Simulated Moving Bed (SMB) Technologies for Pharmaceutical Purification

Prof N-H. Linda Wang
School of Chemical Engineering
Purdue University
Overview

• Size Exclusion SMB for Insulin Purification
  – Principles of Chromatography and SMB
  – Key Barriers
  – Purdue SMB Technologies
    1. Standing Wave Design & Optimization
    2. VERSE Dynamic Simulations
    3. Versatile SMB Equipment
    4. Model Based Design Approach
  – Experimental Validation
  – Key Issues Solved

• Chiral Separations
  – New Low Pressure SMB for Chiral Separations
  – Understanding Molecular Recognition Mechanisms
Size Exclusion SMB Chromatography for Insulin Purification
Biosynthetic Human Insulin (BHI) Process

Recombinant \textit{E. coli.} \rightarrow Trp proinsulin \rightarrow Proinsulin \rightarrow Crude insulin \rightarrow Purified BHI

- Homogenization
- Cleavage, oxidative sulfitolysis, folding
- Enzymatic transformation
- Ion-exchange
- Reversed-Phase HPLC
- Size exclusion chromatography (SEC)
- Crystallization

Isolation & purification steps take 10 to 12 weeks.
Batch Chromatography

Transient column profiles of a ternary SEC process

$C_B \text{ (g/L)}$

$C_A \text{ (mg/L) and } C_C \text{ (g/L)}$

Dimensionless distance from the inlet

B (product)  A  C

Made by Yi Xie
Conventional Size Exclusion Chromatography

- Existing SEC batch process
  - Yield < 90% (As a result of fronting)
  - Purity >99%
  - Resin productivity = 0.3 L / 100 L BV
Limitations of Batch Chromatography

- Difficult to achieve both high purity and high yield.
- Low adsorbent utilization.
- High product dilution.
- High solvent consumption.
- Protein instability.
- Yield loss in multiple steps.
Solution – Moving Port or SMB

Desorbent → ZONE I → Extract

ZONE IV → Step N → ZONE III

Raffinate → ZONE II → Feed

Solute Movement
VERSE Simulation of SMB Dynamic Column Profiles for the Separation of Insulin from ZnCl$_2$
Simulated Moving Bed Chromatography

Phenylalanine-Tryptophan Simulation

Concentration (mg/mL)

Column Number

Phenylalanine

Tryptophan

04/19/2006
Advantages of SMB over Batch

- Only partial separation of solutes is required to obtain high purity.
- Higher yield than batch – 10% more than batch.
- High purity achievable without sacrificing yield.
- High productivity – 5 to 10 fold increase.
- Less solvent – 5 to 10 fold less.
- Reduced environment impact from reduced solvent waste disposal
- Reduced footprint, equipment size, and manpower
- Continuous process.
Key Barriers in SMB

- A four-zone SMB has 9 design parameters - $2^9$ to $3^9$ trials.
- Large number of system & operating parameters to be optimized.
- Multi-component separation difficult.
- Complex equipment required.
- Complex transient and cyclic steady state phenomena.
Purdue’s Platform
SMB Technologies

1. Standing wave design and optimization.
2. VERSE simulations.
3. Versatile SMB equipment.
4. A systematic model-based approach.
Standing Wave Design for Linear, Nonideal Systems

Matching wave velocities to port velocity to ensure high purity and high yield.
Standing Wave Design & Optimization - Advantages

- *Four zone flow rates and port velocity are solved easily.*
- *Little computation time required.*
- *Achieving maximum productivity and minimum solvent consumption for a given configuration.*
- *Easy extension to multi-component separation.*
- *Reduce search space by five dimensions for optimization.*
VERSE
VErsatile Reaction
SEparation Simulator

• *Dynamic simulation, based on a detailed rate model*
• *To predict column profiles and histories*
• *To understand transient phenomena in batch chromatography, carousel, and SMB*
Mechanisms in VERSE

- Fluid Bulk Convection
- Reaction Film Diffusion
- Pore Diffusion
- Interference Adsorption Sites
- Denaturation Size Exclusion
- Solid Phase Reaction
- Sorbent Particle Ion Exchange
- Surface Diffusion
- Pore Fluid
Versatile SMB

To implement complex processes for multicomponent separations
Features of Versatile SMB

• Dedicated manifold for high purity and high yield
• Allows zone bypasses, open loop, multizone, multisolvent and multicomponent operation.
• Easy column expansibility.
• Moving port chromatography.
• Online decoupled regeneration.
• Independent column switching for variable step time
Model Based Approach

Engineering Analysis
- Mobile Phase
  - Stationary Phase
- Selectivity
- Solubility
- Batch
  - Frontal
  - Pulse
- Voids Estimation
- Isotherms
- Mass Transfer Parameters

Process Design & Optimization
- VERSE Simulator
- Profiles
- Histories
- Purity
- Yield
- Standing Wave Design (SWD)
- Cost Optimization

Experimental Validation
- Versatile SMB
- Profiles
- Histories
- Purity
- Yield
- Optimal Design
- Optimal Production Process
Tandem SMB for Insulin Purification

- **ELUENT**
- **EXTRACT**
- **FEED**
- **RAFFINATE**

- **HMWP**
- **Insulin**
- **Zinc Chloride**

04/19/2006
SMB Experimental Validation: Ring I

(a) Effluent histories at the raffinate port

(b) Effluent histories at the extract port

(c) Mid-step column profiles at cyclic steady state
SMB Experimental Validation: Ring II

(a) Effluent histories at the raffinate port

(b) Effluent histories at the extract port

(c) Mid-step column profiles at cyclic steady state
VERSE Simulation of Insulin Ring I Column Profile Animation

Click to activate
Key Issues Solved

SMB
High Purity
High Yield
Low Cost

Splitting Strategies
(Hritzko et al., AICHE J 2002)

Experimental Validation
(Xie et al., Biotech Prog 2002)

Design & Optimization
(Mun et al., IEC Res 2003)

Startup & Shutdown
(Xie et al., IEC Res 2003)

Robust Operation
(Mun et al., IEC Res 2003)

Periodic Regeneration
(Xie et al., WCCBME 2003)

Insulin Aggregation
(Yu et al., JCIS 2006)

Residence Time
(Mun et al., AICHE J 2003)

Batch Identity
(Mun et al., Biotech Prog 2004)

Versatile SMB
(Chin & Wang, Sep Purif Rev 2004)
Insulin Purification

- Lab-scale tandem SMB designed and validated with experiments
- >99% yield, 5X throughput, and 1/3 solvent consumption
- Robust and optimal process-scale operation designed
- Novel strategies created to reduce protein residence time and maintain batch identity
- Pilot scale testing in progress
Chiral Separations


Forney School of Chemical Engineering
Purdue University
Conclusions

• SMB has higher yield, purity, throughput, and requires less solvent than batch chromatography.

• Conventional SMB technologies are limited to binary and isocratic separations. Transient phenomena are not well understood.

• Large number of parameters to be specified and optimized.
Conclusions

• Platform technologies have been developed at Purdue
  – Software tools for design, simulation, and optimization.
  – Versatile SMB equipment for multi-component separation.

• High purity, high yield processes are being developed for the purification of pharmaceuticals and biochemicals.