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SUBSIDIARY OF DAICEL CHEMICAL INDUSTRIES, LTD.

Novel immobilised polysaccharide-derived CSPs to enhance success rate in the resolution of enantiomers

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Higher success rates can be achieved by:

- Screening only LC or SFC with 7 (or more) columns
- Screening LC and SFC with a limited number of columns

What is the best choice?

LC

SFC

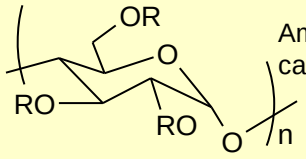
Some of the requirements / challenges

- Resolution of the enantiomeric pair (or isomeric mixture)
- Resolution from impurities
- Short analysis times
- Suitable elution order
- Compatibility of the sample media with mobile phase and column
- Low LOD/LOQ
- Reproducibility and robustness of the method
- Stability of the sample under the analytical conditions

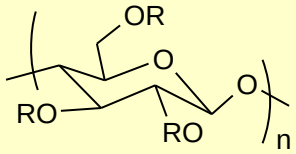
Can we achieve this with a minimum number of columns and efficient screening strategies?

How were we handling in the last years?

- Samples are screened systematically in LC and SFC with a FAST screening
- Systematic screening
  - LC on IA, IB and IC (H/IPA, H/EtOH, H/THF, H/DCM, H/AcOEt, ACN and alcohol)
  - SFC on IA, IB and IC (MeOH, IPA and EtOH)

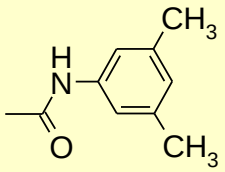


Amylose-based carbamates



Cellulose-based carbamates

CHIRALPAK IA



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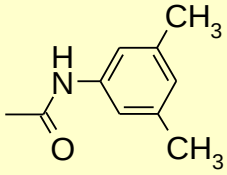
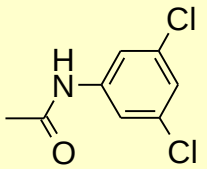


CHIRALPAK IC

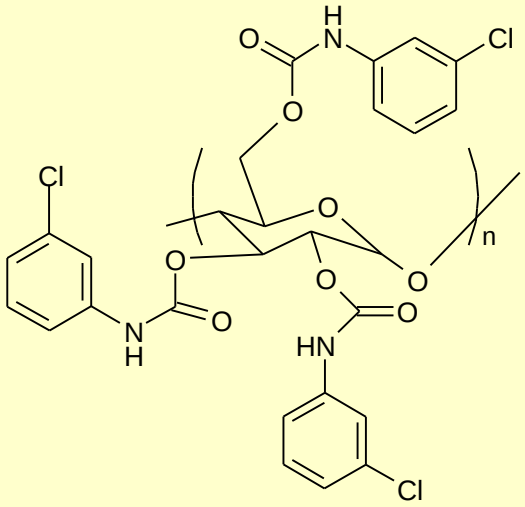


In which aspects solvent versatility was helping?

- Free choice of solvents in the mobile phase to match solubility
- Greater options for chemical stability
- New selectivities (and elution orders)
- Favouring elution kinetics with certain solvents
- Choice in the sample solvent dictated by sample solubility
- Column and method robustness

T. Zhang et al., *J. Chromatogr. A* 1191 (2008) 214

CHIRALPAK ID

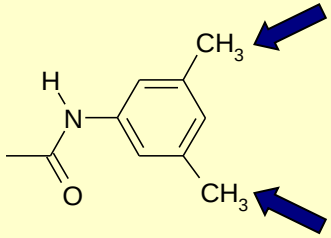


Based on
amylose *tris*-(3-chlorophenylcarbamate)

A new selector
for the immobilised series!!

Different substituents
New enantiorecognition

CHIRALPAK IA
CHIRALPAK IB



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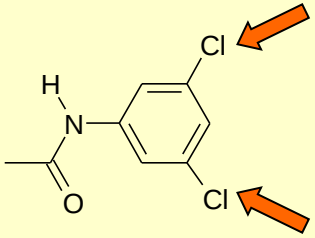
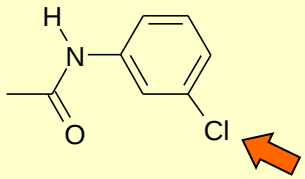


CHIRALPAK ID



Looking for complementary recognition patterns

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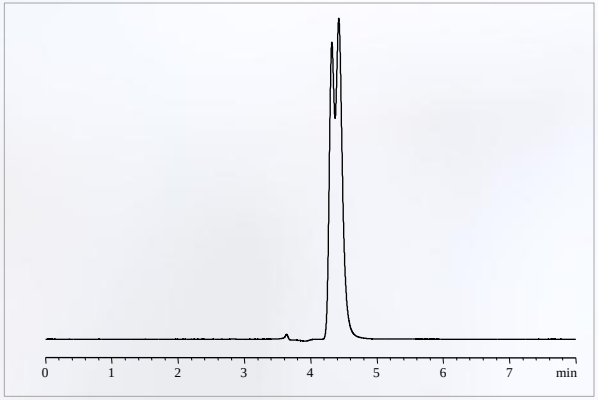
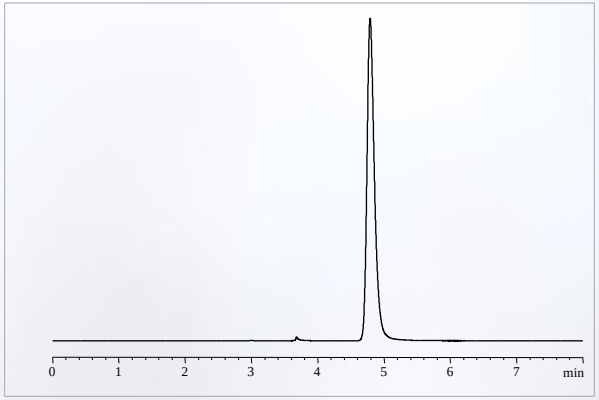
HPLC method development

CHIRALPAK ID
Complementary properties

Examples in HPLC

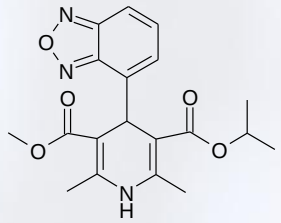


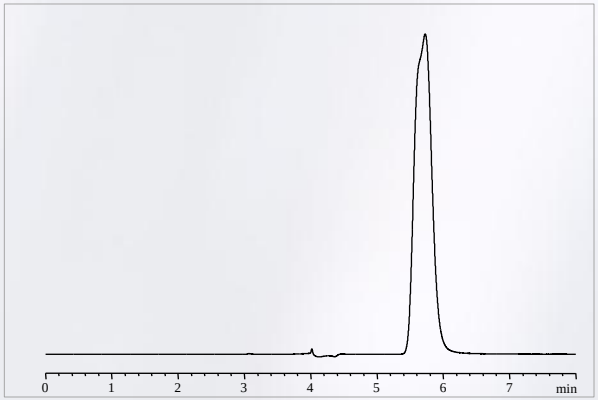
CHIRALPAK **IA**



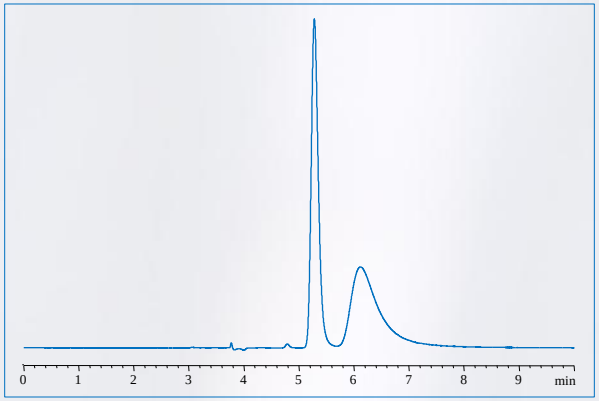
CHIRALPAK **IB**

Isradipine





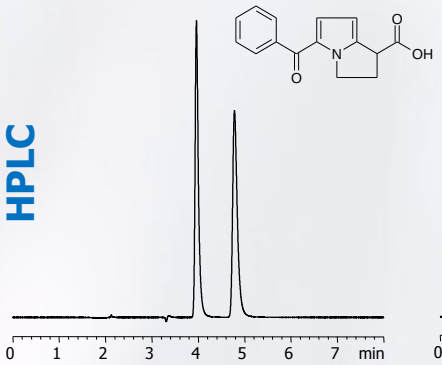
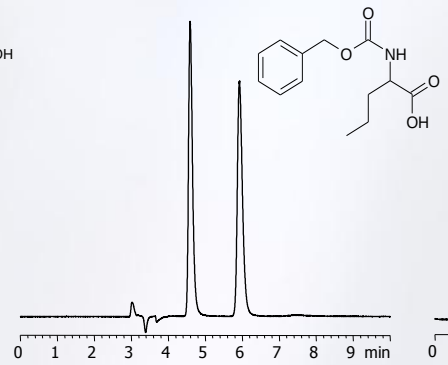
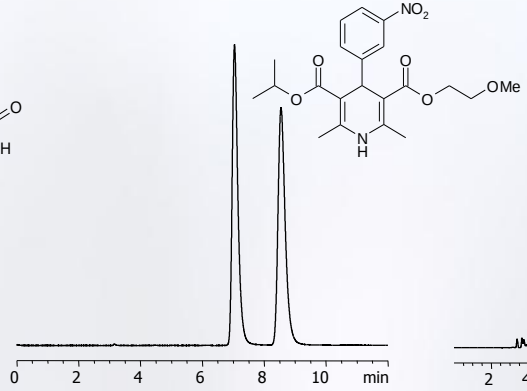
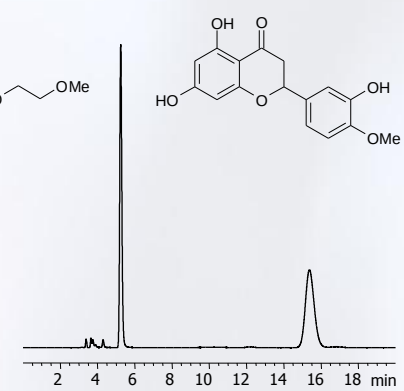
CHIRALPAK **IC**



CHIRALPAK **ID**

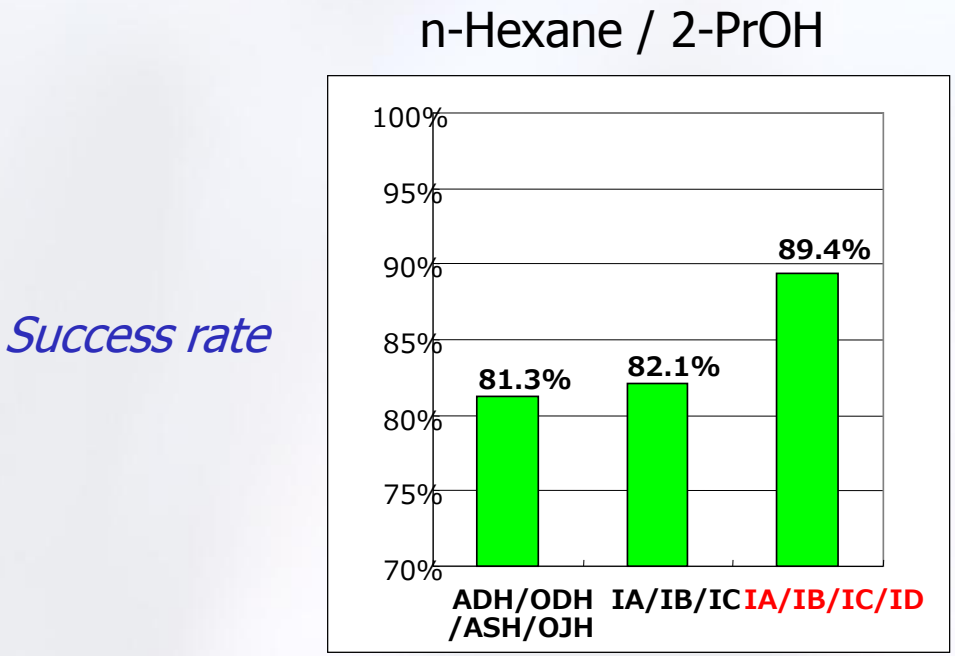
Hexane/2-PrOH/DEA 80/20/0.1 (250 x 4.6 mm, 5 µm); 1.0 mL/min; 25 C

Mobile phase selection in HPLC
Analytical methods

CHIRALPAK IA	CHIRALPAK IB	CHIRALPAK IC	CHIRALPAK ID
HPLC			
			
ACN/IPA/TFA 95/5	Hex/IPA/TFA 80/20/0.1	Hex/THF/DEA 85/15/0.1	MtBE/MeOH/TFA 90/10/0.1

Column dimensions: 250 x 4.6 mm, 5 µm; 1.0 mL/min; 25 C

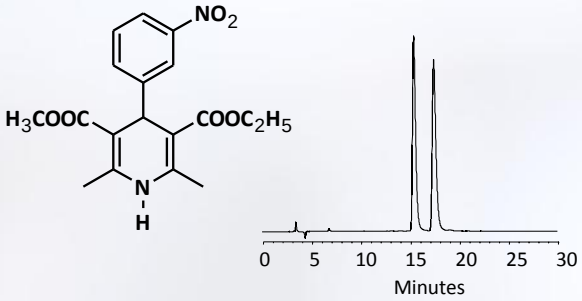
Comparison of success rates between immobilized type columns and representative coated type columns for 123 compounds under Hexane/2-PrOH



Success rate with a single mobile phase combination!

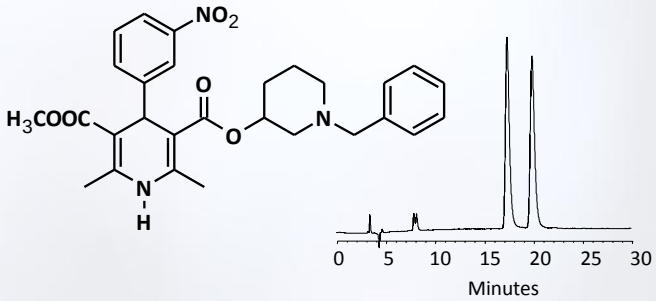
Dihydropyridine-type drugs on CHIRALPAK ID

Nitrendipine



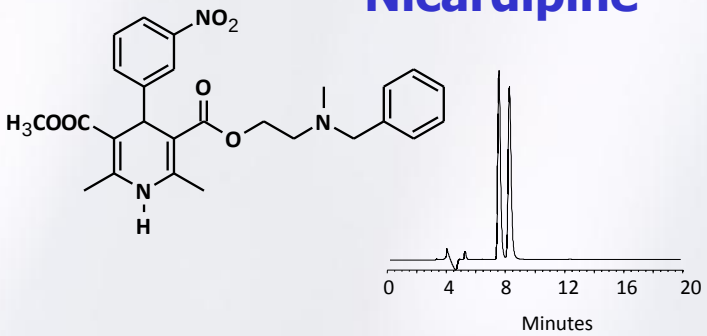
***n*-Hex-THF-DEA**
90:10:0.1

Benidipine



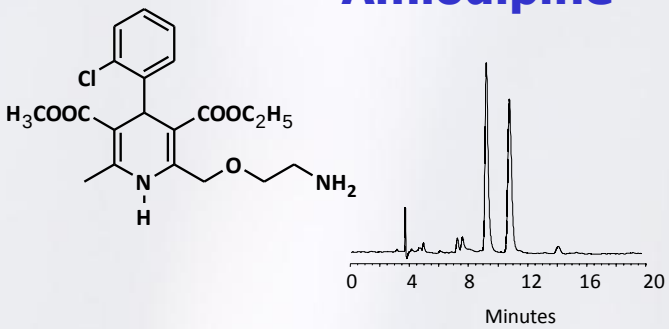
***n*-Hex-THF-DEA**
90:10:0.1

Nicardipine



***n*-Hex-MTBE-EtOH-DEA**
50:50:1:0.1

Amlodipine

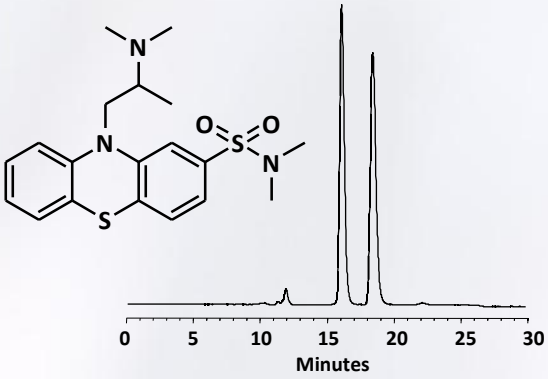


***n*-Hex-IPA-Isopropylamine**
80:20:0.1

CHIRALPAK ID (250 x 4.6 mm, 5 µm); 1.0 mL/min; 254 nm; 25 C

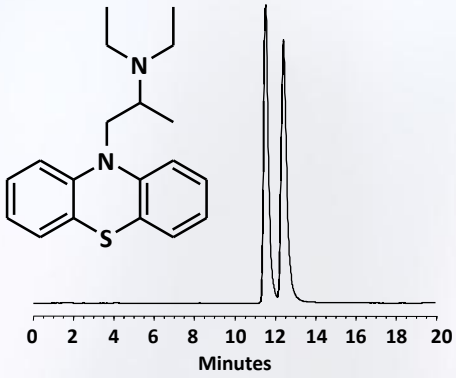
Phenothiazine-type drugs on CHIRALPAK ID

Dimetotiazine



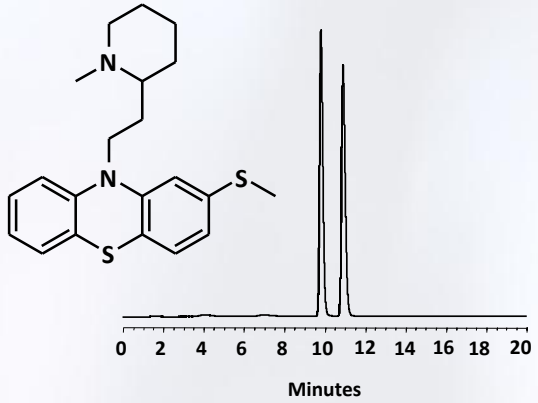
n-Hex-IPA-DEA
80:20:0.1

Profenamine



n-Hex-EtOH-DEA
100:0.1:0.1 (0.5mL/min.)

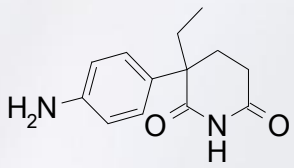
Thioridazine



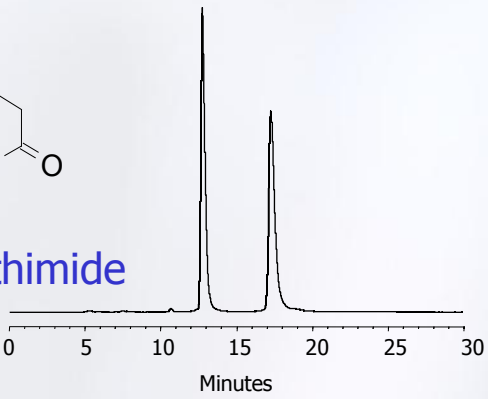
n-Hex-CH_2Cl_2-EtOH-DEA
95:5:1:0.1

CHIRALPAK ID (250 x 4.6 mm, 5 µm); 1.0 mL/min; 254 nm; 25 C

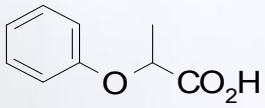
Recognition in RP-mode



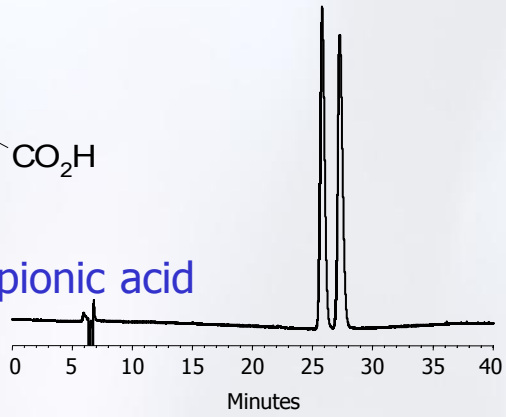
Aminoglutethimide



20mM NH_4HCO_3aq. (pH=9)/ACN=30/70



2-Phenoxypropionic acid



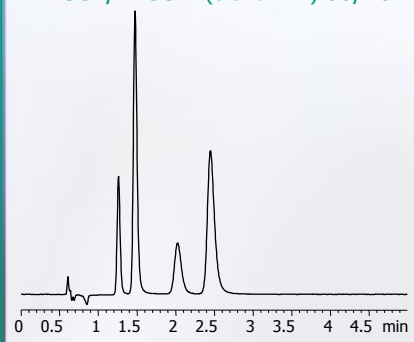
HCOOH aq.(pH=2.0)/ACN=85/15

CHIRALPAK ID (250 x 4.6 mm, 5 µm); 0.5 mL/min; 25 C

Different elution profile and method optimisation

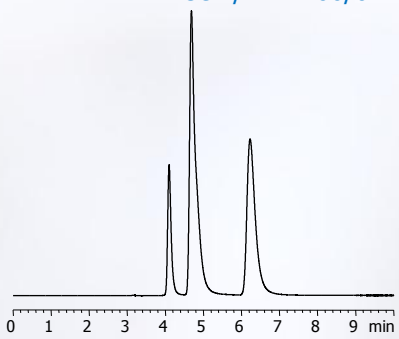
CHIRALPAK IA
(4.6 x 150mm)

SFC
CO_2/ MeOH (0.5% DEA) 80/20



CHIRALPAK IA
(4.6 x 250mm)

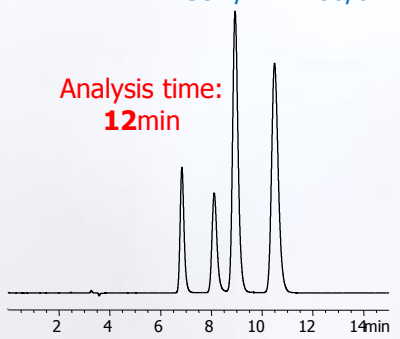
HPLC
MeOH/DEA 100/0.1



CHIRALPAK **IC**
(4.6 x 250mm)

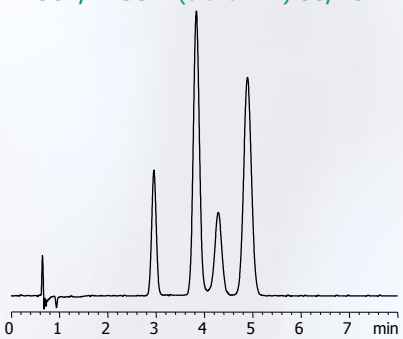
HPLC
MeOH/DEA 100/0.1

Analysis time:
12min



CHIRALPAK IC
(4.6 x 150mm)

SFC
CO_2/ MeOH (0.5% DEA) 80/20

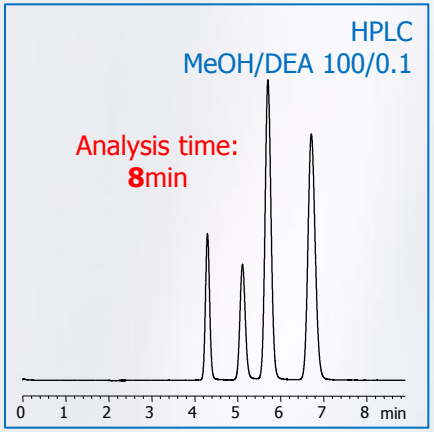


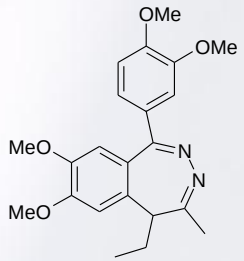
Column transfer from 5µm to 3µm

CHIRALPAK **IC-3**
(4.6 x 150mm)

HPLC
MeOH/DEA 100/0.1

Analysis time:
8min





Tofisopam

- Same enantioselectivity
- Reduced column length
- Reduced analysis time
- No loss in resolution degree

SFC method development

Primary Screen

CHIRALPAK IA
CHIRALPAK IB
CHIRALPAK IC
CHIRALPAK ID

Mobile phase system

EtOH, MeOH, 2-PrOH
Acetonitrile

Dichloromethane
Ethyl acetate
THF
MtBE

Secondary Screen

CHIRALPAK AD-H
CHIRALPAK AS-H
CHIRALPAK AY-H
CHIRALPAK AZ-H

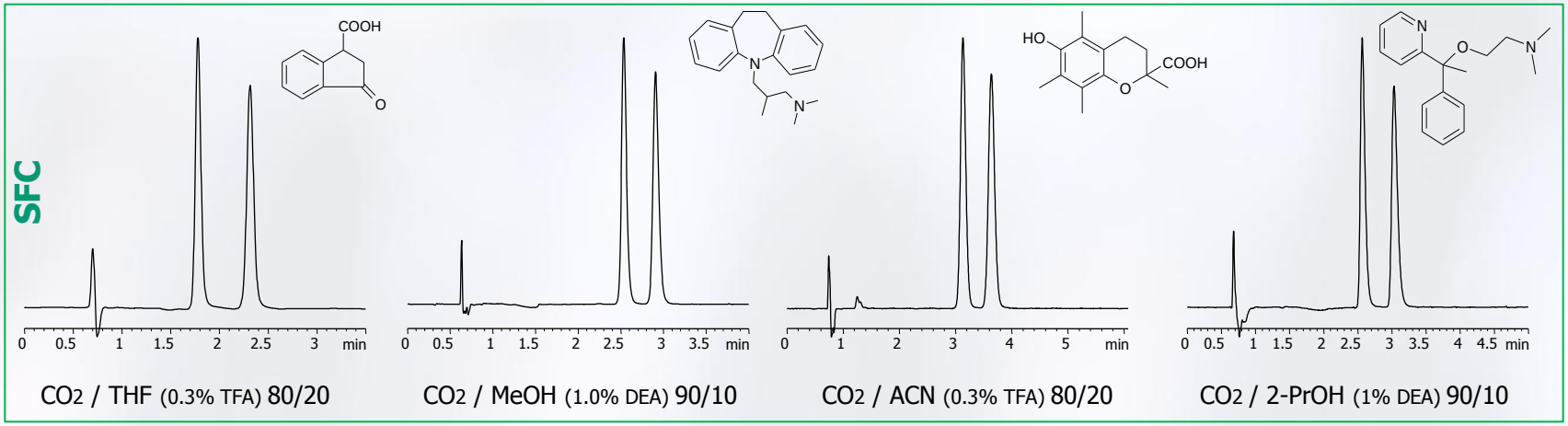
CHIRALCEL OD-H
CHIRALCEL OJ-H
CHIRALCEL OZ-H
CHIRALCEL OX-H

Co-solvents

EtOH, MeOH, 2-PrOH
Acetonitrile

Mobile phase selection in SFC
Examples

SFC



CO_2 / THF (0.3% TFA) 80/20 — CHIRALPAK IA

CO_2 / MeOH (1.0% DEA) 90/10 — CHIRALPAK IB

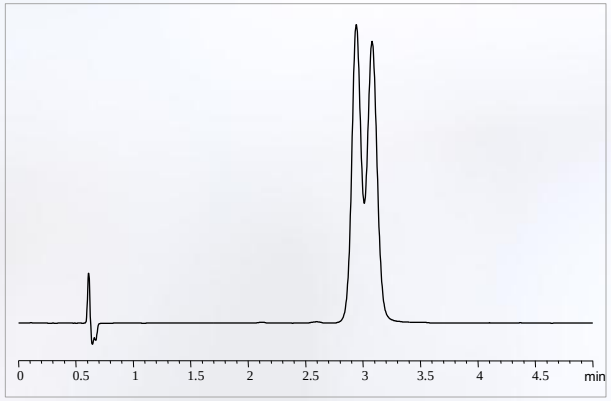
CO_2 / ACN (0.3% TFA) 80/20 — CHIRALPAK IC

CO_2 / 2-PrOH (1% DEA) 90/10 — CHIRALPAK ID

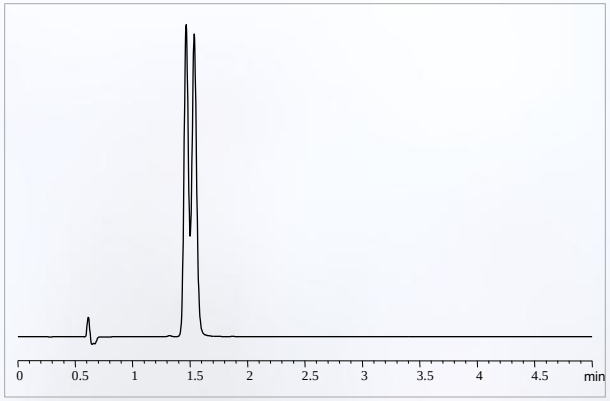
Column dimensions: 150 x 4.6 mm, 5 µm; 3.0 mL/min; 25 C

CHIRALPAK ID
Complementary properties

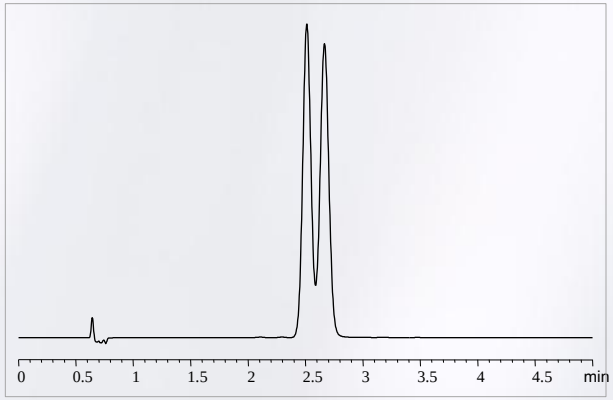
Examples in SFC



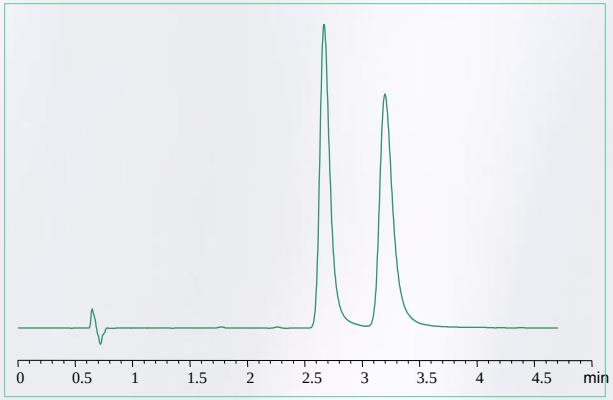
CHIRALPAK **IA**



CHIRALPAK **IB**

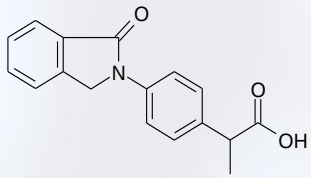


CHIRALPAK **IC**



CHIRALPAK **ID**

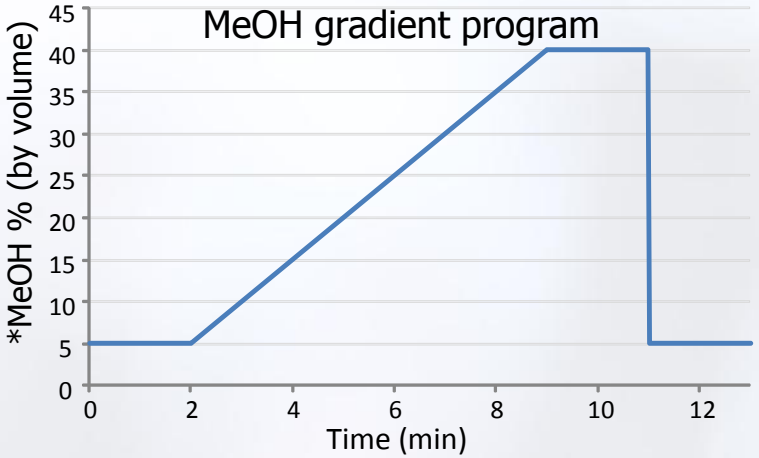
Indoprofen



30% MeOH (+0.2% TFA) in CO_2 (150 x 4.6 mm, 5 µm); 3.0 mL/min; 150 bar

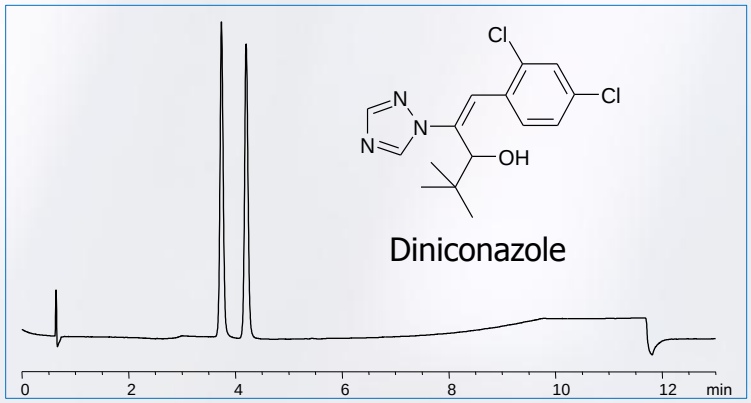
Isocratic or gradient?

CTE examples in SFC

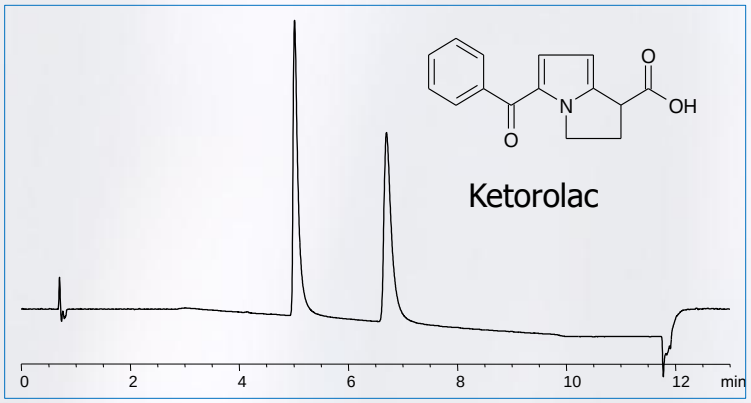


Back pressure: 150bar, Flow rate: 3.0ml/min,
Temperature: 35°C

* Containing 0.3% DEA for screening of basic compounds



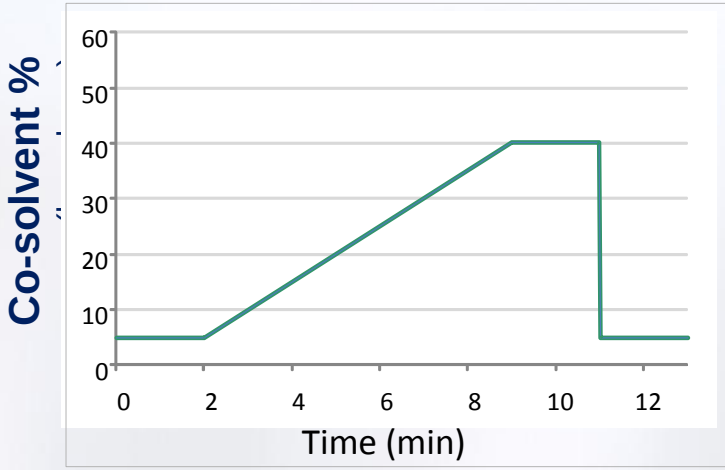
CHIRALPAK IA



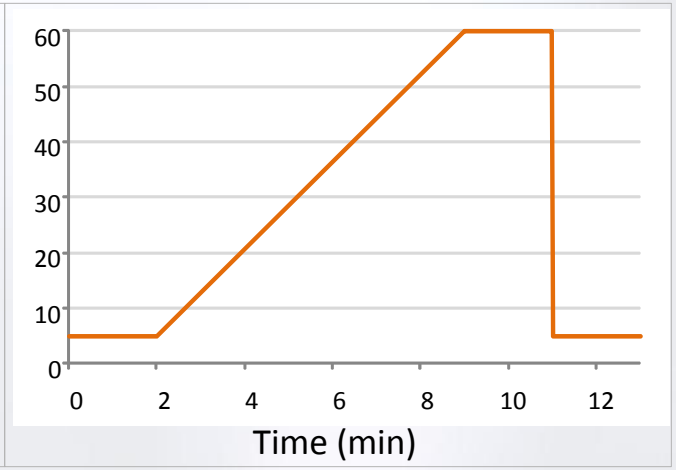
CHIRALPAK ID

Method development - SFC gradient programs

MeOH-CO_2 gradient



ACN- or THF-CO_2 gradient



Back pressure: 150 bar, Flow rate: 3.0ml/min,
Temperature: 35 C
Containing 0.2-0.3% DEA for basic compounds

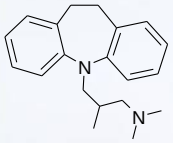
Main co-solvents and their relative eluting strength

MeOH > EtOH > 2-PrOH

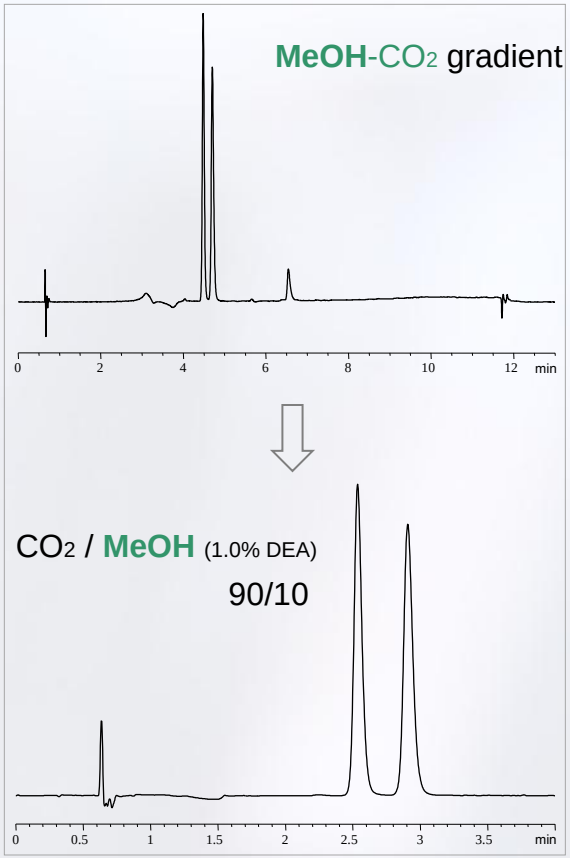
MeOH > ACN ≈ THF

SFC-From gradient to isocratic

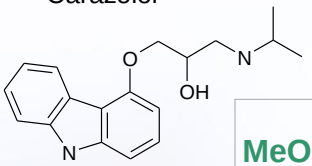
Trimipramine



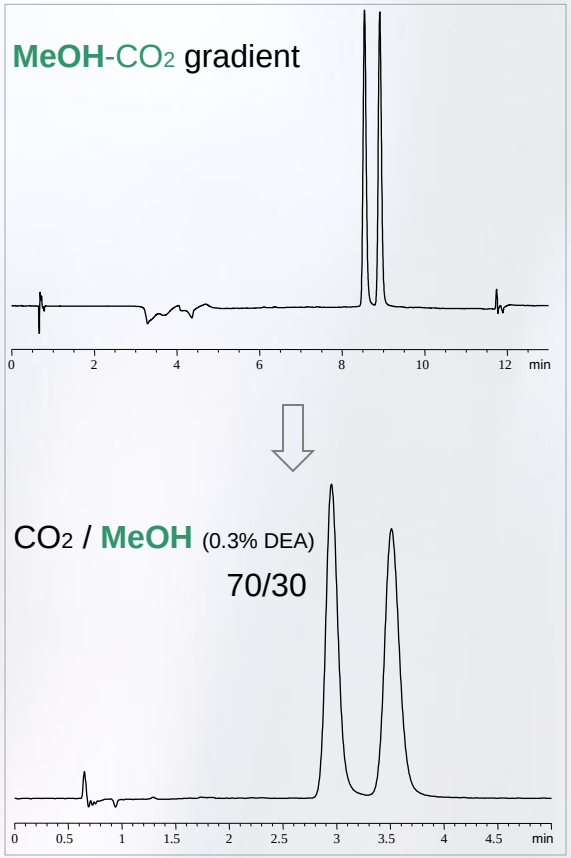
CHIRALPAK IB



Carazolol

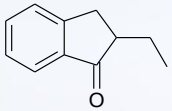


CHIRALPAK IC

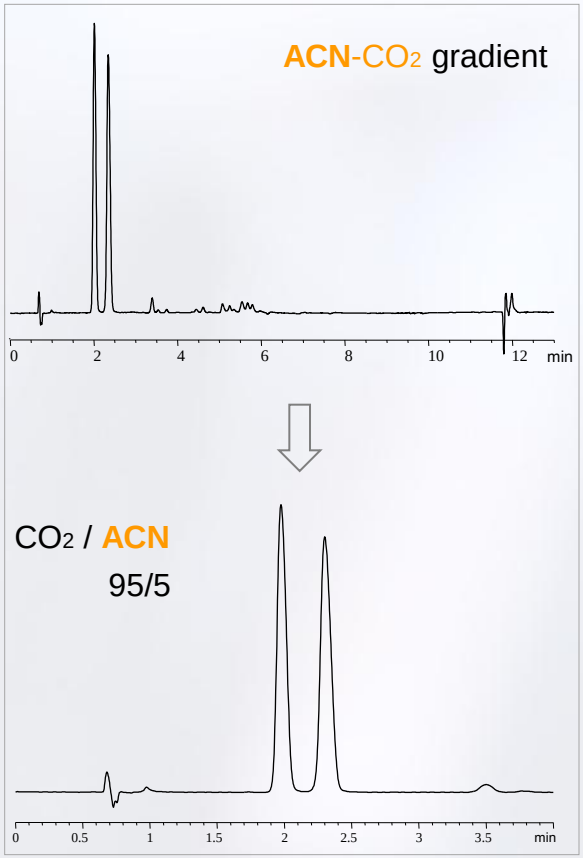


SFC-From gradient to isocratic

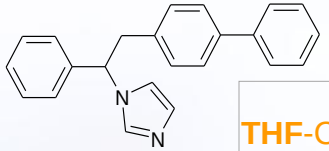
2-Ethyl-1-indanone



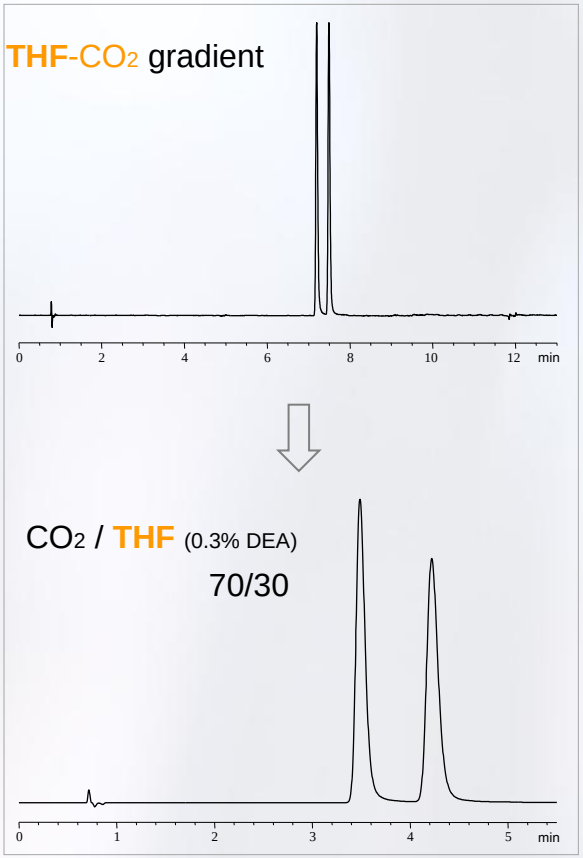
CHIRALPAK IA



Bifonazole



CHIRALPAK ID



Screening strategies
by LC and SFC

- First objective is *fast* screen with high success rate
- Different derivatives introduce additional recognition options
- Solvent versatility is necessary to match
  resolution, solubility and chemical stability

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