**Objective**

Introduce Process Chromatography and in particular MCC and SMB Chromatography for synthetic and bio-molecules

Highlight challenges and how to overcome them

Drivers are:
- Introducing continuous manufacturing and integrated DSP
- Increased titers of fermentation processes, and continuous upstream technologies; thus, DSP the *bottleneck*
- **Improve production rate and robustness and reduce capital and operational costs of pharmaceutical processes**
Introduction - History

1903 - M.S. Tswett and the invention of chromatography for the separation of plant pigments

1906 - 1st use of the word "Chromatography"

1931 - E. Lodder and S. L. Heinseberg applied Partition and Paper Chromatography for egg yolk pigments

1961 - SMB process description UOP Patent (Broughton and et al)

1970 - "Modern Liquid Chromatography" (10)

1976 - 1st drug approved by FDA using SMB

1979 - Large-scale CSP production (Daicel)

1980 - SMB for Pharmaceuticals

1990 - 1st SMB production unit installed

2000 - Several 1,000 mm unit installed

Technology & Stationary Phase improvements

Block diagram of generic downstream process

Introduction – Downstream Purification

<table>
<thead>
<tr>
<th>Capture</th>
<th>Purification</th>
<th>Polishing</th>
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<tr>
<td>Isolation</td>
<td>bulk impurity removal: variants, DNA, HCPs, and endotoxins</td>
<td>removal of trace impurities</td>
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<tr>
<td>Concentration</td>
<td>IEX, SEC, and membranes</td>
<td>IEX, RP, SEC and membranes</td>
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<tr>
<td>Affinity/Protein A</td>
<td>Membrane filtration</td>
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<tr>
<td>IEX, HIC and filtration</td>
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Introduction – Chromatography of Synthetic Molecules

Manufacturing

- Multi tons
- SMB/Batch

Introduction – Mode of Operation

Batch Chromatography

Single injections of compound mixture to be analyzed, separated or purified

Continuous Chromatography

- Continuously feeding of compound mixture into chromatographic unit,
- Continuously separating / purifying of this mixture and
- Continuously collecting of the product streams
Introduction – Mode of Operation
Multi-Column Continuous Counter-Current Chromatography
or
Simulated Moving Bed Chromatography

Multi-Column Continuous Counter-Current Chromatography

True Moving Bed

Simulated Moving Bed

Raffinate
Feed
Extract

Raffinate
1

4

2

3

Extract

Eluent

Feed

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Multi-Column Continuous Chromatography
Multi-Column Continuous Counter-Current Chromatography

SMB system

Solvent

Cleaning of solid

Feed

Cleaning of liquid phase

Recycle

Extract

Separation

Raffinate

Recycle to I

I

II

III

IV

Challenges of MCC Chromatography

Advantages of SMB Chromatography:

Established technology for 24/7 operation

Process design tools based on thermodynamic (adsorption isotherms and kinetic (mass transfer) principles

Reduced operational costs by reduced solvent consumption, increased product purities and productivities

Safe, economical and environmental friendly processing

Reduced capital costs for equipment (skids and columns), packing materials, and facilities

Eliminates holding points due to continuous operation
Multi-Column Continuous Counter-Current Chromatography

Petro-Chemicals:
ethyl benzene, m-xylene, indene from alkyl aromatics, p-chloro nitrobenzene, toluene di-isocyanate, p-toluidine

Food:
Fatty Acids, mono-/tri glycerides, Sugars (500T/d)

Bio-Molecules:
Citric Acid, Phenylalanine, Lactic acid and API’s (?)

Synthetic Molecules: Chiral and achiral Separation, Impurity Removal, SMB Mining™

Introduction – Mode of Operation

Multi-Column Continuous Chromatography using parallel/sequential separation of mixture
Continuous Sequential Purification

Cost – Performance - Risk Assessment

At least two pumps:
- Feed pump
- Pump for wash, elution (low pressure mixing when gradient), CIP, regeneration, and equilibration

Two columns with smaller dimension
- Better packing efficiency
- Better separation performance, productivity
- Less packing material
- Better utilization of packing
- Less equipment and process complexity
- But higher buffer consumption
**Process Design – MCC for Capture**

Single column batch chromatography

Bind-Elute or Flow-Through mode with specific binding mechanisms:

High resolutions and generally high yields balance between through-put and capacity as well as buffer consumption

Ideal case

Broad breakthrough

**Challenges of MCC Chromatography**

Complex feed solutions that might vary in composition

Implementation of PAT tools: online/inline UV detectors, pH and conductivity meters

Limited experience in transfer batch to continuous operation for biomolecules (existing processes vs process design for new molecules)

Mechanical and chemical stability of resin (caustic wash) and packing characteristics (shrinking and expanding)

Increased loadibility (concentration step on column), however, due to the continuous operation longer/higher loads – packing life time

24/7 operation – cleanability (CIP/SIP and re-equilibration) and life time
Regulatory Challenge

API of biopharmaceutical processes created in fermenter, not in the last step of the processing scheme of synthetic molecules.

Transition from batch to continuous 24/7 processing

Exposure time of molecule to process conditions causing any denaturation, association, or aggregation; therefore, immunogenic reactions

Risk assessment of the product, process and equipment based on ICH Q9

Regulatory Challenge

QC/QA (impurity profile), product and process comparability, deviations

Validation of the MCC process for cGMP environment.

- Definition of batch size
- Batch integrity
- CIP protocol for continuous process
- Long-term testing to guarantee the cleanability
How to overcome all of the challenges?

By implementing MCC Chromatography into the pharmaceutical manufacturing processes

ありがとう.

Thank you!

Danke!

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