The Future is NOW for Continuous Manufacturing
- Part 3 –
Multi-Column Continuous (MCC) Chromatography

Dr. Kathleen Mihlbachler
Global Director of Separation Development
LEWA Process Technologies

15-01-2015

Objective

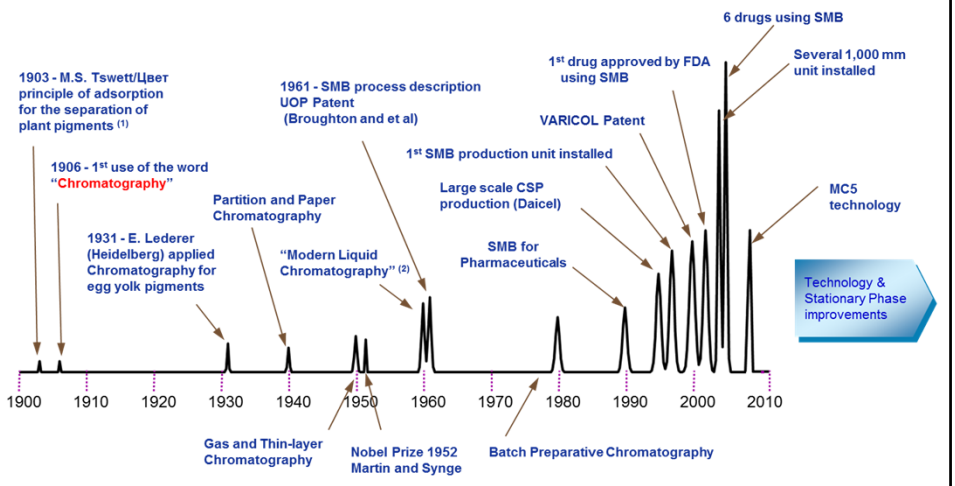
Introduce Process Chromatography and
in particular MCC and SMB Chromatography
for synthetic and bio-molecules

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



(1) "M.S. Tswett and the invention of Chromatography" L.S. Ettre LCGC North America Vol 2, Number 5, May 2003

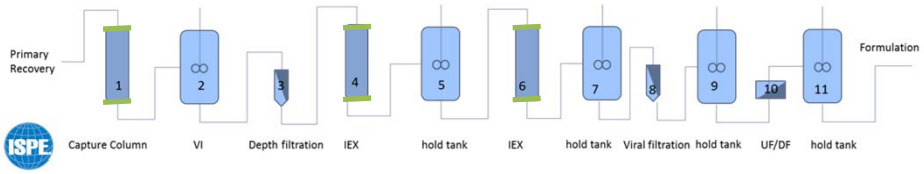
(2) "Introduction to Modern Liquid Chromatography" L.R. Snyder, J.J. Kirkland, Whiley Interscience 1974

Workshop: Preparative chromatography: Dr. Olivier Dapremont and Dr. Kathleen Mihlbachler

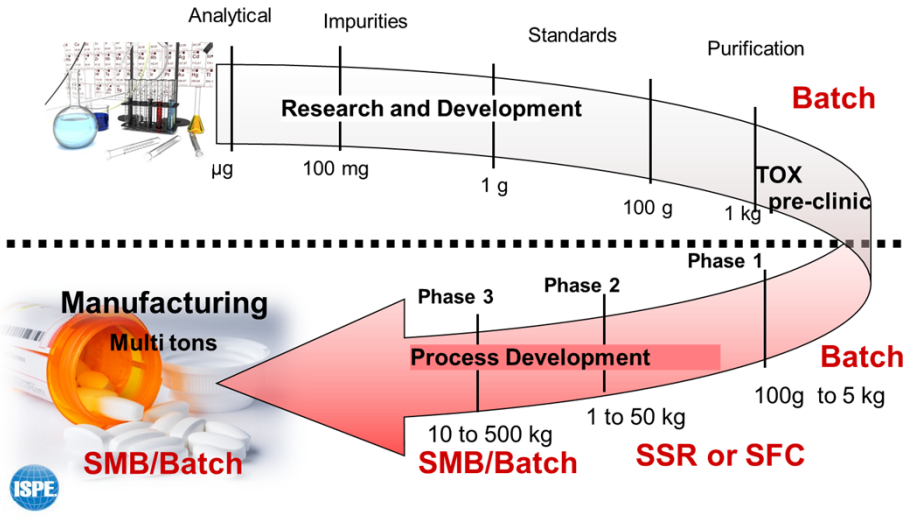
Introduction – *Downstream Purification*

Capture	Purification	Polishing
Isolation Concentration	bulk impurity removal: variants, DNA, HCPs, and endotoxins	removal of trace impurities
Affinity/Protein A IEX, HIC and filtration	IEX, SEC, and membranes	IEX, RP, SEC and membranes

Block diagram of generic downstream process



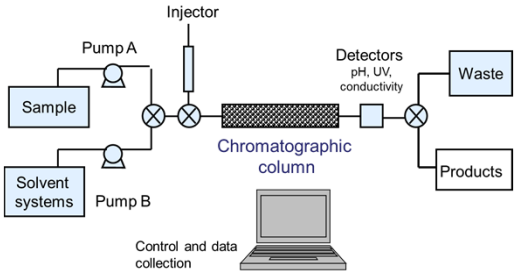
Introduction – *Chromatography of Synthetic Molecules*

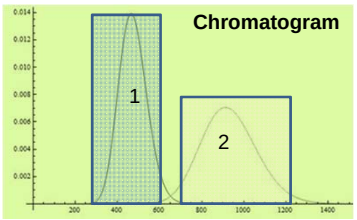


Introduction – Mode of Operation

Batch Chromatography

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



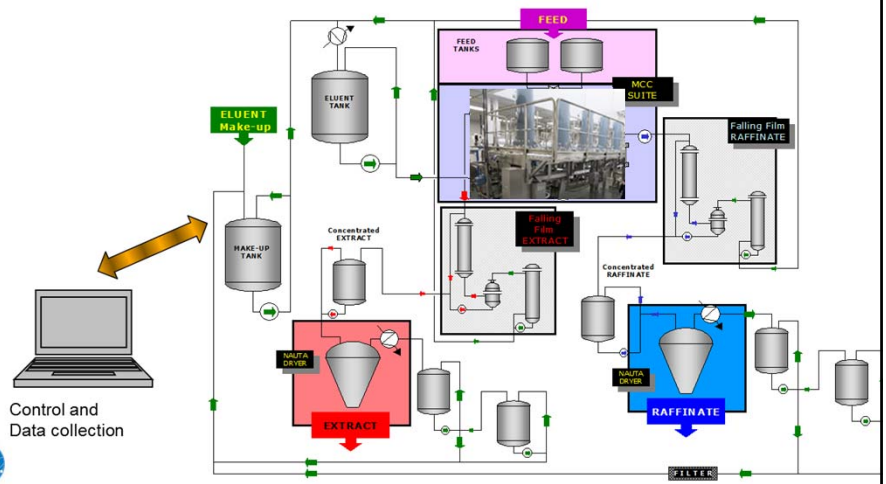


Continuous Chromatography

- 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

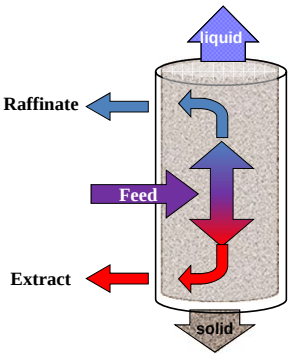
Multi-Column Continuous Counter-Current Chromatography
or
Simulated Moving Bed Chromatography



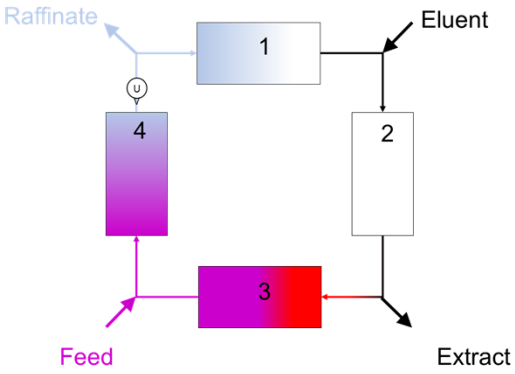
Workshop: Preparative chromatography: Dr. Olivier Dapremont and Dr. Kathleen Mihlbachler

Multi-Column Continuous Counter-Current Chromatography

True Moving Bed

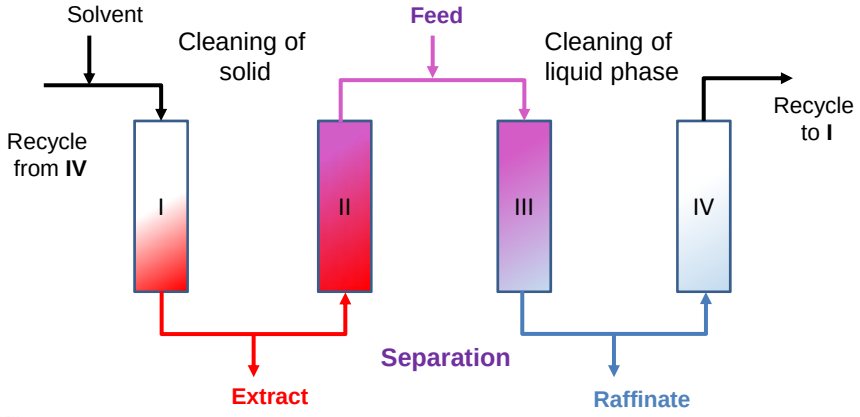


Simulated Moving Bed



Multi-Column Continuous Counter-Current Chromatography

SMB system



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

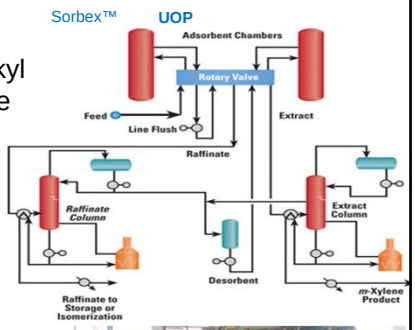
Multi-Column Continuous Counter-Current Chromatography

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)

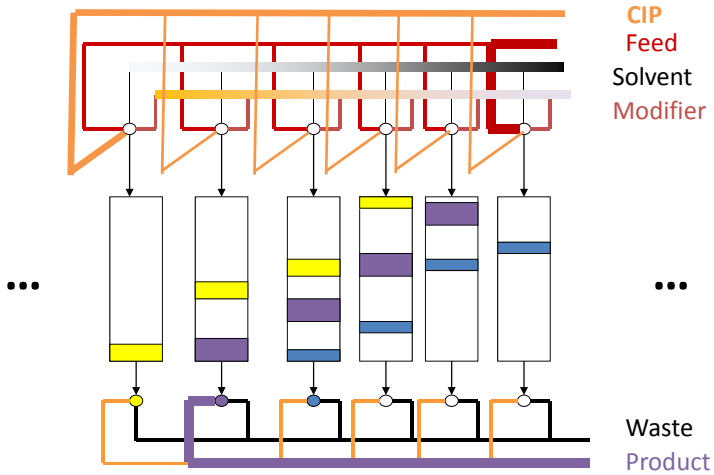
Bio-Molecules:
Citric Acid, Phenylalanine, Lactic acid and API's (?)

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



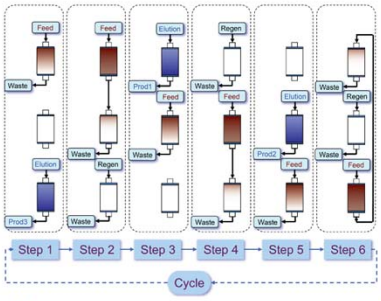
Introduction – Mode of Operation

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



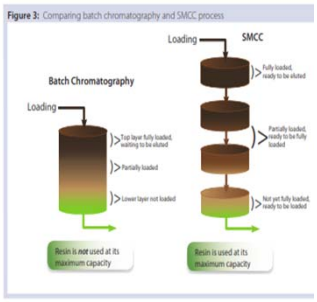
Continuous Sequential Purification

PCC from GE



Biotechnology and Bioengineering, Vol. 109, No. 12, December, 2012

SMCC from NovaSep



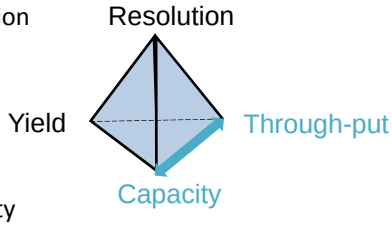
CaptureSMB by ChromaCon

www.chromacon.com

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

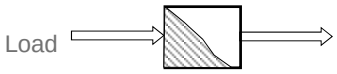


Two columns with smaller dimension
- better packing efficiency
- better separation performance, productivity
- less packing material
- better utilization of packing
- less equipment and process complexity

but higher buffer consumption

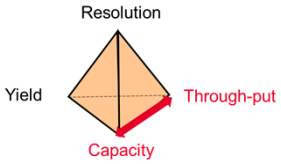
Process Design – MCC for Capture

Single column batch chromatography

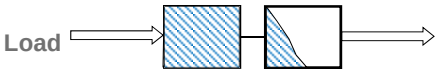


Bind-Elute or Flow-Through mode with specific binding mechanisms:

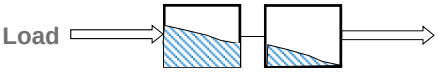
High resolutions and generally high yields
balance between
through-put and capacity
as well as buffer consumption

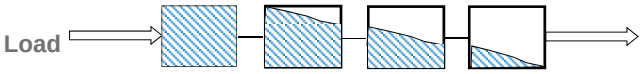


Ideal case



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 bio-molecules (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 !

contact: KMihlbachler@LEWApt.com

www.LEWApt.com,
www.LEWA.com or www.NIKKISO.com