Preparative Chromatography with Supercritical Fluids - Operation and Optimisation

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Outline

1 Introduction

2 Equipment and methods

- Preparative Batch-SFC
- Preparative SMB-SFC
- Modeling

3 Applications

- Method development
- Determination of adsorption equilibrium
- Simulation / Optimization
- Analysis of profitability

4 Summary

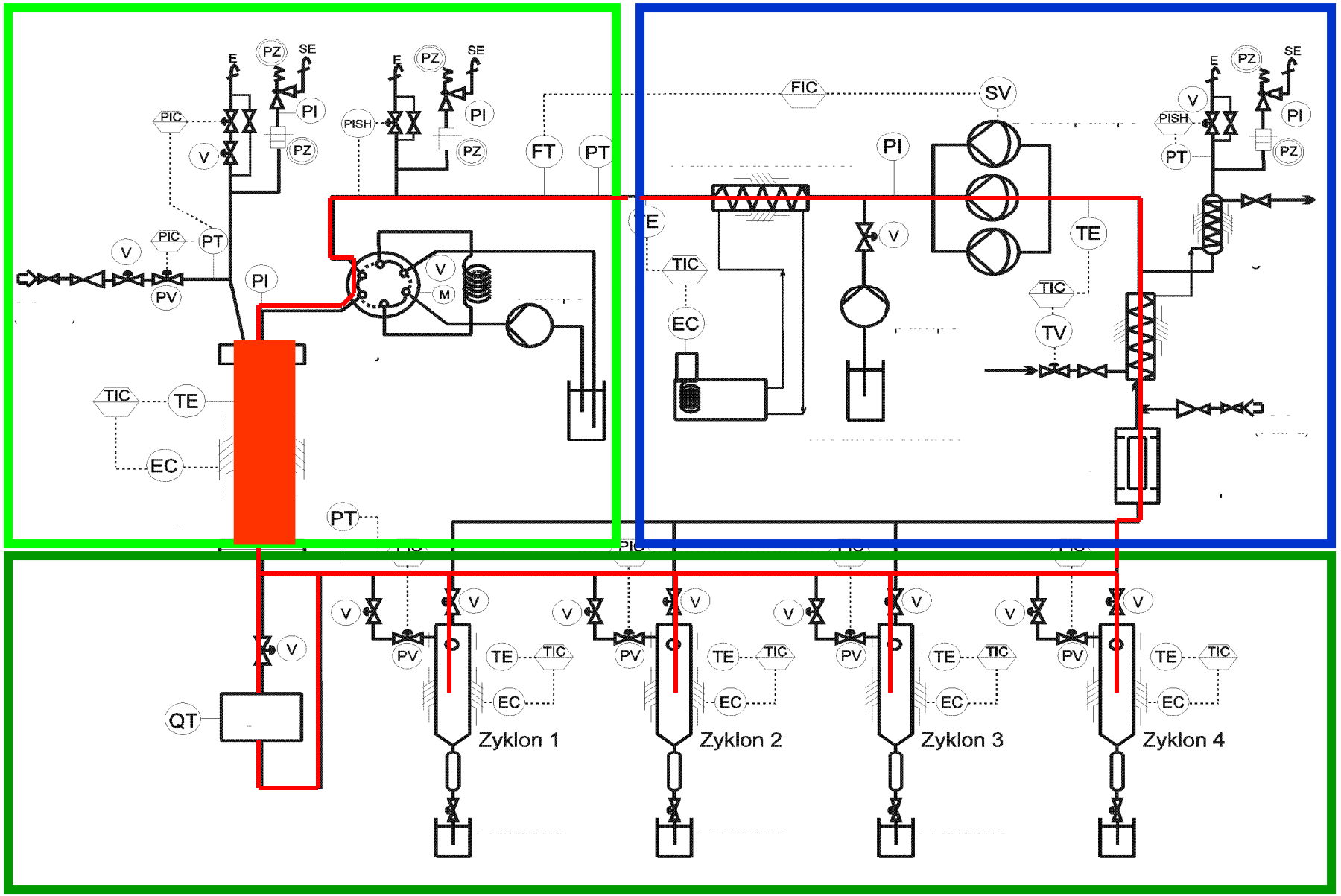
Preparative chromatography

- **Process with high selectivities** due to large number of stationary and mobile phase combinations
- For the separation of **high value products** for highest purity

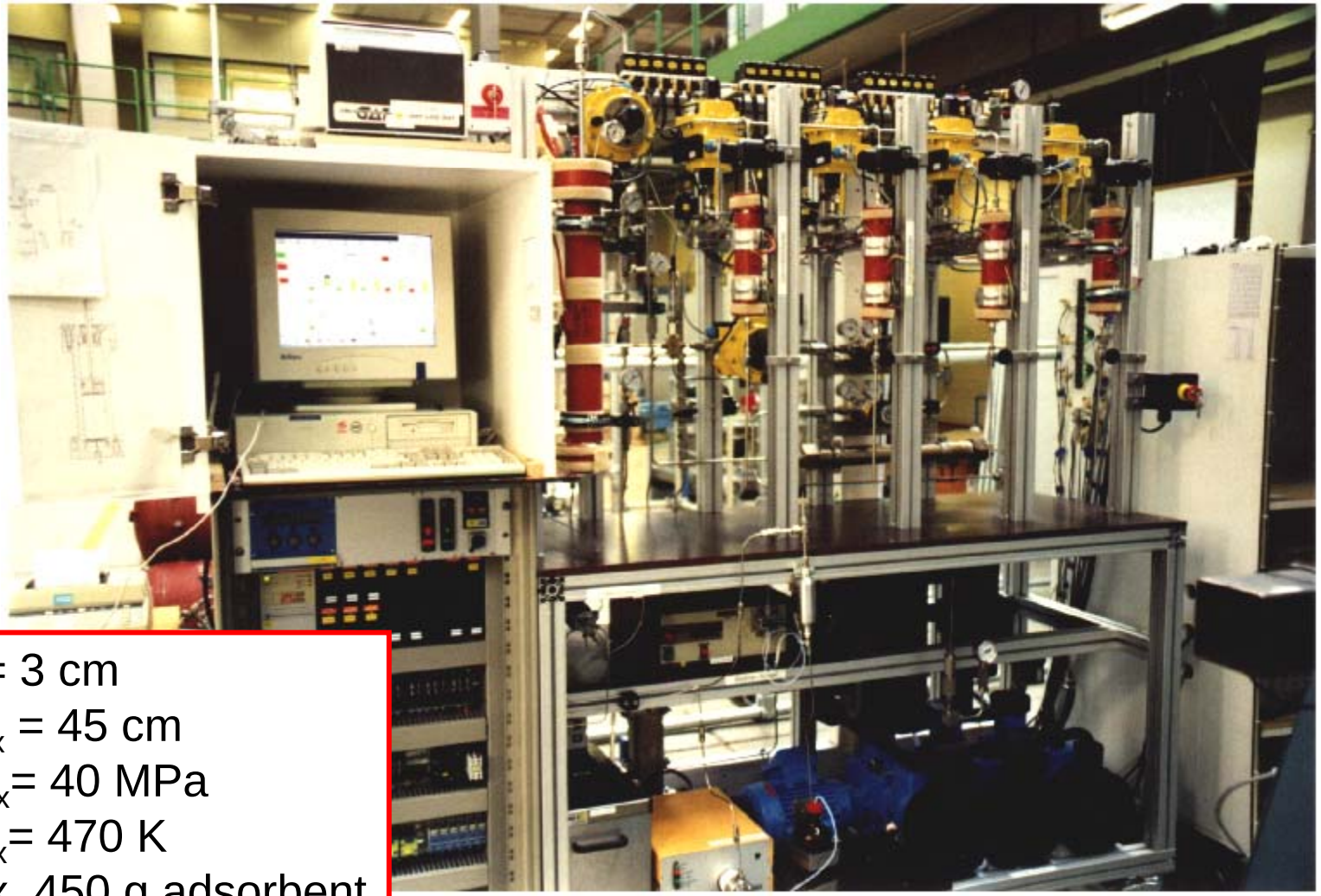
Techniques:
- Liquid chromatography (LC/HPLC)
- Supercritical fluid chromatography (SFC)
- Gas chromatography (GC)

Modes:
- Batch-chromatography
- Simulated Moving Bed (SMB)

Preparative Batch-SFC

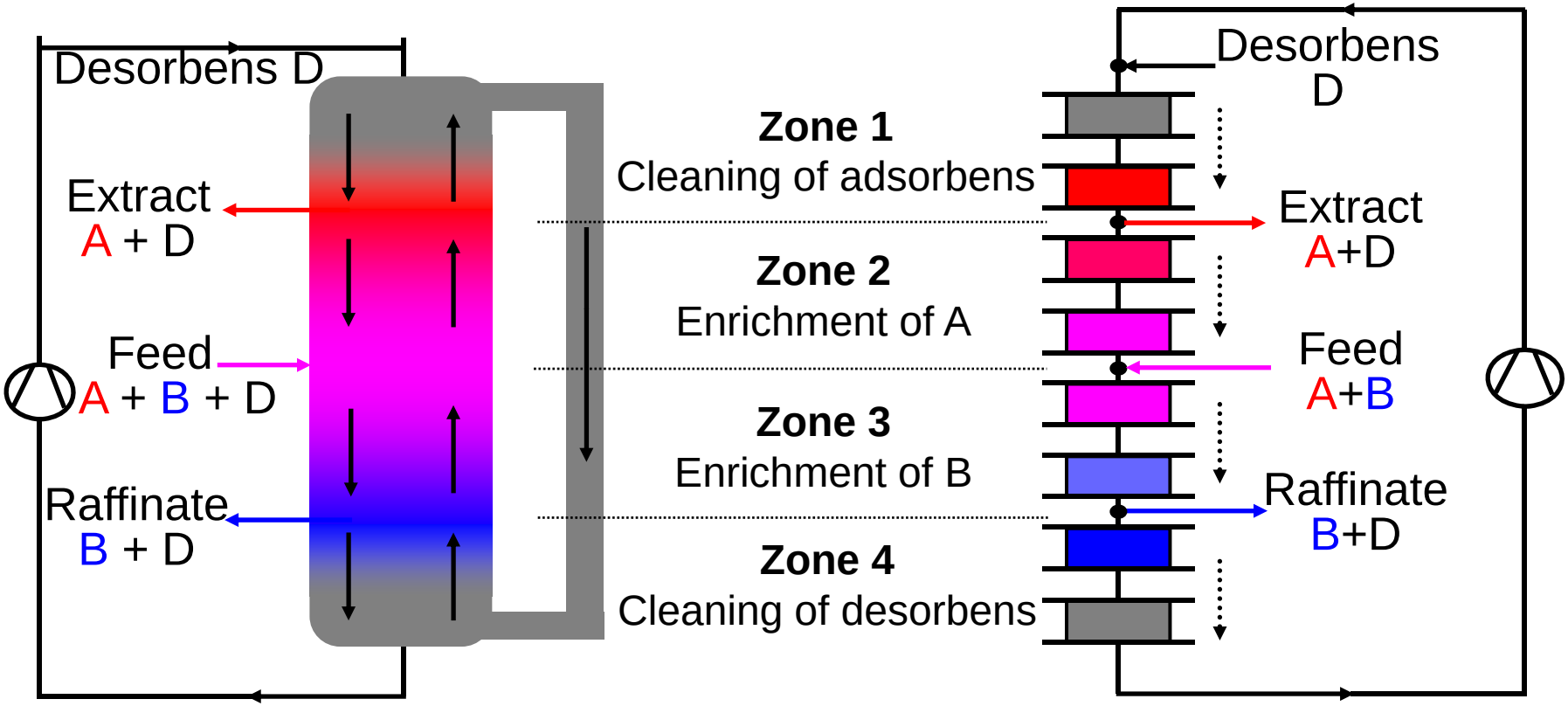


Preparative Batch-SFC



ID = 3 cm
L_{max} = 45 cm
P_{max}= 40 MPa
T_{max}= 470 K
max. 450 g adsorbent

Continuous chromatography



True **M**oving **B**ed **(TMB)**

Simulated **M**oving **B**ed **(SMB)**

Chromatography: Batch versus SMB

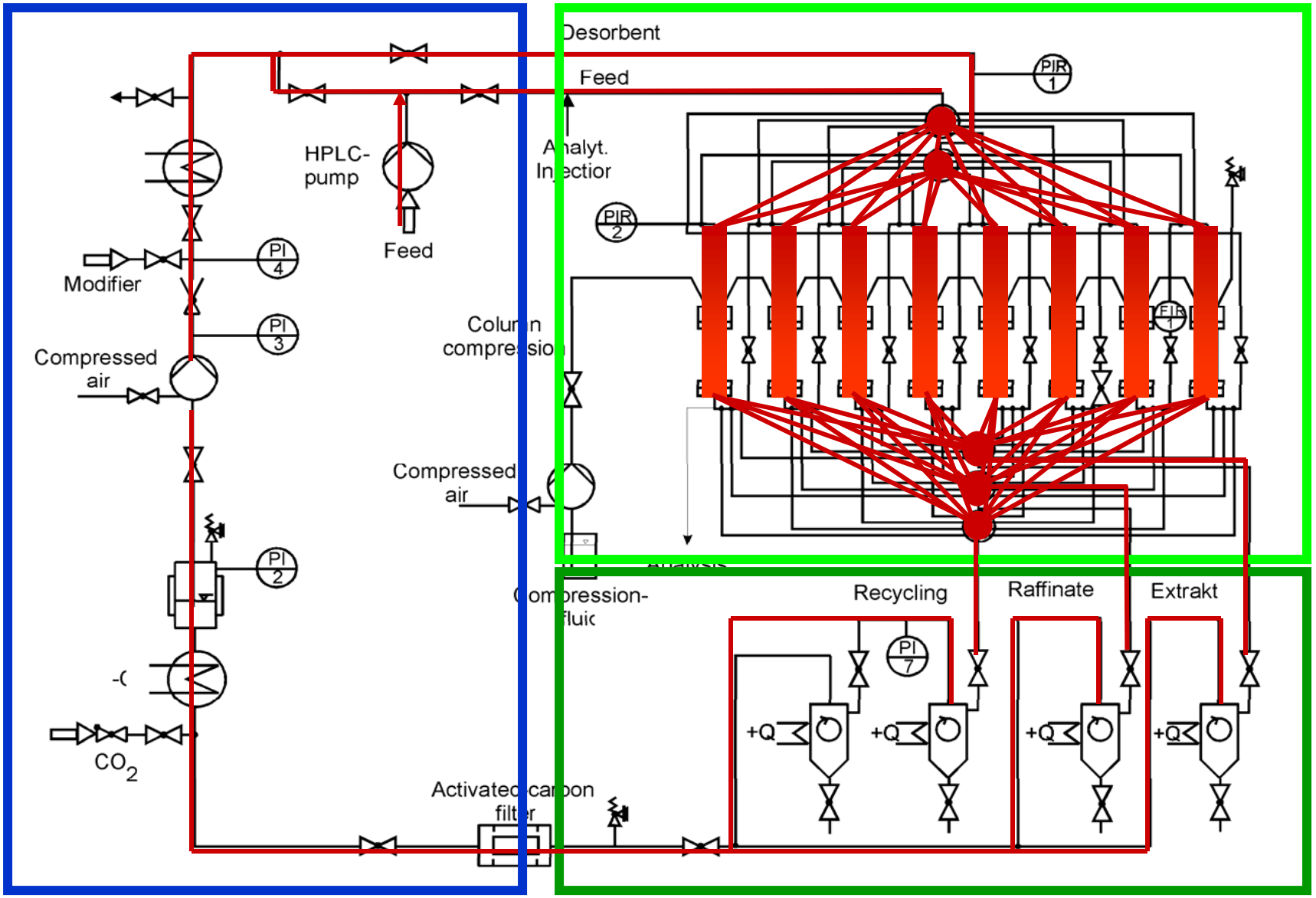
Batch-Chromatography

- ↓ discontinuity
- ↓ high solvent consumption
- ↓ dilution of products
- ↓ lost in yield due to waste fractions
- ↑ multi-component separations possible
- ↑ simple up-scaling

SMB-Technique

- ↑ continuous process
- ↑ lower solvent consumption
- ↑ higher concentrated products
- ↑ high yield (no waste fraction)
- ↓ especially for binary separations
- ↓ more complicated process development / technically demanding

SMB-SFC


Desorbent
Feed
PIR 1
HPLC-pump
Analyt. Injection
PIR 2
Feed
PI 4
Modifier
PI 3
Compressed air
Column compression
Compressed air
PI 2
Compression-fluid
Recycling
Raffinate
Extrakt
PI 7
+Q
+Q
+Q
+Q
CO_2
Activated carbon filter

SMB-SFC

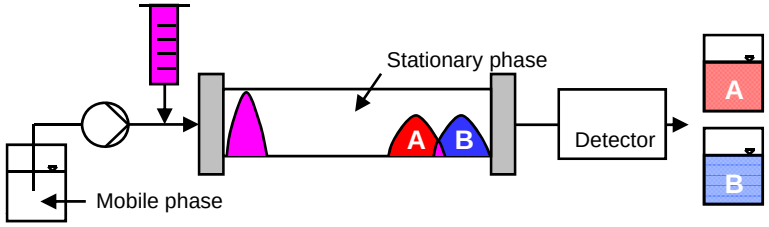
ID = 3 cm
L_{max} = 19 cm
P_{max}= 40 MPa
T_{max}= 470 K
max. 8 x 100 g adsorbent

Preparative SFC: Applications at TUHH

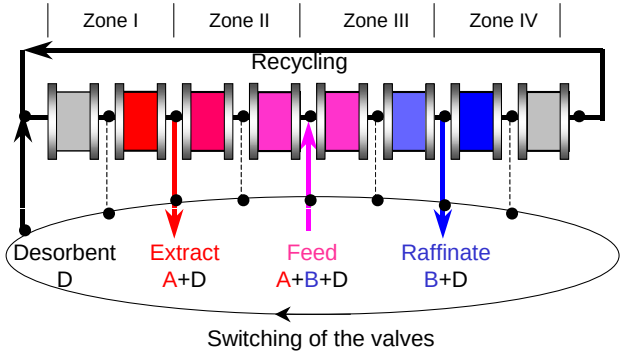
- **Prostaglandines** on LiChrosorb Si60
- **Fish oil ethyl esters (DPA/DHA)** on Alumina
- **cis-/trans-Phytol** on LiChrospher Si60
- **Vitamin D_3** on Zorbax Pro 10-60 CN
- **γ-/δ-Tocopherol** on LiChrospher Si60
- **R-/S-Ibuprofen** on Kromasil CHI-TBB
- **R-/S-Binaphthol** on Kromasil CHI-DMB
- **R-/S-Lacton** on Chiralpak AS
- **R-/S-1-Phenyl-1-propanol** on Chiralcel OD
- **Tocochromanols** on Kromasil KR60-10-SIL

Process development

Batch-SFC



SMB-SFC



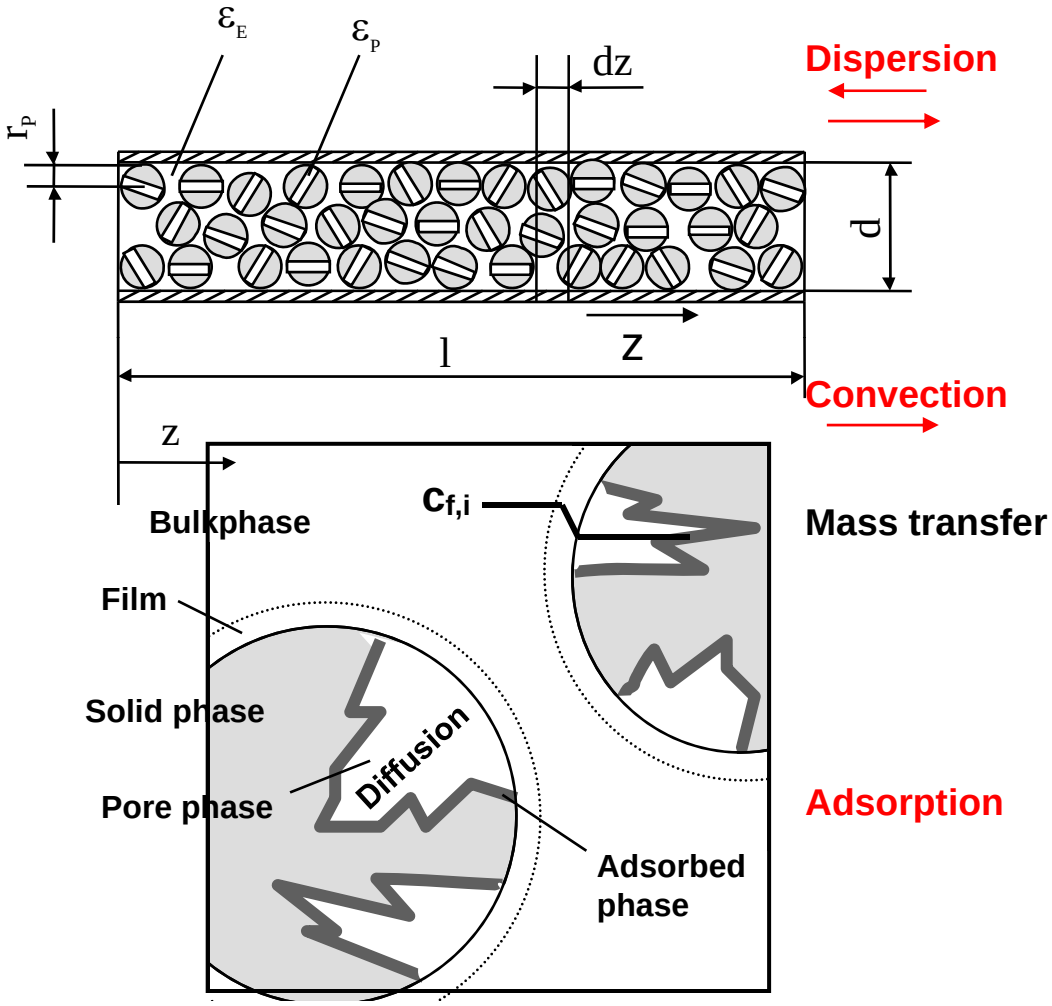
Parameters of influence:

- Separation system (adsorbent, particle size, mobile phase composition)
- Column geometry
- Operation parameter (pressure, temperature, flow rate, injection volume, fraction period)

Additional parameters:

- Column configuration
- Flow rates in the different zones
- Switching time of the valves

Model assumptions



Used balance equation:

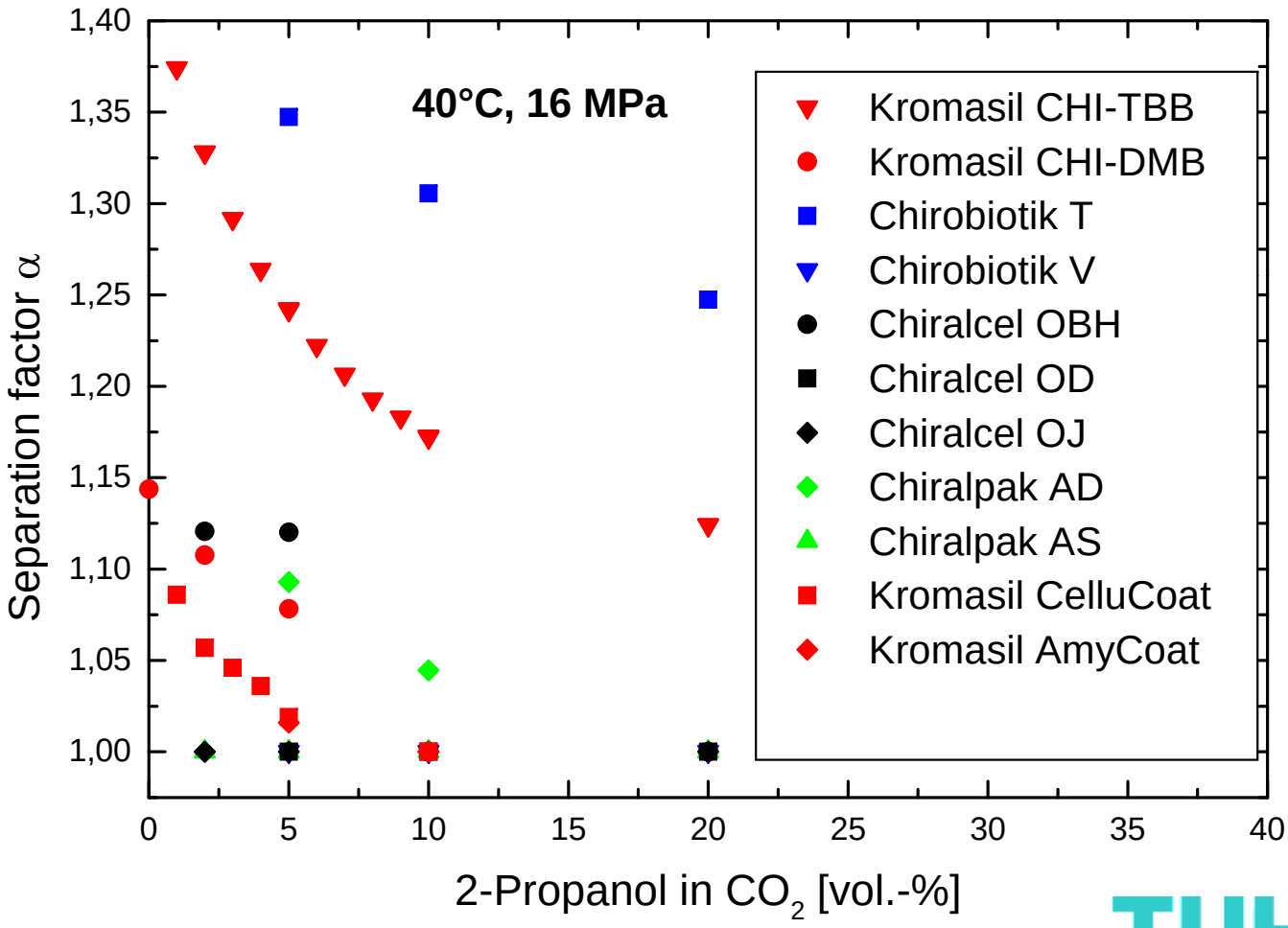
- Equilibrium dispersive model
- Mobile phase velocity is considered to be variable

Adsorption:

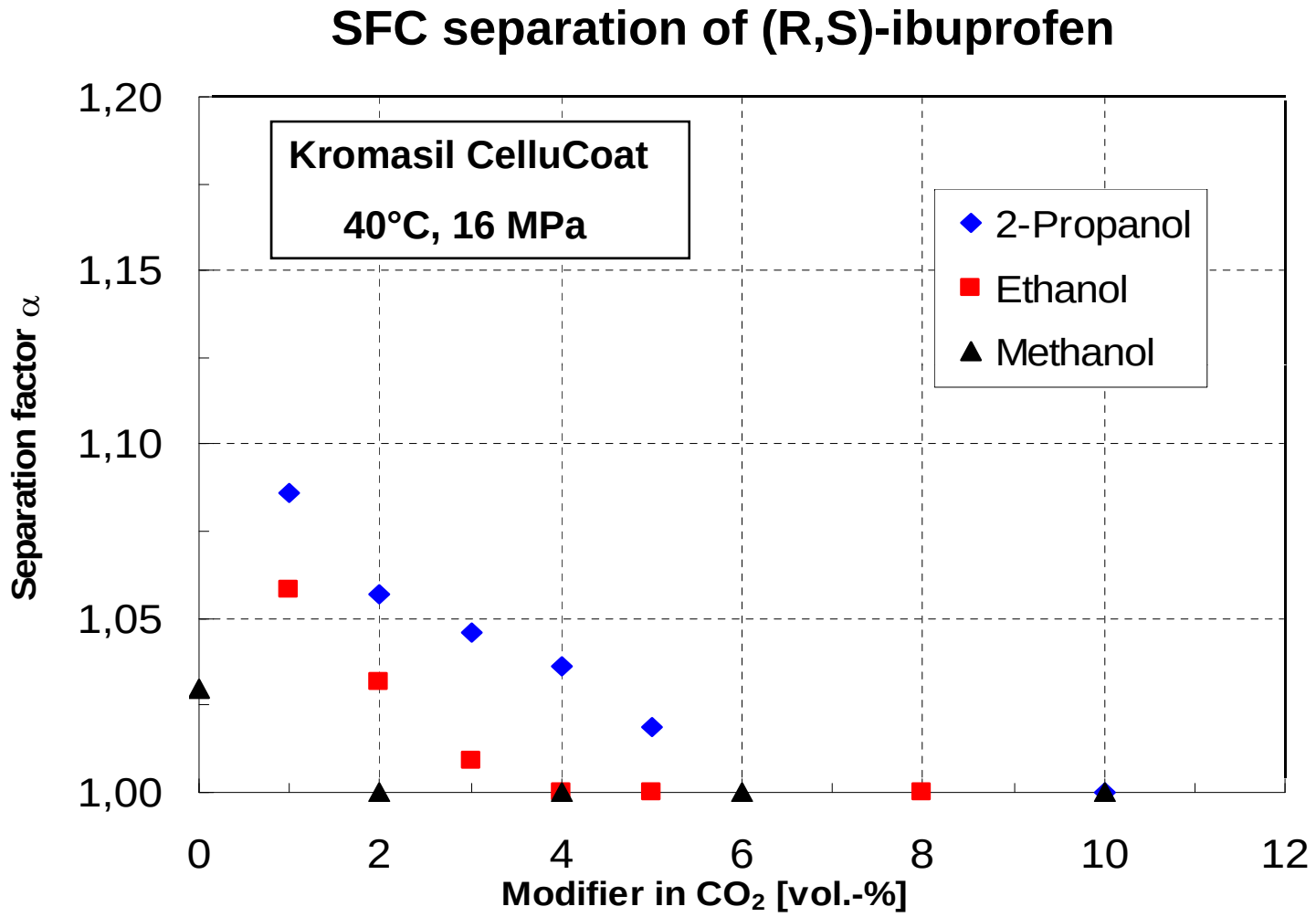
- Single component isotherms determined (cubic Hill isotherm)
- Describing binary adsorption by the ideal adsorbed solution theory (IAST)

Selection of stationary phase

SFC separation of (R,S)-ibuprofen

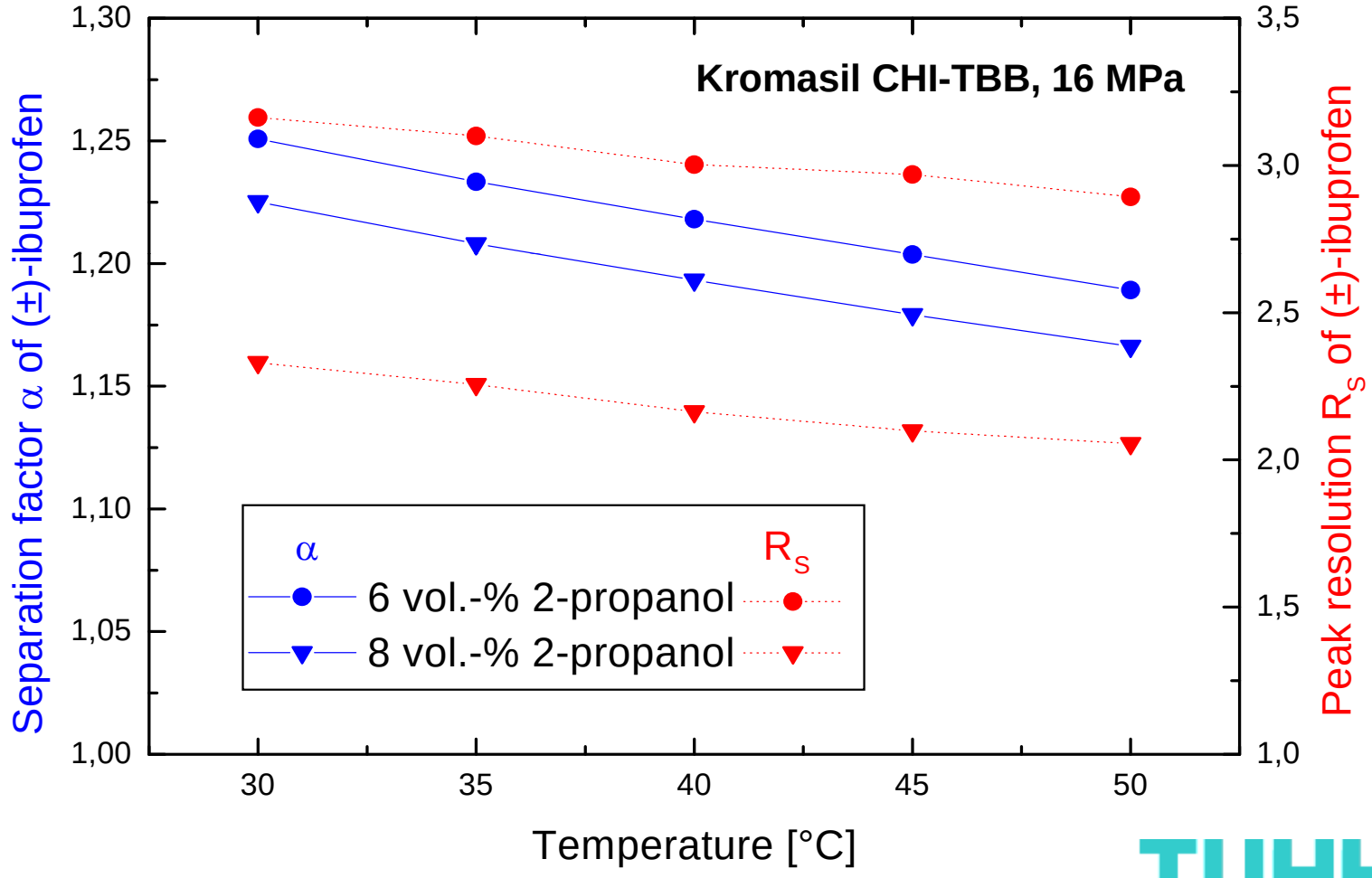


Selection of mobile phase



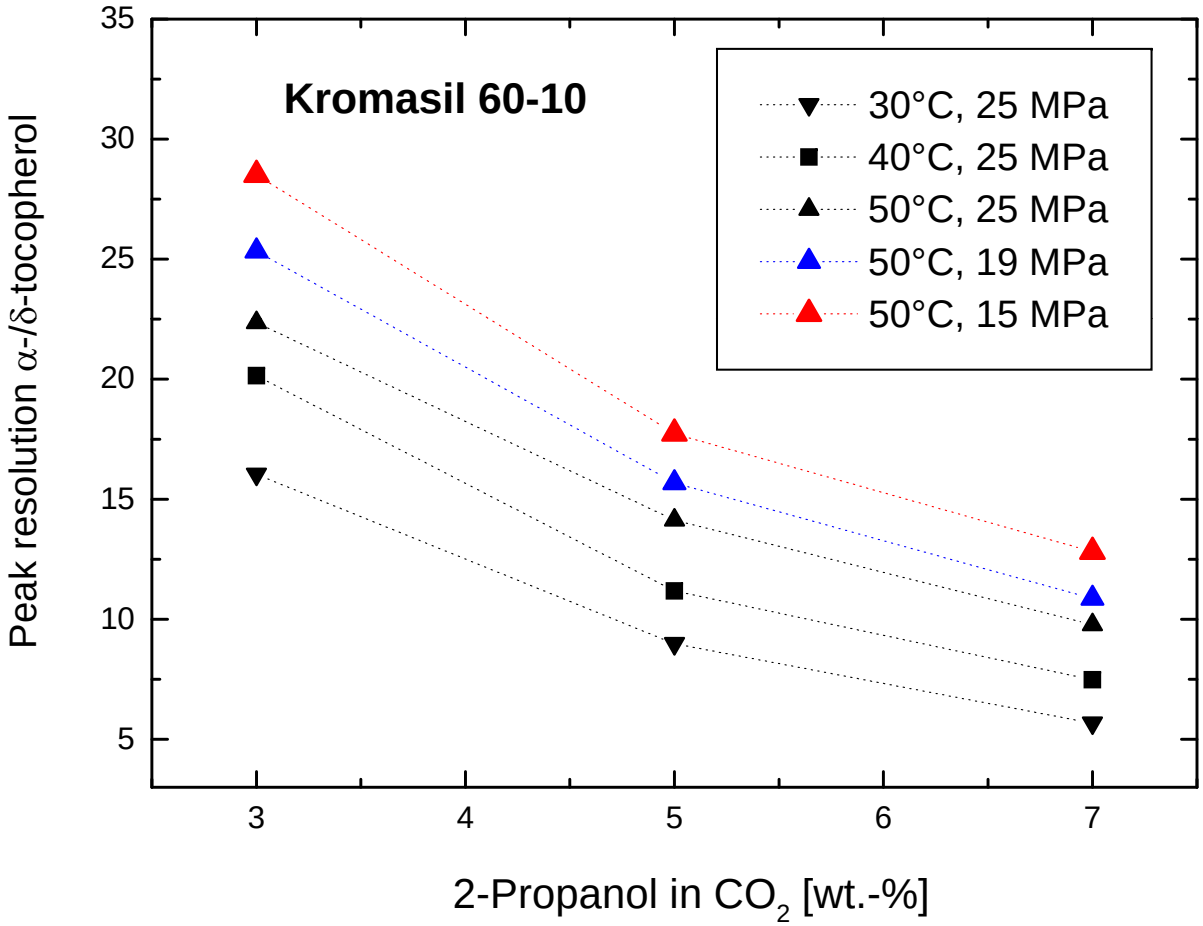
Influence of temperature

SFC separation of (R,S)-ibuprofen



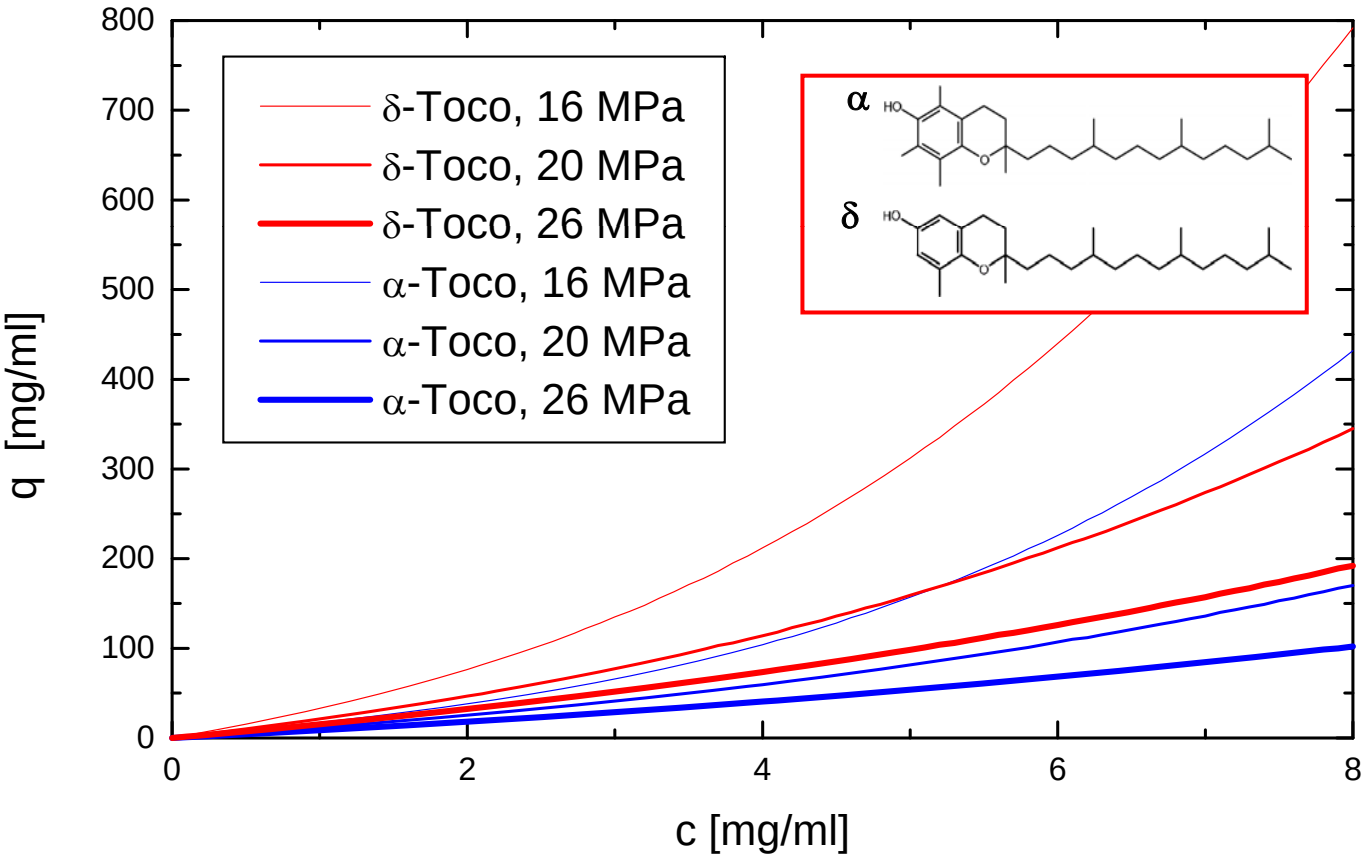
Influence of temperature and pressure

SFC separation of α-/δ- tocopherol



Measurement of adsorption isotherms

Adsorption of α-/δ-tocopherol on Kromasil 60-10,
313 K, 5% 2-Propanol in CO_2



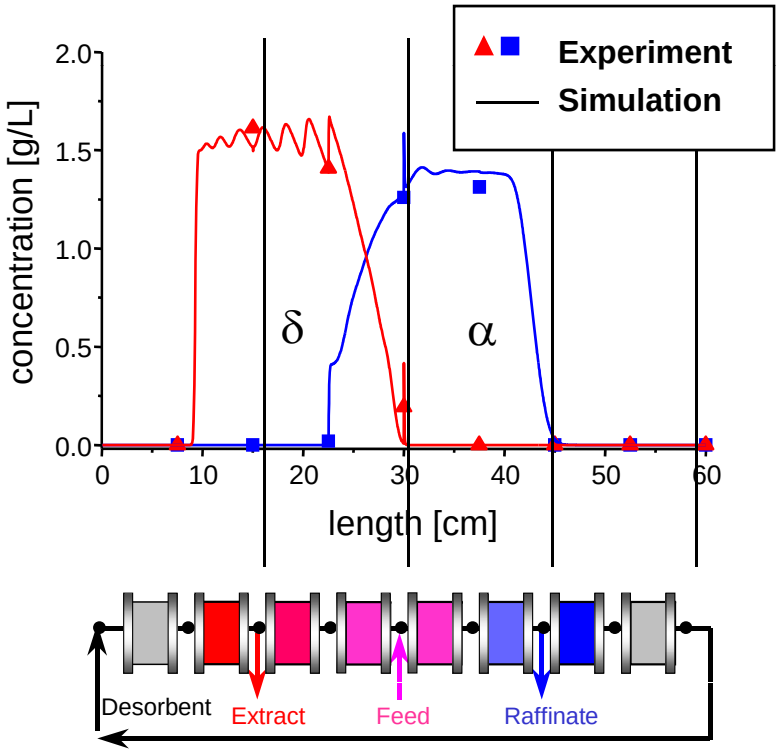
[Lübbert et al., 2006]

Comparison experiment – simulation

Separation of α-/δ-tocopherol on Kromasil (5 wt.-% 2-propanol in CO_2)

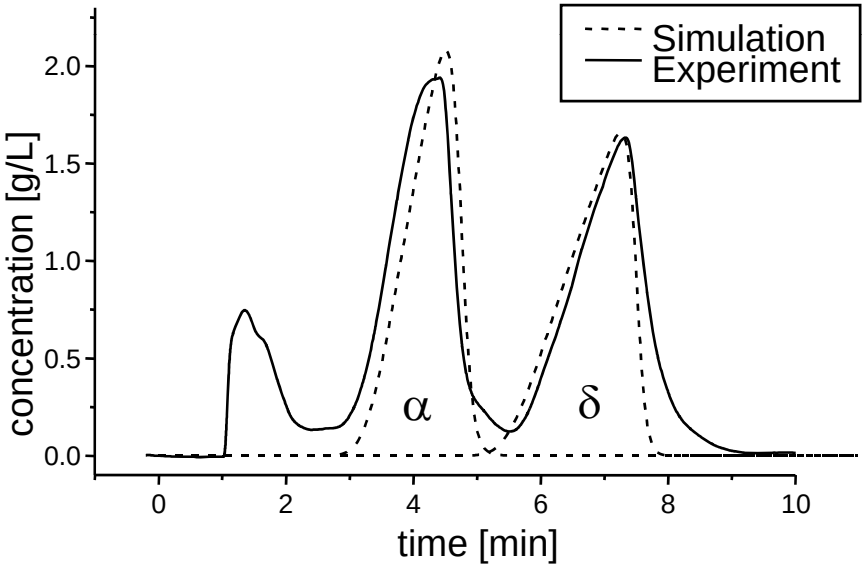
SMB-SFC

c_{Feed} = 10 g/L; p_m = 20 MPa; T = 314 K



Batch-SFC

c_{Feed} = 40 g/L; V_{inj} = 10 ml; p_m = 20 MPa;
T = 313 K; L_{col} = 16.6 cm



Comparison experiment – simulation

Separation of α-/δ-tocopherol on Kromasil (5 wt.-% 2-propanol in CO_2)

SMB-SFC

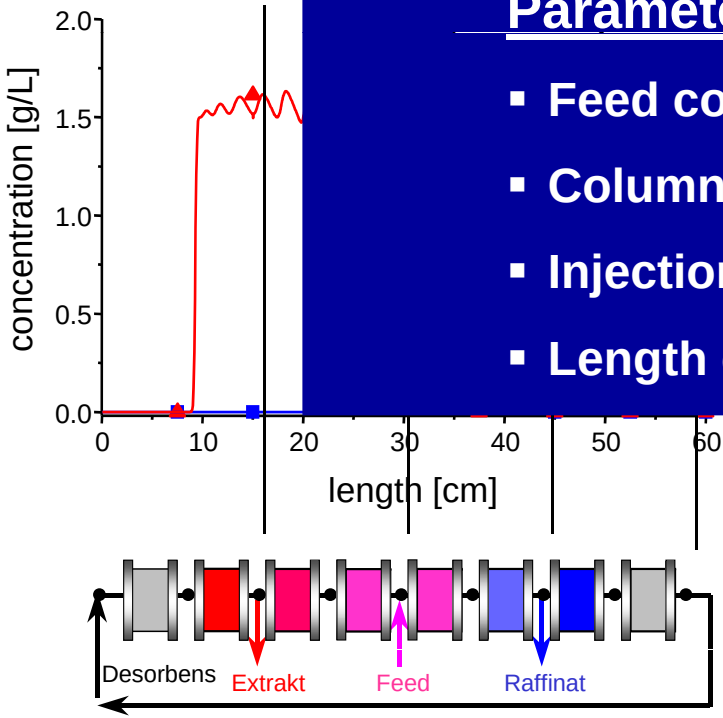
c_{Feed} = 10 g/L; p_m = 20 MPa; T = 314 K

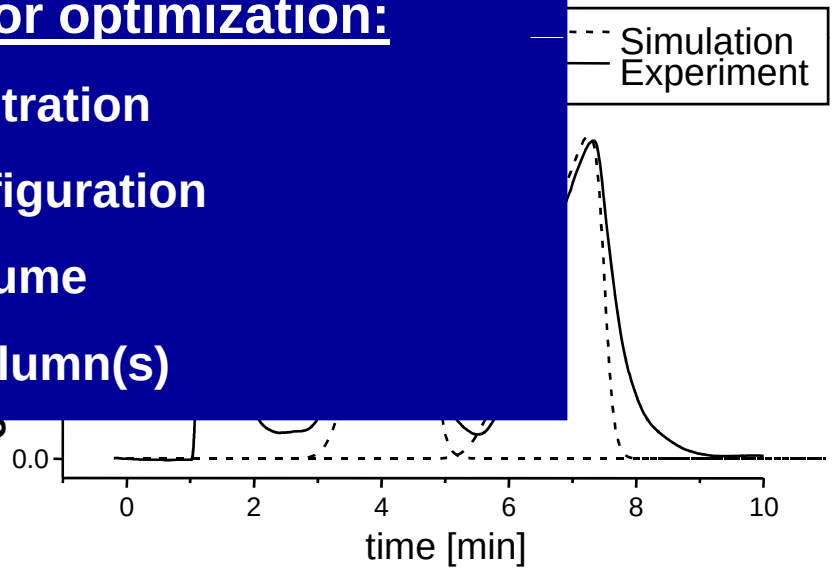
Batch-SFC

c_{Feed} = 40 g/L; V_{inj} = 10 ml; p_m = 20 MPa;

Parameters for optimization:

- Feed concentration
- Column configuration
- Injection volume
- Length of column(s)

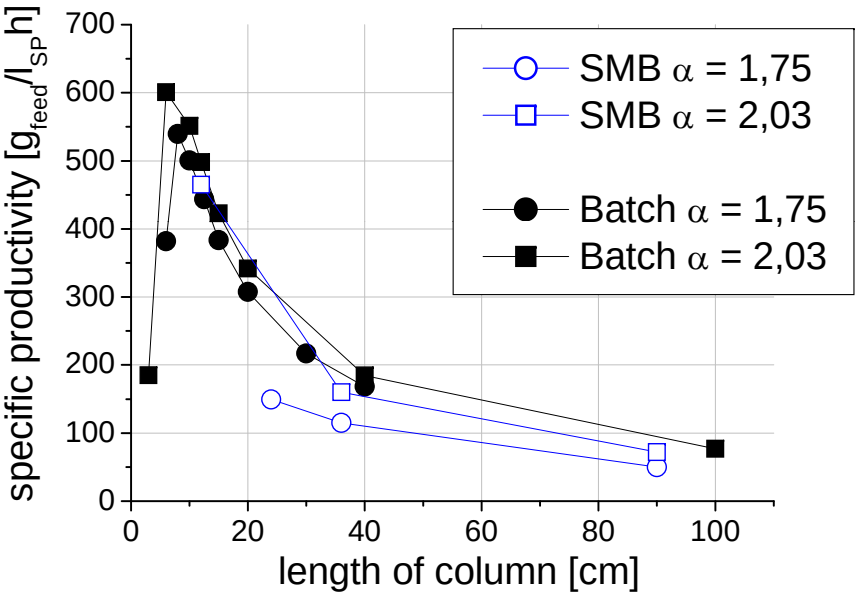




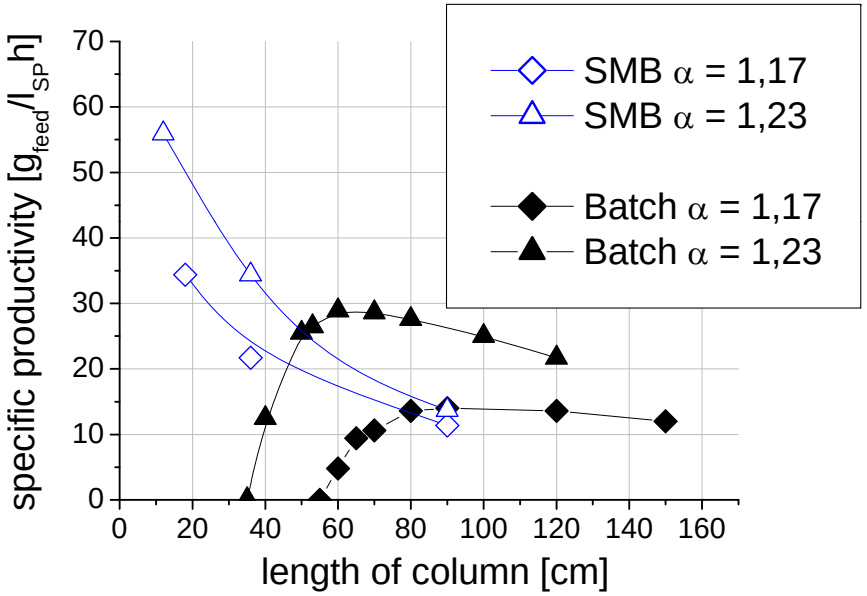
Specific productivities

N_{th} = 2500 m^{-1}, u_{max} = 0.84 cm/s; SMB column configuration: 1/2/2/1

High separation factor



Low separation factor

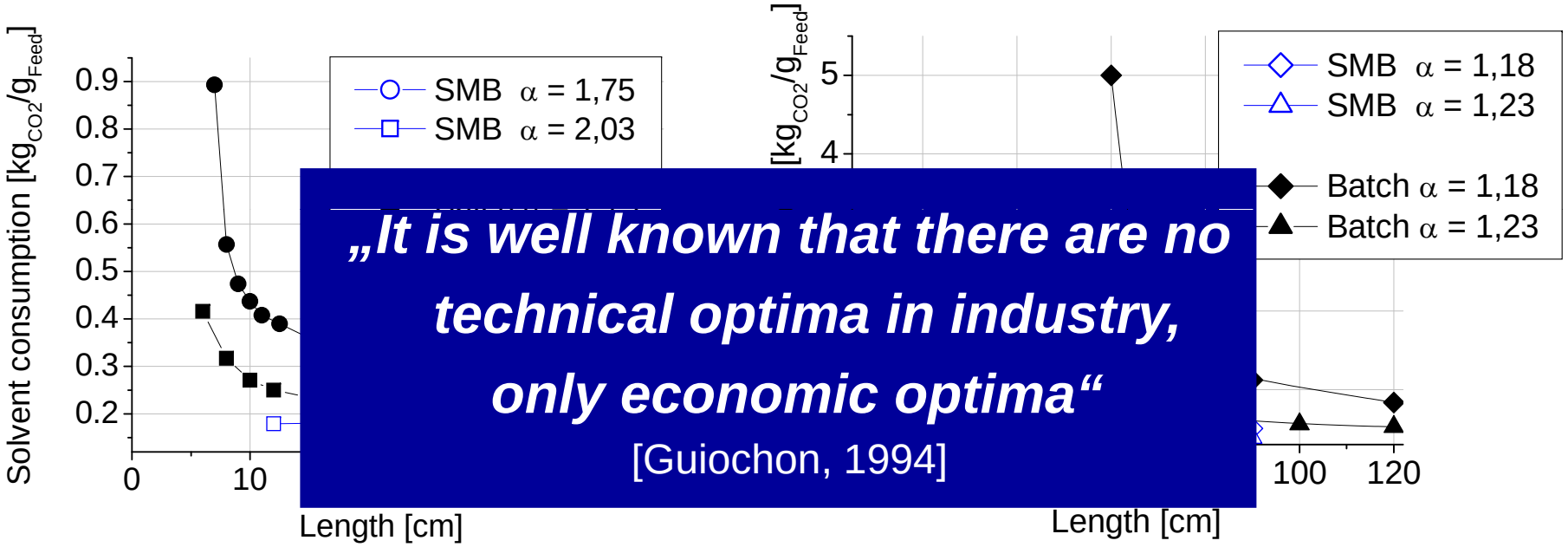


- **<u>High separation factor:</u> Specific productivities nearly the same for both processes (Batch and SMB)**
- **<u>Low separation factors:</u> Specific productivities of the SMB-process significant higher**

Solvent consumption

N_{th} = 2500 m^{-1}, u_{max} = 0.84 cm/s; SMB column configuration: 1/2/2/1

High separation factor **Low separation factor**

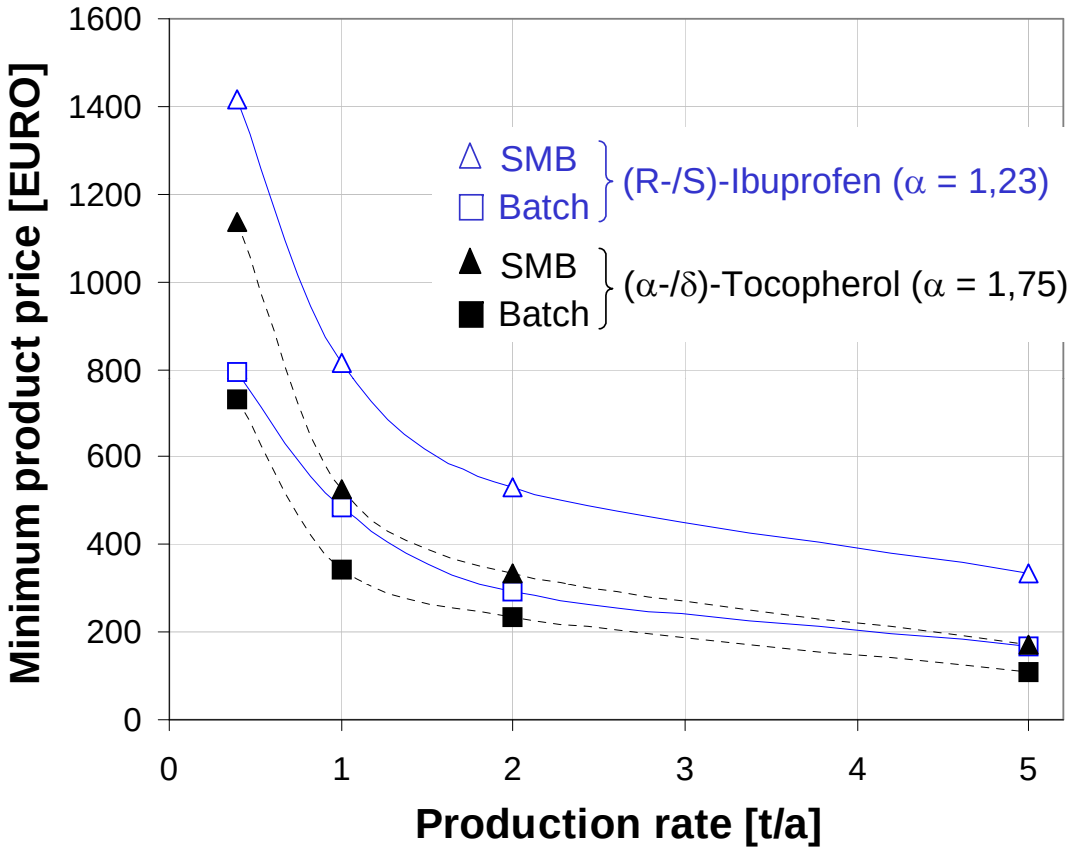


„It is well known that there are no technical optima in industry, only economic optima“

[Guiochon, 1994]

- **The solvent consumption depends on the separation factor**
- **Solvent consumption of SMB-process significant lower**

Minimum product price



[Peper et al., 2007]

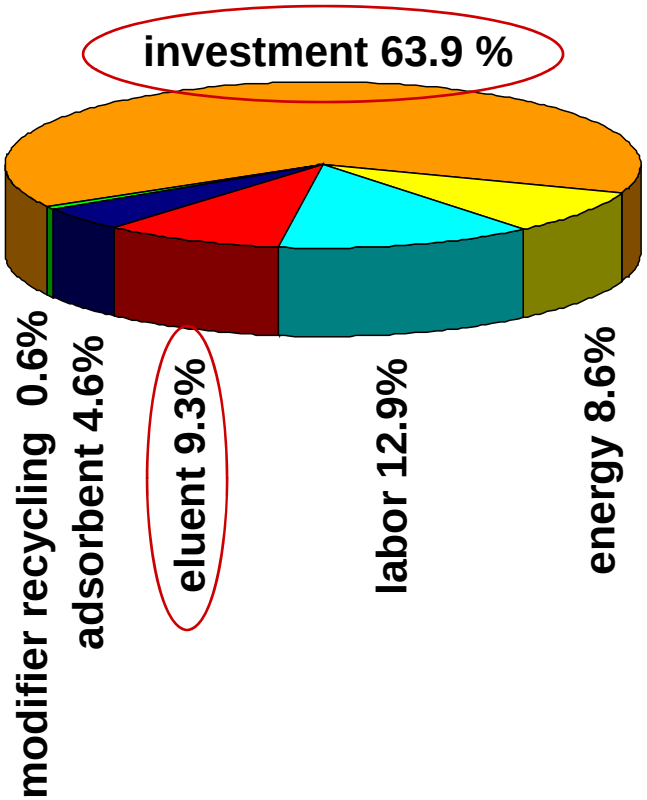
- **In the range of investigated production rates, the Batch-process is the cheaper process**

Distribution of costs

Separation of (R,S)-ibuprofen: 5 t/a (eluent: CO_2 + 2-propanol)

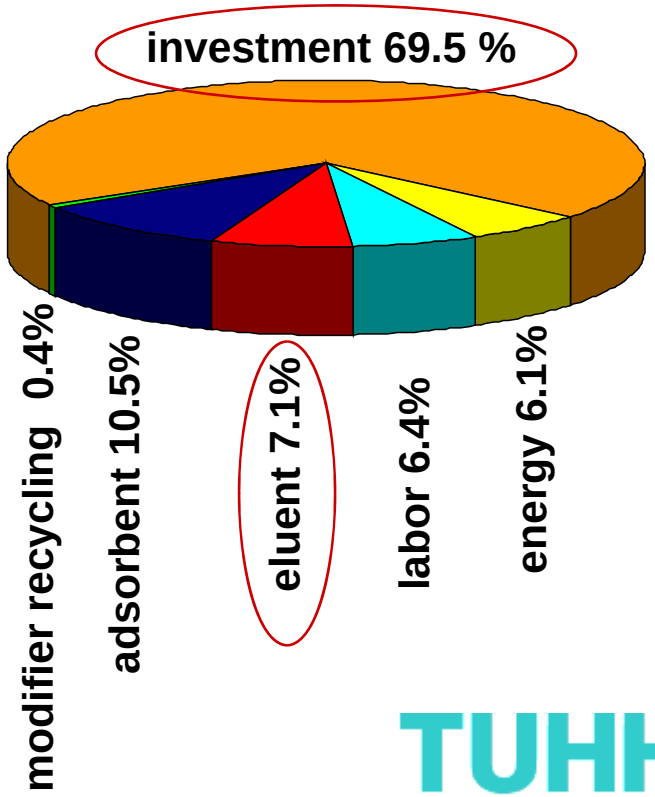
Batch-SFC

167 €/kg



SMB-SFC

337 €/kg



Summary

- Instruments for SFC at different scales are commercially available
- Batch-SFC (250 g st. phase) and SFC-SMB with up to 8 axial compressed columns (700 g st. phase) at TUHH
- Miscellaneous preparative SFC separations were carried out at TUHH successfully
- Adsorption equilibria as basis for optimisation of chromatographic processes
- Methods for process optimisation in SFC (Batch and SMB) are at hand
- In the range of the investigated production rates, the Batch-SFC is the more profitable process compared to SMB-SFC (cheap and easy!)

Summary

- Instruments for SFC at different scales are commercially available
- Batch-SFC (450 g st. phase) and SFC-SMB with up to 8 axial compressed columns (800 g st. phase) at TUHH

Supercritical fluid chromatography:

Ready for broad application as successful separation process in chemical and pharmaceutical industry!

- Methods for process optimisation in SFC (Batch and SMB) are at hand
- In the range of the investigated production rates, the Batch-SFC is the more profitable process compared to SMB-SFC (cheap and easy!)

THANKS

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Thar Instruments

Eka Chemicals

YOU !