Contichrom® API Process Solutions
Contichrom® Equipment Line
Contichrom®: the MCSGP equipment line

All-in-one process capabilities at same price as gold standard

<table>
<thead>
<tr>
<th>Contichrom®</th>
<th>Preparative HPLC/FPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCSGP</td>
<td></td>
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<tr>
<td>Capture-SMB®/SMB</td>
<td></td>
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<tr>
<td>Sequential chromatography</td>
<td></td>
</tr>
<tr>
<td>Batch</td>
<td>Batch</td>
</tr>
</tbody>
</table>

http://www.chromacon.ch/products/
Contichrom®: Equipment Lines

Discovery
• Enabling on-line enrichment of lead targets for enhanced discovery via LC-MS/MS

Lab-scale
• Cost-competitive, all-in-one process capabilities

Pilot-scale (GMP)
• High performance process for preclinical and clinical material

Production-scale (GMP)
• High throughput, reduced CAPEX and COG

(in development)
(launched world-wide)
customized equipment
customized equipment
Chromatography for API purification

- Chromatography – a very efficient purification method, to date in chemicals mostly used for chiral separations
- As chemical APIs become increasingly complex, often containing two or more chiral centres, there is a growing need for advanced purification technologies to reach the required chemical but also enantiomeric purity
- Trend by pharmaceutical companies to employ chromatography in high value API purification
- Chromatography often used for separation of compounds from natural extracts, i.e. Taxol, PUFAS
- “Old“ Chromatography: Liquid (LC), Supercritical fluid (SFC) → not scaleable, simulated moving bed (SMB) → scaleable but only good for binary separations (chiral separations)
- “New“ Chromatography: MCSGP: scalable and good for ternary separations
Chromatography players

- Two key players are using chromatography for chemicals purification:
  - SAFC
  - Novasep: "Novasep invests EUR 30 million to build world’s largest chromatography plant for the pharmaceutical industry - (10/10/2012)"
Process Chromatography Overview

Evolution of Chromatography

Scale
1'000'000 kg
100'000 kg
10'000 kg
1'000 kg
100 kg
10 kg
1 kg
0.1 kg

Non-scaleable

HPLC
SFC

Scaleable

SMB
MCSGP

Commercial Production
Late Development
Early Development

MCSGP
Proprietary technology by ChromaCon

© ChromaCon AG // www.chromacon.ch // Contichrom Platform
MCSGP can purify complex mixtures in a single step

- Two SMB units needed for the same task: ⇒ low throughput, high buffer consumption, large equipment effort
Contichrom®: all-in-one process solutions

- Capture step
  - (large selectivities)
  - Sharp breakthrough curve
  - Diffuse breakthrough curve

- Ternary separation
  - Very difficult separation
  - Difficult separation
  - Baseline separated

- Binary separation
  - Difficult separation
  - Baseline separated

- Polish step
  - Batch
  - CaptureSMB
  - MCSGP

- Purification challenge
  - Batch
  - MCSGP
  - SMB
  - Batch

Contichrom®
USP - Unique Sales Proposition

ENABLES
- the large volume purification of chemicals and biologics
- the generation of lifecycle extensions for marketed biologics

SAVES
- 30% CAPEX & 50% OPEX
- Purity increase by 50%
- Yield increase by 50%
- Throughput increase 10x
- Buffer reduction -75%

ACCELERATES
- Discovery of leads
- Development retaining product profile at upscaling
MCSGP Chromatography Applications

**Research**
- Optimization of synthesis route by impurity isolation and analysis

**Development**
- Isolation of impurities for toxicology studies / reference impurity material
- Process development
- Generation of pure reference drug substance material

**Production**
- Purification of API
- Purification of highly potent API
- Second crop of drug substance from spent mother liquor/wastestreams by pre-purification of API from wastestreams for subsequent cooling re-crystallization
API process optimization and control
## Issues in API development and manufacture

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>patent infringement</td>
<td>Freedom to operate with MCSGP</td>
</tr>
<tr>
<td>inconsistent raw material quality and supply</td>
<td>separation efficiency of chromatography provides API batch consistency</td>
</tr>
<tr>
<td>low yields</td>
<td>Second crop with chromatographic pre-purification</td>
</tr>
<tr>
<td>difficult-to-achieve levels of purity</td>
<td>chromatography provides control of batch purity</td>
</tr>
<tr>
<td>scale-up</td>
<td>MCSGP can be easily scaled to very large scales</td>
</tr>
<tr>
<td>polymorphism-related issues</td>
<td>Better control with chromatographic pre-purification</td>
</tr>
<tr>
<td>Environmental footprint</td>
<td>very high process yields with MCSGP and solvent recovery</td>
</tr>
</tbody>
</table>
API Manufacturing Optimization Goals

- Increase mass and energy efficiency of process
- Retain impurity specifications and crystal polymorphism
Maximizing API yield and polymorph control

Material to be purified contains:
- Desired compound
- Soluble impurities

Crystallization Filtration

Desired compound in specs. recovered

Mother Liquor contains 5-25% compound of interest and re-crystallization does not produce compound in specs

MCSGP Chromatography removes interfering impurities

Precipitation Filtration Re-crystallization

API second crop

API first crop
Recovery of API from Wastestreams

Input material

Product to isolate 7.7% w/w

Output material
(combined fractions 1-6)

94.6% purity by HPLC
Recovery of API from Wastestreams

- Cooling crystallisation
- 87% yield (based on 94% pure input material)

99.65% purity by HPLC

Crystallised product purity matches IG specifications
MCSGP process design
Design of the MCSGP process – overview

Batch

Resin / buffer / loading conditions

Batch run design (Wizard)

Run “design” batch chromatogram, analyze fractions

Separation?

yes

no

MCSGP Design (Wizard)

MCSGP Run

Yield/ Purity OK

End

no

yes

MCSGP fine tuning

End
In order to achieve a required threshold quality with an optimized batch process, extensive process development has to be performed. Switching to MCSGP from a simple, non-optimized batch process yields a superior product quality in a shorter time.
Automated conversion of batch to MCSGP method

1. Load chromatogram of batch run

Product peak
ANIMATION: Automated conversion of batch to MCSGP method

2. Interactive definition of product fraction

(view in presentation mode to see animation)
Easy conversion of batch to MCSGP chromatography

side fractions stay in unit until pure

waste

pure product is withdrawn continuously

waste
Case Study: Impurity Isolation
Impurity isolation

- Application of preparative and semi-preparative HPLC becomes necessary when the identification of an impurity cannot be carried out with acceptable certainty by means of the simple use of analytical (chromatographic, spectroscopic, hyphenated) techniques. In this case (semi)preparative HPLC isolation followed by spectroscopic (MS, NMR) investigation is the solution.

- The quantity of the isolated impurity, needed for the subsequent spectroscopic measurements is generally in the order of 50-150 mg.

- Owing to the low relative concentration of the impurity of interest in the starting material, in most cases it is not possible to perform the isolation in one preparative HPLC separation step, but several consecutive separations must be done, that is an isolation strategy has to be elaborated. This strategy consists of one or more enrichment steps and a final purification step. Different separation steps of an isolation strategy are often carried out with different HPLC methods.

- The second aspect is that after carrying out the HPLC separation, the enriched or purified impurity has to be recoverable from the mobile phase without degradation.
Applications in Process R&D

- Purify the impurities present in the bulk drug
- Formulation units check stability of drug product and isolate related impurities
- Preclinical/Tox: Isolate highly pure drug material required for toxicity studies
- Preclinical/Tox: Isolate highly pure impurity material for toxicity studies and as a reference standard for the synthesis of impurities
- Process Labs: develop processes to minimize impurities and to have the analytical and preparative tools
Application example: peptide purification

- Acknowledgments:

Purification of a therapeutic peptide by continuous chromatography (MCSGP)

Thomas Müller-Späth¹, Guido Ströhlein¹, Olav Lyngberg², Derek Maclean³

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³KAI Pharmaceuticals, 270 Littlefield Avenue, South San Francisco, CA 94080, USA

- Aim of project: Purify a peptide from chemical synthesis with high yield and high purity
Comparison of Batch and MCSGP chromatography

- Overview of results

[Graph showing comparison of Batch and MCSGP chromatography with Contichrom™: +70% yield, 10x in productivity, and 50% less impurities.]
Continuous purification - polypeptide

- Comparison of process scales:

  - **Batch**: bed height 25cm, diameter 18cm ⇒ 6L resin (process scale chromatography)

  - **MCSGP**: 10x in productivity ⇒ 0.6L resin
    
    = 2 x 0.3L ⇒ 2 columns,
    
    each with bed height 15cm, diameter 5cm

  - **Contichrom® lab-scale** (50mL/min, benchtop system) can perform such a separation scale with an output of 110 g/d.
Impurity isolation using Contichrom® (MCSGP)

- **Aim:** Isolate weakly adsorbing impurity of Fibrinopeptide A using preparative RP chromatography

- **Options:**
  - Batch chromatography process
  - MCSGP process

![Graph showing impurity isolation](run on C18 -10μm)

- **Fibrinopeptide A** (main compound, 30% of feed)
- **Impurity to be isolated** (1.2% of feed)
Impurity isolation using Contichrom® (MCSGP)

- Fibrinopeptide A: Analytical chromatograms showing feed, purest side component fractions of batch and MCSGP process

**Zoom**

Blue: Feed  
Red: Side component by MCSGP  
Green: Side component by batch  
(fraction size was the same for batch and MCSGP)
## Impurity isolation using Contichrom® (MCSGP)

- **Process performance (Fibrinopeptide A case)**

<table>
<thead>
<tr>
<th>Process</th>
<th>Purity</th>
<th>Concentration factor</th>
<th>Enrichment factor (w.r. to main compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCSGP</td>
<td>&gt; 80%</td>
<td>10x</td>
<td>&gt;600x</td>
</tr>
<tr>
<td>Batch</td>
<td>&lt; 20%</td>
<td>1x</td>
<td>n.a. (purity too low)</td>
</tr>
</tbody>
</table>

Blue: Feed
Red: Side component by MCSGP
Green: Side component by batch
Contichrom® Twin-column MCSGP process principle
Contichrom® & MCSGP explained
MCSGP simplified: recycle until it's pure
Contichrom® & MCSGP explained

(view in presentation mode to see animation)
Contichrom® & MCSGP explained

Feed
Contichrom® & MCSGP explained

Step 1:
- elute waste

Step 2:
- recycle overlap

Step 3:
- elute product
- feed column

Step 4:
- recycle overlap
Contichrom® & MCSGP explained

Step 1:
- elute waste

Step 2:
- recycle overlap

Step 3:
- elute product
- feed column

Step 4:
- recycle overlap
Contichrom® & MCSGP explained

Step 1:  
• elute waste

Step 2:  
• recycle overlap

Step 3:  
• elute product  
• feed column

Step 4:  
• recycle overlap
Contichrom® & MCSGP explained

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Contichrom® & MCSGP explained

Step 1:
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Step 3:
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- feed column

Step 4:
- recycle overlap

Cycle complete, start next cycle
Contichrom® & MCSGP explained

Step 1:
- elute waste

Step 2:
- recycle overlap

Step 3:
- elute product
- feed column

Step 4:
- recycle overlap
Contichrom® Software
Contichrom® software

Fast and secure process development
- Wizards with graphical user interface for easy method programming
- Automated conversion from batch to MCSGP process
- Extensive library of pre-defined methods for all standard operations

Easy to operate
- Intuitive software for operation of batch and MCSGP
- Active flow path highlighted in flowsheet
- Pause/continue functionality, even for continuous chromatographic operations

Integrated evaluation and reporting
- Detailed evaluation capabilities with standardized PDF reports
- Data export functions

Full data security and traceability
- Full audit trail and change control
- User management hierarchy provides high operational and data security
- FDA 21 CFR Part 11 compliant
Main window: status & flowsheet tab

Main - Flowsheet Tab

- active connections are highlighted
- display of status/measurement of
  - valve position
  - pump parameters
  - UV-signals / settings
  - conductivity
  - pH / temperature
  - tank levels
- run time information
  - method in operation
  - duration of time step
Batch wizard for fast method programming

**Batch wizard**
- pre-defined blocks with up to 3 blocks per step
- standard blocks for:
  - load
  - wash
  - (gradient) elution
  - strip
  - CIP/ re-equilibration
- option to select unit as:
  - time
  - volume
  - column volume

**Choice of standard blocks:** equilibration, load, wash, elution, CIP, re-equilibration

**Visualization of gradient**
Automated conversion of batch to MCGSP method

Step 1: retrieve chosen chromatogram of batch run from database

Step 2: interactive definition of product range (red) and recycling fractions (blue): pull bars to define boundaries (dotted lines)

Step 3: push button to convert batch to MCGSP process
Contichrom®: Online Signal Analysis

- Overlay of UV-signals for cyclic processes (MCSGP) allows fast and reliable detection of steady-state.
Evaluation of data: easy-to-use tools

View and integrate signals

Evaluation center
- view recorded data
- integrate UV-signals
- optimized view of data from cyclic process (e.g. MCSGP)
- superimpose different runs (batch and MCSGP)
- display tank levels
- print important log book information
- create PDF reports containing several experiments, log book

Overlay of MCSGP cycles

Super-impose experiments