

Edited by
Henner Schmidt-Traub

 WILEY-VCH

Preparative Chromatography

of Fine Chemicals and Pharmaceutical Agents



Introduction

1 Introduction 1

R. Ditz

1.1 Liquid Chromatography – its History 1

1.2 Focus of the Book 4

1.3 How to Read this Book 6

2 Fundamentals and General Terminology 9

M. Schulte, A. Epping

2.1 Principles of Adsorption Chromatography 9

2.1.1 Adsorption Process 10

2.1.2 Chromatographic Process 12

2.2 Basic Effects and Chromatographic Definitions 13

2.2.1 Chromatograms and their Parameters 13

2.2.2 Voidage and Porosity 15

2.2.3 Influence of Adsorption Isotherms on the Chromatogram 18

2.3 Fluid Dynamics 20

2.3.1 Extra Column Effects 21

2.3.2 Column Fluid Distribution 21

2.3.3 Packing Non-idealities 22

2.3.4 Sources for Non-ideal Fluid Distribution 22

2.4 Mass Transfer Phenomena 23

2.4.1 Principles of Mass Transfer 23

2.4.2 Efficiency of Chromatographic Separations 25

2.4.3 Resolution 28

2.5 Equilibrium Thermodynamics 32

2.5.1 Definition of Isotherms 32

2.5.2 Models of Isotherms 33

2.5.2.1 Single-component Isotherms 34

2.5.2.2 Multi-component Isotherms 36

2.5.2.3 Ideal Adsorbed Solution (IAS) Theory 37

2.6 Thermodynamic Effects on Mass Separation 41

2.6.1 Mass Load 41

2.6.2 Linear and Nonlinear Isotherms 41

2.6.3 Elution Modes 46

- 2.7 Practical Aspects of Parameter Determination 47
 - 2.7.1 Linearized Chromatography 48
 - 2.7.2 Nonlinear Chromatography 49
- 3 Columns, Packings and Stationary Phases 51**
K. K. Unger, C. du Fresne von Hohenesche, M. Schulte
 - 3.1 Column Design 51
 - 3.1.1 Column Hardware and Dimensions 51
 - 3.1.2 Columns with Particles (Particulate Column Beds) 54
 - 3.1.3 Columns with a Continuous Bed (Monolithic Columns) 55
 - 3.1.4 Column Pressure Drop 56
 - 3.1.5 Frit Design 57
 - 3.2 Column Packings 62
 - 3.2.1 Survey of Packings and Stationary Phases 62
 - 3.2.2 Generic, Designed and Tailored Adsorbents 63
 - 3.2.2.1 Generic Adsorbents 63
 - 3.2.2.2 Tailored Adsorbents 66
 - 3.2.2.3 Designed Adsorbents 66
 - 3.2.3 Reversed Phase Silicas 67
 - 3.2.3.1 Silanisation of the Silica Surface 68
 - 3.2.3.2 Reversed Phase Packings with Polymer Coatings (Types of Polymer Coatings) 72
 - 3.2.3.3 Physico-chemical Properties of Reversed Phase Silicas 74
 - 3.2.3.4 Chromatographic Characterization of Reversed Phase Silicas 76
 - 3.2.4 Cross-linked Organic Polymers 78
 - 3.2.4.1 General Aspects 79
 - 3.2.4.2 Hydrophobic Polymer Stationary Phases 82
 - 3.2.5 Chiral Stationary Phases 83
 - 3.2.6 Properties of Packings and their Relevance to Chromatographic Performance 86
 - 3.2.6.1 Chemical and Physical Bulk Properties 87
 - 3.3 Column Packing Technology 93
 - 3.3.1 Characterization of the Column Bed Structure 95
 - 3.3.2 Assessment of Column Performance 96
 - 3.4 Column Testing 97
 - 3.4.1 Test Systems 97
 - 3.4.2 Hydrodynamic Properties and Column Efficiency 98
 - 3.4.3 Mass Loadability 99
 - 3.4.4 Comparative Rating of Columns 100
 - 3.5 Column Maintenance and Regeneration 101
 - 3.5.1 Cleaning in Place (CIP) 101
 - 3.5.2 Conditioning of Silica Surfaces 103
 - 3.5.3 Sanitization in Place (SIP) 104
 - 3.5.4 Column and Adsorbent Storage 105

- 3.6 Guidelines for Choosing Chromatographic Columns and Stationary Phases 105

- 4 Selection of Chromatographic Systems 107**
W. Wewers, J. Dingenen, M. Schulte, J. Kinkel
- 4.1 Definition of the Task 110
- 4.2 Properties of Chromatographic Systems 114
 - 4.2.1 Mobile Phases for Liquid Chromatography 114
 - 4.2.1.1 Stability 117
 - 4.2.1.2 Safety Concerns 117
 - 4.2.1.3 Operating Conditions 117
 - 4.2.2 Adsorbent and Phase System 120
 - 4.2.2.1 Normal Phase System 121
 - 4.2.2.2 Reversed Phase Chromatography 122
- 4.3 Criteria for Choice of Chromatographic Systems 124
 - 4.3.1 Choice of Phase System Dependent on Solubility 125
 - 4.3.1.1 Improving Loadability for Poor Solubilities 127
 - 4.3.1.2 Dependency of Solubility on Sample Purity 129
 - 4.3.1.3 Generic Gradients for Fast Separations 130
 - 4.3.2 Criteria for Choice of NP Systems 130
 - 4.3.2.1 Pilot Technique Thin-layer Chromatography 131
 - 4.3.2.2 Retention in NP Systems 131
 - 4.3.2.3 Solvent Strength in Liquid–Solid Chromatography 133
 - 4.3.2.4 Selectivity in NP Systems 136
 - 4.3.2.5 Mobile Phase Optimization by TLC Following the PRISMA Model 136
 - 4.3.2.6 Strategy for an Industrial Preparative Chromatography Laboratory 145
 - 4.3.3 Criteria for Choosing RP Systems 150
 - 4.3.3.1 Retention and Selectivity in RP Systems 150
 - 4.3.3.2 Gradient Elution for Small amounts of Product on RP Materials 152
 - 4.3.3.3 Rigorous Optimization for Isocratic Runs 154
 - 4.3.3.4 Rigorous Optimization for Gradient Runs 156
 - 4.3.3.5 Practical Recommendations 160
 - 4.3.4 Criteria for Choosing CSP Systems 162
 - 4.3.4.1 Suitability of Preparative CSP 162
 - 4.3.4.2 Development of Enantioselectivity 163
 - 4.3.4.3 Optimization of Separation Conditions 165
 - 4.3.4.4 Practical Recommendations 166
 - 4.3.5 Conflicts During Optimization of Chromatographic Systems 168

- 5 Process Concepts 173**
M. Schulte, K. Wekenborg, W. Wewers
- 5.1 Design and Operation of Equipment 173
 - 5.1.1 Solvent and Sample Delivery System 175
 - 5.1.1.1 HPLC Pumps 175
 - 5.1.1.2 Gradient Formation 175

- 5.1.1.3 Eluent Degassing 176
- 5.1.1.4 Eluent Reservoir 176
- 5.1.1.5 Sample Injection 177
- 5.1.2 Chromatographic Column 177
- 5.1.3 Detection and Separation System 177
 - 5.1.3.1 Solvent-sensitive Detectors 181
 - 5.1.3.2 Fraction Collection 182
- 5.2 Discontinuous Processes 183
 - 5.2.1 Isocratic Operation 183
 - 5.2.2 Flip-flop Chromatography 184
 - 5.2.3 Closed-loop Recycling Chromatography 185
 - 5.2.4 Steady State Recycling Chromatography 187
 - 5.2.5 Gradient Chromatography 188
- 5.3 Continuous Processes 190
 - 5.3.1 Column Switching Chromatography 190
 - 5.3.2 Annular Chromatography 190
 - 5.3.3 Multiport Switching Valve Chromatography (ISEP/CSEP) 191
 - 5.3.4 Simulated Moving Bed (SMB) Chromatography 193
 - 5.3.5 SMB Chromatography with Variable Conditions 197
 - 5.3.5.1 VariCol 197
 - 5.3.5.2 PowerFeed 199
 - 5.3.5.3 Partial feed 199
 - 5.3.5.4 ISMB 200
 - 5.3.5.5 ModiCon 201
 - 5.3.6 Gradient SMB Chromatography 201
 - 5.3.6.1 Solvent-gradient SMB Chromatography 201
 - 5.3.6.2 Supercritical Fluid SMB Chromatography 202
 - 5.3.6.3 Temperature-gradient SMB Chromatography 203
- 5.4 Guidelines 204
 - 5.4.1 Scale 204
 - 5.4.2 Range of k' 205
 - 5.4.3 Number of Fractions 206
 - 5.4.4 Example 1: Lab Scale; Two Fractions 206
 - 5.4.5 Example 2: Lab Scale; Three or More Fractions 206
 - 5.4.6 Example 3: Production Scale; Wide Range of k' 209
 - 5.4.7 Example 4: Production Scale; Two Main Fractions 210
 - 5.4.8 Example 5: Production Scale; Three Fractions 211
 - 5.4.9 Example 6: Production Scale; Multi-stage Process 213
- 6 Modeling and Determination of Model Parameters 215**
 - M. Michel, A. Epping, A. Jupke*
 - 6.1 Introduction 215
 - 6.2 Models for Single Chromatographic Columns 216
 - 6.2.1 Classes of Chromatographic Models 216
 - 6.2.2 Derivation of the Mass Balance Equations 217

- 6.2.2.1 Mass Balance Equations 218
- 6.2.2.2 Convective Transport 221
- 6.2.2.3 Axial Dispersion 222
- 6.2.2.4 Intraparticle Diffusion 222
- 6.2.2.5 Mass Transfer 222
- 6.2.2.6 Adsorption Kinetics 224
- 6.2.2.7 Adsorption Equilibrium 224
- 6.2.3 Ideal Equilibrium Model 226
- 6.2.4 Models with One Band-broadening Effect 229
 - 6.2.4.1 Equilibrium Dispersive Model 230
 - 6.2.4.2 Transport Model 232
 - 6.2.4.3 Reaction Model 233
- 6.2.5 Lumped Rate Models 233
 - 6.2.5.1 Transport Dispersive Model 234
 - 6.2.5.2 Reaction Dispersive Model 235
- 6.2.6 General Rate Models 235
- 6.2.7 Initial and Boundary Conditions of the Column 238
- 6.2.8 Stage Models 239
- 6.2.9 Assessment of Different Model Approaches 240
- 6.2.10 Dimensionless Model Equations 242
- 6.3 Modeling HPLC Plants 244
 - 6.3.1 Experimental Set-up and Simulation Flowsheet 244
 - 6.3.2 Modeling Extra Column Equipment 246
 - 6.3.2.1 Injection System 246
 - 6.3.2.2 Piping 246
 - 6.3.2.3 Detector 246
- 6.4 Numerical methods 247
 - 6.4.1 General Solution Procedure 247
 - 6.4.2 Discretization 248
- 6.5 Parameter Determination 251
 - 6.5.1 Parameter Classes for Chromatographic Separations 251
 - 6.5.1.1 Design Parameters 251
 - 6.5.1.2 Operating Parameters 252
 - 6.5.1.3 Model Parameters 252
 - 6.5.2 Determination of Model Parameters 253
 - 6.5.3 Evaluation of Chromatograms 255
 - 6.5.3.1 Moment Analysis and HETP Plot 257
 - 6.5.3.2 Parameter Estimation 263
 - 6.5.3.3 Peak Fitting Functions 265
 - 6.5.4 Detector Calibration 268
 - 6.5.5 Plant Parameters 269
 - 6.5.6 Determination of Packing Parameters 271
 - 6.5.6.1 Void Fraction and Porosity of the Packing 271
 - 6.5.6.2 Axial Dispersion 271
 - 6.5.6.3 Pressure Drop 273

6.5.7	Isotherms	273
6.5.7.1	Determination of Adsorption Isotherms	273
6.5.7.2	Determination of the Henry Coefficient	276
6.5.7.3	Static Methods	277
6.5.7.4	Dynamic Methods	278
6.5.7.5	Frontal Analysis	278
6.5.7.6	Analysis of Disperse Fronts (ECP/FACP)	283
6.5.7.7	Peak-maximum Method	285
6.5.7.8	Minor Disturbance/Perturbation Method	285
6.5.7.9	Curve Fitting of the Chromatogram	288
6.5.7.10	Calculation of Mixture Behavior from Single Component Data	288
6.5.7.11	Data Analysis and Accuracy	289
6.5.8	Mass Transfer	291
6.6	Validation of Column Models	292
6.7	Modeling of SMB Processes	297
6.7.1	Process Principle	297
6.7.2	SMB Process Models	299
6.7.3	TMB Model	301
6.7.4	Comparison between TMB and SMB model	302
6.7.5	Process and Operating Parameters	304
6.7.6	Experimental validation	304
6.7.6.1	Introduction	304
6.7.6.2	Results	307
7	Model Based Design and Optimization	313
	<i>A. Susanto, K. Wekenborg, A. Epping, A. Jupke</i>	
7.1	Basic Principles	314
7.1.1	Objective Functions	314
7.1.1.1	Characterization of Process Performance	314
7.1.1.2	Total Separation Cost	316
7.1.2	Degrees of Freedom	317
7.1.2.1	Classification of Optimization Parameters	317
7.1.2.2	Dimensionless Representation of Operating and Design Parameters	318
7.1.3	Scaling Up and Down	322
7.1.3.1	Influence of Different HETP Coefficients for Every Component	323
7.1.3.2	Influence of Feed Concentration	324
7.1.3.3	Examples for a Single Batch Chromatographic Column	325
7.1.3.4	Examples for SMB Processes	329
7.2	Batch chromatography	330
7.2.1	Fractionation Mode (Cut Strategy)	330
7.2.2	Design and Optimization Strategy for Batch Chromatographic Column	331
7.2.3	Process Performance Depending on Number of Stages and Loading Factor	335
7.2.4	Design and Optimization Strategies from Other Authors	341

- 7.3 SMB Chromatography 344
 - 7.3.1 Optimization of Operating Parameters 345
 - 7.3.1.1 Process Design Based on TMB Models (Short-cut Methods) 346
 - 7.3.1.2 Process Design Based on SMB Models 354
 - 7.3.2 Optimization of Design Parameters 360
- 7.4 Comparison of Batch and SMB Chromatography 366

- 8 Chromatographic Reactors 371**
T. Borren, J. Fricke
 - 8.1 Introduction 371
 - 8.2 Types of Chromatographic Reactors 372
 - 8.2.1 Chromatographic Batch Reactor 372
 - 8.2.2 Continuous Annular Reactors 373
 - 8.2.3 Counter-current Chromatographic Reactors 374
 - 8.2.3.1 True Moving Bed Reactor 374
 - 8.2.3.2 Simulated Moving Bed Reactor 375
 - 8.2.3.3 Hashimoto Process 377
 - 8.3 Modeling of Chromatographic Reactors 378
 - 8.3.1 Models of Chromatographic Batch Reactors 378
 - 8.3.2 Models of Continuous Annular Chromatographic Reactors 380
 - 8.3.3 Models of Counter-Current Chromatographic Reactors 380
 - 8.3.3.1 SMBR Model 382
 - 8.3.3.2 Ideal TMBR Model 382
 - 8.3.3.3 Comparison of Modeling Approaches 384
 - 8.3.4 Determination of the Model Parameters 384
 - 8.4 Operation and Design of Chromatographic Reactors 385
 - 8.4.1 Choice of the Process Conditions for Chromatographic Reactors 385
 - 8.4.2 Operating Conditions of Batch Reactors 385
 - 8.4.3 Operating Conditions of SMB Reactors 387
 - 8.4.3.1 Deduction of the Design Criteria 387
 - 8.4.3.2 Application of Design Criteria 391
 - 8.5 Design Examples 392
 - 8.5.1 Esterification of β -Phenethyl Alcohol with Acetic Acid 393
 - 8.5.2 Isomerization of Glucose 395

- 9 Advanced Control of Simulated Moving Bed Processes 401**
A. Toumi, S. Engell
 - 9.1 Introduction 401
 - 9.2 Model Predictive Control 402
 - 9.3 State-of-the-art in Control of SMB Processes 404
 - 9.4 Online Optimizing Control of a Reactive Simulated Moving Bed Process 406
 - 9.4.1 Process Description 406
 - 9.4.2 Formulation of the Online Optimizing Controller 407
 - 9.4.3 Simulation Study 409

XII | *Introduction*

9.4.4 Experimental Study 411

9.5 Conclusions 416

Outlook 417

References 421

Appendix A 435

A1 Scale-up Factors Between Different Columns 435

A1.1 Example Determination of the Scale-up Factor 435

A.2 Standard Operating Procedures for Column Packing 435

Appendix B: Data of Test Systems 443

B.1 EMD53986 443

B.2 Tröger's Base 445

B.3 Glucose and Fructose 447

B.4 β -Phenethyl Acetate 449

Index 435