

Process Analytical Technology

Second Edition

Process Analytical Technology – Second Edition

Spectroscopic Tools and Implementation Strategies
for the Chemical and Pharmaceutical Industries

Edited by

Katherine A. Bakeev

CAMO Software, Inc, NJ, USA



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Preface to the Second Edition

Process analytical technology (PAT) continues to evolve and develop, with new tools and more areas of implementation constantly emerging. In such a dynamic area, it is difficult to be current on all that is new. It is exciting to be able to present a second edition of this book, in an effort to cover some of the more recent advances in the five short years since the release of the first edition.

PAT has been around for some time now, providing a strong foundation of knowledge and well-defined tools that should serve as a starting point for anyone wishing to work in this area. All practitioners can benefit by learning from examples, keeping in mind that the similarities of the technology and approach make them applicable to numerous problems. One needs to be open to the fact that PAT work done in any industry does provide lessons that can be applied to new problems we may have to tackle.

With such a multidisciplinary topic as PAT, one can look at such work from many perspectives: chemist, engineer, manufacturing engineer, controls, regulatory, QA, production, chemometrics. The important thing, regardless of one's specific niche, is to acknowledge that it is truly multidisciplinary in nature and hence requires people from many areas of expertise working as a team to reach successful implementations that deliver business value.

This book is presented from the viewpoint of a spectroscopist, and as such focuses on spectroscopic tools, while also providing some guidance on important considerations for the successful implementation of an analyzer to monitor and control a process. Regardless of the industry in which PAT is used, there is a need to focus on the science and use these tools in the scientific understanding of processes and in the manufacture of quality product, consistently.

The contents of the book are intended to help a newcomer in the field, as well as to provide current information including developing technologies, for those who have practiced process analytical chemistry and PAT for some time. The main spectroscopic tools used for PAT are presented: NIR, Raman, UV-Vis and FTIR, including not just the hardware, but many application examples, and implementation issues. As chemometrics is central for use of many of these tools, a comprehensive chapter on this, now revised to more specifically address some issues relevant to PAT is included. In this second edition many of the previous chapters have been updated and revised, and additional chapters covering the important topic of sampling, and the additional techniques of NMR, fluorescence, and acoustic chemometrics are included.

I would like to thank all of the people that have helped make this book possible, including the numerous teachers and mentors I have had in my life. Of course the strong support of my family allows me to indulge in the exercise of editing, and for this I am grateful. Thanks also to those who contributed chapters to this and the previous edition, as I have learned from each of them. I also salute them for their dedication in writing, when they already have so many other activities in their lives.

Katherine A. Bakeev
Newark, DE
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List of Contributors

Katherine A. Bakeev

CAMO Software Inc.
One Woodridge Center, Ste. 319
Woodbridge, NJ, USA

Manel Alcalá Bernárdez

Universitat Autònoma de Barcelona
Cerdanyola del Vallès, Barcelona, Spain

Lewis C. Baylor

Equitech International Corp.
New Ellenton, SC, USA

Ann M. Brearley

Biostatistical Design and Analysis Center
University of Minnesota
Minneapolis, MN, USA

John P. Coates

Coates Consulting
Newtown, CT, USA

Jason E. Dickens

GlaxoSmithKline
Research Triangle Park, NC, USA

John C. Edwards

Process NMR Associates, LLC,
Danbury, CT, USA

Kim H. Esbensen

ACABS research group
Aalborg University, campus Esbjerg (AAUE)
Esbjerg, Denmark

Susan J. Foulk

Guided Wave Inc
Rancho Cordova, CA, USA

Paul J. Giammatteo

Process NMR Associates, LLC
Danbury, CT, USA

Robert Guenard

Merck and Co.
Global Pharmaceutical Commercialization
Merck Manufacturing Division.
West Point, PA, USA

Maths Halstensen

ACRG (Applied Chemometrics Research
Group)
Telemark University College
Porsgrunn, Norway

Nancy L. Jestel

SABIC Innovative Plastics
New R&E
Selkirk, NY, USA

Linda H. Kidder

Malvern Instruments
Columbia, MD, USA

Eunah Lee

Horiba Jobin Yvon
Edison, NJ, USA

E. Neil Lewis
Malvern Instruments
Columbia, MD, USA

Marcel A. Liauw
ITMC, RWTH Aachen University
Aachen, Germany

Lisa Makein
Malvern Instruments
Malvern, UK

Jose C. Menezes
Institute for Biotechnology and Bioengineering
IST
Technical University of Lisbon
Lisbon, Portugal

Charles E. Miller
Merck and Company
West Point, PA, USA

Patrick E. O'Rourke
Equitech International Corp.
New Ellenton, SC, USA

Peter Paasch-Mortensen
Novozymes A/S
Kalundborg, Denmark

Marcelo Blanco Romía
Department of Chemistry
Universitat Autònoma de Barcelona
Cerdanyola del Vallès, Barcelona, Spain

Joseph W. Schoppelrei
National Geospatial Intelligence Agency
Reston, VA, USA

Michael B. Simpson
ABB Analytical Measurements
Quebec, Canada

Brandye Smith-Goettler
Merck and Co., Inc.
West Point, PA, USA

Gert Thureau
Merck and Co.
Global Pharmaceutical Commercialization
Merck Manufacturing Division
West Point, PA, USA

List of Abbreviations

ADC	analog-to-digital circuit	CIP	clean-in-place
AE	acoustic emission	CLS	classical least squares
ANN	artificial neural network	COGM	cost of goods manufactured
ANOVA	analysis of variance	COW	correlation optimized warping
AOTF	acousto-optical tunable filter	CPAC	Center for Process Analytical Chemistry
API	active pharmaceutical ingredient	C_{pk}	process capability
AQ	analyzer questionnaire	CPMG	Carr-Purcell-Meiboom-Gill
AR	antireflection (as in antireflection, AR coated optics)	CPP	critical process parameter
ASO	acid soluble oils	CQA	critical quality attribute
ASTM	American Society for Testing and Materials	CQV	continuous quality verification
ATR	attenuated total reflectance	CRDS	cavity ring down spectroscopy
ATR FTIR	attenuated total reflectance Fourier transform infrared	CSA	Canadian Standards Association
BEST	bootstrap error-adjusted single- sample technique	CSE ₁	small-scale fluctuations
BSPC	Batch Statistical Process Control	CSE ₃	<i>cyclic</i> fluctuations
BTEM	band target entropy minimization	CVD	chemical vapor deposition
CBZ	carbamazepine	CVF	circular variable filter
CCD	charge coupled device; chemical composition distribution	DA	discriminant analysis
CD	compact disk	DAQ	data acquisition
CE	European certification	DCS	distributed control system
CE	capillary electrophoresis	DH	distributional heterogeneity
CEC	capillary electrochromatography	DOE	design of experiments
CF	cash flow	DP	degree of polymerization
CFE	cyclic fluctuation error	DRIFT-IR	diffuse reflectance Fourier-transform infrared
CFR	Code of Federal Regulations	DS	design space; direct standardization
cGMP	current Good Manufacturing Practice	DSC	differential scanning calorimetry
CH	constitutional heterogeneity	DTGS	deuterated triglycine sulfate (detector)
CHO	Chinese hamster ovary	EMA	European Medicines Agency (formerly known as EMEA)
CIE	Commission Internationale de L'éclairage	EMEA	European Medicines Agency (changed to EMA, December 2009)

EMSC	extended multiplicative signal correction	IQ/OQ/PQ	installation qualification/operational qualification/performance qualification
EPA	Environmental Protection Agency	IR	infrared
ESR	electron spin resonance	IRE	internal reflectance element
EU	European Union	IRR	initial rate of return
FALLS	forward angle laser light scattering	IRRAS	infrared reflection-absorption spectroscopy
FAT	factory acceptance test	ISE	incorrect sampling errors
FBRM	focus beam reflectance measurements	ISP	integrated sensing and processing
FDA	Food and Drug Administration	ISPE	International Society of Pharmaceutical Engineers
FFT	fast Fourier transformation	IT	information technology
FIA	flow injection analysis	IWE	increment weighing error
FID	free induction decay	J–T	Joule–Thompson
FM	factory mutual	KBr	potassium bromide
FMEA	failure modes and effects analysis	KF	Karl Fischer
FOV	field of view	KNN	K-nearest neighbor
FPA	focal-plane array	LCO	light cycle oil
FPE	Fabry-Perot etalon	LCTF	liquid crystal tunable filter
FSE	fundamental sampling error	LD	laser diode
FSP	fundamental sampling principle	LDA	linear discriminant analysis
FTIR	Fourier transform infrared	LDPE	low-density polyethylene
GA	genetic algorithms	LED	light-emitting diode
GC	gas chromatography	LIBS	laser induced breakdown spectroscopy
GEE	global estimation error	LIF	laser-induced fluorescence or light-induced fluorescence
GLP/GMP	good laboratory practice/good manufacturing practice	LLDPE	linear low-density polyethylene
GLS	generalized least squares	LOD	loss on drying
GSE	grouping and segregation error	LPG	liquid petroleum gas
HCA	hierarchical cluster analysis	LTCO	long-term cost of ownership
HME	hot melt extrusion	LV	latent variable
HPLC	high performance liquid chromatography	LVF	linear variable filter
HR	hurdle rate	MCR	multivariate curve resolution
HR-NMR	high-resolution NMR	MCR-ALS	multivariate curve resolution alternating least-squares
HTS	high-throughput screening	MCT	mercury-cadmium-telluride
ICH	International Conference on Harmonization	MCWPCA	mean-centered window principal component analysis
ICS	incorrect sampling errors	MEMS	micro-electromechanical systems
IDE	increment delimitation error	mid-IR	mid-infrared
IEE	increment extraction error	MIM	molecularly imprinted monolayer
II	initial investment	MIR	mid-infrared
InGaAs	indium gallium arsenide	MLR	multiple linear regression
InSb	indium antimonide	MMA	methyl methacrylate
IP	index of profitability	MON	motor octane number
IPE	increment preparation error		

MPE	minimum practical error	PC	principal component
MS	mass spectrometry	PCA	principal component analysis
MSA	measurement system analysis	PC-MBEST	principal component modified bootstrap error-adjusted single- sample technique
MSC	multiplicative scatter correction, multiplicative signal correction	PCR	principal component regression
MSPC	multivariate statistical process control	PCS	process control system
MST	minimal spanning tree	PDA	photodiode array
MTBF	mean time between failure	PDS	piecewise direct standardization
MTTR	mean time to repair	PET	photoinduced electron transfer; polyethylene terphthalate
MVDA	multivariate data analysis	PFM	potential function method
MVI	multivariate identification	PID	proportional-integral derivative
MWS	multivariate wavelength standardization	PIE	process integration error
N6	nylon 6	PLS	partial least squares or projection to latent structures
N66	nylon 6,6	PLS-DA	partial least squares-discriminant analysis
NAS	net analyte signal	PLSR	partial least squares regression
NCCW	no contact check weighing	PM	preventive maintenance
NDIR	nondispersive infrared	PMT	photomultiplier tube
NEP	noise equivalent power	PoC	proof of concept
NeSSI	new sampling/sensor initiative	PP	polypropylene
NFPA	National Fire Prevention Association	PRIMA	pattern recognition by independent multicategory analysis
NIR	near-infrared	PRM	pattern recognition method
NIR-CI	near-infrared chemical imaging	PSD	particle size distribution
NIRS	near-infrared spectroscopy	PUC	process understanding and control
NIST	National Institute of Standards and Technology	PVA	parallel vector analysis
NOC	normal operating conditions	PVM	particle vision monitor
NPV	net present value	PX	p-xylene
OD	optical density	Q	number of increments per sample
OEM	original equipment manufacturer	QA	quality assurance
OPA	orthogonal projection approach	QbD	quality by design
OSC	orthogonal signal correction	QC	quality control
OTC	over the counter	QCL	quantum cascade laser
P&ID	process and instrument diagram	QCM	quartz crystal microbalance
PA	process analytics	r	sampling rate
PAC	process analytical chemist/chemistry	ra	random sampling
PACLS	prediction augmented classical least squares	RAM	random access memory
PAI	process analytical instruments	RBG	red blue green
PAR	proven acceptable range	RET	resonance energy transfer
PASG	Pharmaceutical Analytical Sciences Group	RF	radio frequency
PAT	process analytical technology	RFI	radio frequency impedance
PbS	lead sulphide	RFP	request for proposal
PbSe	lead selenide	RMSEP	root-mean-squared error of prediction
PC	personal computer		