality. Effectively, the configuration can significantly contribute towards creation of an integrated continuous bioprocessing platform.

Coiled Flow Inversion Reactor (CFIR)

- Modified Coiled Flow Reactor (CFR)
- Flow Inversion: Helical coils bent at equidistant right angles
- Better Cross Sectional and Radial Mixing in the laminar flow regime
- Sharper Residence Time Distribution (RTD)

Comparison between (A) straight helical reactor and (B) Coiled flow inversion reactor with 90° bend.

References


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Continuous Refolding

- Reduced Inclusion Bodies
- Coiled Flow Inverter
- Inline Mixer
- Redefining Buffer
- Peristaltic Pumps
- Surge vessel

Comparison of Batch with CFIR

<table>
<thead>
<tr>
<th>Aspect for Comparison</th>
<th>Batch</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process</td>
<td></td>
<td></td>
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<tr>
<td>Reaction</td>
<td></td>
<td></td>
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<tr>
<td>Process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilution</td>
<td>10X</td>
<td>5X</td>
</tr>
<tr>
<td>Time to reach purity</td>
<td>~90min</td>
<td>&lt;60min</td>
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<tr>
<td>Shut Down Time</td>
<td>Required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Reactor Volume</td>
<td>~15 times smaller than batch</td>
<td></td>
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</tbody>
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Industrial Significance

- Refolding at higher protein concentration due to enhanced Mixing
- Faster refolding kinetics
- 15 times higher reactor specific productivity

Continuous Precipitation

- Host cell DNA, HCP fold clearance and product recovery were found to be comparable or better in CFIR than in batch operations
- Productivity increase of 6-16X

Overall Process

- Eliminates need for large volume Process Vessels
- Higher productivity and consequent decrease in facility footprint
- Consistent Product quality and Less hold steps
- Increased equipment utilization and Lower manufacturing cost

Technology Readiness Level

- Prototype is ready
- Looking for commercial manufacturers for collaboration