

ADVANCES IN PHARMACEUTICAL TECHNOLOGY

Editor

Defang Ouyang

Exploring Computational Pharmaceutics - AI and Modeling in Pharma 4.0

WILEY

Exploring Computational Pharmaceutics – AI and Modeling in Pharma 4.0

ADVANCES IN PHARMACEUTICAL TECHNOLOGY

A Wiley Book Series

Series Editors:

Dennis Douroumis, University of Greenwich, UK

Alfred Fahr, Friedrich–Schiller University of Jena, Germany

Jurgen Siepmann, University of Lille, France

Martin Snowden, University of Greenwich, UK

Vladimir Torchilin, Northeastern University, USA

Titles in the Series

Hot-Melt Extrusion: Pharmaceutical Applications

Edited by Dionysios Douroumis

Drug Delivery Strategies for Poorly Water-Soluble Drugs

Edited by Dionysios Douroumis and Alfred Fahr

Computational Pharmaceutics: Application of Molecular Modeling in Drug Delivery

Edited by Defang Ouyang and Sean C. Smith

Pulmonary Drug Delivery: Advances and Challenges

Edited by Ali Nokhodchi and Gary P. Martin

Novel Delivery Systems for Transdermal and Intradermal Drug Delivery

Edited by Ryan Donnelly and Raj Singh

Drug Delivery Systems for Tuberculosis Prevention and Treatment

Edited by Anthony J. Hickey

Continuous Manufacturing of Pharmaceuticals

Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen

Pharmaceutical Quality by Design

Edited by Walkiria S Schlindwein and Mark Gibson

***In Vitro* Drug Release Testing of Special Dosage Forms**

Edited by Nikoletta Fotaki and Sandra Klein

Characterization of Pharmaceutical Nano- and Microsystems

Edited by Leena Peltonen

Biopharmaceutics: From Fundamentals to Industrial Practice

Edited by Hannah Batchelor

Forthcoming Titles:

Process Analytics for Pharmaceuticals

Edited by Jukka Rantanen, Clare Strachan and Thomas De Beer

Mucosal Drug Delivery

Edited by Rene Holm

Exploring Computational Pharmaceutics – AI and Modeling in Pharma 4.0

Edited by

DEFANG OUYANG

University of Macau

Taipa, Macao

WILEY

This edition first published 2024
© 2024 John Wiley & Sons Ltd

All rights reserved, including rights for text and data mining and training of artificial technologies or similar technologies. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by law. Advice on how to obtain permission to reuse material from this title is available at <http://www.wiley.com/go/permissions>.

The right of Defang Ouyang to be identified as the author of this work has been asserted in accordance with law.

Registered Offices

John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Trademarks: Wiley and the Wiley logo are trademarks or registered trademarks of John Wiley & Sons, Inc. and/or its affiliates in the United States and other countries and may not be used without written permission. All other trademarks are the property of their respective owners. John Wiley & Sons, Inc. is not associated with any product or vendor mentioned in this book.

Limit of Liability/Disclaimer of Warranty

In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. While the publisher and authors have used their best efforts in preparing this work, they make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives, written sales materials or promotional statements for this work. The fact that an organization, website, or product is referred to in this work as a citation and/or potential source of further information does not mean that the publisher and authors endorse the information or services the organization, website, or product may provide or recommendations it may make. This work is sold with the understanding that the publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for your situation. You should consult with a specialist where appropriate. Further, readers should be aware that websites listed in this work may have changed or disappeared between when this work was written and when it is read. Neither the publisher nor authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

Library of Congress Cataloging-in-Publication Data

Names: Ouyang, Defang, editor.

Title: Exploring computational pharmaceuticals : AI and modeling in Pharma
4.0 / edited by Defang Ouyang

Other titles: Advances in pharmaceutical technology.

Description: Hoboken, NJ : Wiley, 2024. | Series: Advances in
pharmaceutical technology | Includes index.

Identifiers: LCCN 2024008997 (print) | LCCN 2024008998 (ebook) | ISBN
9781119987130 (hardback) | ISBN 9781119987246 (adobe pdf) | ISBN
9781119987253 (epub)

Subjects: MESH: Drug Design—methods | Artificial Intelligence | Computer
Simulation | Computational Biology—methods

Classification: LCC RM301.25 (print) | LCC RM301.25 (ebook) | NLM QV 745
| DDC 615.1/9—dc23/eng/20240313

LC record available at <https://lccn.loc.gov/2024008997>

LC ebook record available at <https://lccn.loc.gov/2024008998>

Cover Design: Wiley

Cover Image: © everything possible/Shutterstock

Set in 10/12pt TimesLTStd by Straive, Chennai, India

Contents

<i>List of Contributors</i>	xv
<i>Preface</i>	xxi
1 Introduction to Computational Pharmaceutics	1
<i>Nannan Wang, Wei Wang, Hao Zhong, and Defang Ouyang</i>	
1.1 Current Pharmaceutical Research	2
1.2 What is Computational Pharmaceutics?	5
1.3 About This Book	7
References	8
2 Opportunities and Challenges of Artificial Intelligence (AI) in Drug Delivery	10
<i>Zhuyifan Ye and Defang Ouyang</i>	
2.1 Introduction	12
2.2 Machine Learning Algorithms	14
2.2.1 Linear Models	16
2.2.2 Artificial Neural Networks	17
2.2.3 Deep Learning	18
2.2.4 Genetic Algorithm	19
2.2.5 Fuzzy Neural Network	20
2.2.6 Support Vector Machine	20
2.2.7 Decision Tree	21
2.2.8 Ensemble Learning	21
2.3 Applications of Machine Learning in Pharmaceutics	22
2.3.1 Immediate-Release Tablets	22
2.3.2 Hard Gelatin Capsules	33

2.3.3	Oral Sustained-Release Preparations	33
2.3.4	Emulsion, Microemulsion, and Nanoemulsion Drug Delivery Systems	34
2.3.5	Hydrogel Transdermal Drug Delivery Systems	35
2.3.6	Nanoparticle Drug Delivery Systems	35
2.3.7	Solid Dispersions	39
2.3.8	Cyclodextrin Complexations	39
2.4	Applications of Large-Scale Models in Drug Discovery and Development	40
2.4.1	Language Model Pre-Training for Downstream Drug Discovery and Development Tasks	41
2.4.2	Multi-Task Learning and Multi-Property Prediction Pre-Training for Downstream Drug Discovery and Development Tasks	41
2.4.3	Drug–Target Interaction Prediction	42
2.4.4	Antimicrobial Peptide Prediction	42
2.4.5	Pharmacokinetic Property Prediction	42
2.4.6	Generative Models for New Molecule Design	43
2.4.7	Clinical Medical Image Processing	43
2.4.8	Medical Document Retrieval and Recommendation	44
2.4.9	Clinical Rational Drug Use and Drug–Drug Interaction Prediction	44
2.4.10	Automated Experimental Platform and Machine Learning Interpretability	44
2.5	AI in the Clinic and Precision Medicine	44
2.6	Opportunities and Challenges	45
2.7	Summary	48
	References	48
3	Computational Resources in Pharmaceutics	59
	<i>Jie Dong</i>	
3.1	Concept and Overview of Computational Pharmaceutics	60
3.2	Databases	62
3.2.1	Database Technology Promotes Efficient Communication in Pharmaceutics	62
3.2.2	Databases for Drug Formulation	63
3.3	Computational Platforms/Web Servers	67
3.3.1	Artificial Intelligence Promotes Rapid Screening and Evaluation of Drug Formulations	67
3.3.2	Artificial Intelligence Models in Pharmaceutics	69
3.3.3	Computational Platforms/Web Servers	74
3.4	Implementation Methods for Databases and Computing Platforms	79
3.5	Summary and Outlook	81
	References	83

4	Computational Modeling of Dry Powder Inhalation	85
	<i>Jiawei Hu, Ling Zhang, and Chuan-Yu Wu</i>	
4.1	Introduction	86
4.2	Discrete Element Methods (DEMs)	87
4.3	Modeling of Agglomeration	89
4.3.1	Formation of Drug-Only Agglomerates	89
4.3.2	Formation of Carrier-Based Agglomerates	89
4.4	Modeling of De-agglomeration	91
4.4.1	De-agglomeration Due to Aerodynamic Forces	92
4.4.2	De-agglomeration Due to Mechanical Impact	92
4.5	Modeling of Particle Dispersion in DPIs	95
4.5.1	DEM-CFD Modeling at the Device Scale	95
4.5.2	Multiscale Modeling of Aerosolization	96
4.5.3	CFD-DPM Modeling of Aerosolization	96
4.6	Summary and Perspectives	98
	References	98
5	Molecular Modeling in Drug Delivery: Polymer Protective Coatings as Case Study	104
	<i>Alex Bunker and Josef Kehrein</i>	
5.1	Introduction	107
5.1.1	Prodrugs and Nanomedicine: Easing the Balancing Act of Drug Delivery	107
5.1.2	Polymers in Drug Delivery	109
5.1.3	Mechanistic Understanding: Paradigm of Biophysics in Pharmaceutics	116
5.1.4	Molecular Dynamics Simulation: Tool to Obtain Mechanistic Understanding	117
5.2	Molecular Dynamics Simulation of Polymers in Drug Delivery	125
5.2.1	Lipid-Based Systems	126
5.2.2	Polymer-Based Systems	131
5.2.3	Protein-Based Systems	150
5.2.4	Inorganic Nanoparticles	157
5.3	Conclusion	163
	References	165
6	3D Structural Investigation of Solid Dosage Forms	199
	<i>Xianzhen Yin, Chenxi Huang, Zeying Cao, Li Wu, Tiqiao Xiao, Peter York, and Jiwen Zhang</i>	
6.1	Structure of Solid Dosage Forms and Methods of Investigation – An Overview	200
6.2	Synchrotron Radiation X-ray Computed Microtomography	204
6.3	3D Structure Reconstruction Based on SR- μ CT	205

6.3.1	Preparation of Samples	205
6.3.2	Image Acquisition and 3D Reconstruction	207
6.3.3	Model Construction and Analysis	209
6.4	3D Visualization and Quantitative Characterization	210
6.4.1	Microstructure of Particles and Granular Systems	211
6.4.2	Static Structure and Material Distribution of Solid Dosage Form	214
6.4.3	Dynamic Structure of Hydrophilic Matrix Tablets	216
6.4.4	Dynamic Structure of Osmotic Pump Tablets	219
6.5	Future Prospects	229
	References	229
7	Dissolution Mechanism of Pharmaceuticals and Formulations by Nonequilibrium Thermodynamic Modeling	235
	<i>Yuanhui Ji, Zheng Zhang, Kai Ge, Raphael Paus, and Gabriele Sadowski</i>	
7.1	Introduction	236
7.2	Theoretical Basis and Models	238
7.2.1	Phase Equilibrium and Chemical Potential	238
7.2.2	Chemical Potential Gradient Model	240
7.2.3	Statistical Rate Theory	241
7.2.4	Perturbed Chain Statistical Associating Fluid Theory (PC-SAFT)	242
7.2.5	Activity Coefficient Calculation by PC-SAFT	243
7.2.6	Calculation of the Dissolution Profiles	244
7.3	Experimental Methods	244
7.3.1	Measurement of API Solubility	244
7.3.2	Measurement of Calorimetric Properties	244
7.3.3	Preparation of API/Polymer Formulations	244
7.3.4	Characterizations of DSC, XRD, and SEM	245
7.3.5	<i>In vitro</i> Intrinsic Dissolution Measurement	245
7.3.6	UV–Vis Spectrophotometric Analysis	245
7.4	Mechanism Analysis and Model Predictions	246
7.4.1	Dissolution Kinetics and Mechanism of Crystalline APIs	246
7.4.2	Dissolution Kinetics of API/Polymer Formulations	252
7.5	Conclusions and Outlook	261
	References	262
8	Physiologically Based Pharmacokinetics	267
	<i>Ruihu Du and Dongyang Liu</i>	
8.1	Definition and History of Physiologically Based Pharmacokinetics	268
8.2	Principles and Structures of the Physiologically Based Pharmacokinetics Model	269
8.2.1	Intrinsic Clearance, Extraction Ratio, and Well-Stirred Model	269
8.2.2	Allometric Scaling Method	272
8.2.3	<i>In vitro–In vivo</i> Extrapolation Method	275

8.2.4	Basic Model Structure and Important Parameters of Physiologically Based Pharmacokinetics	278
8.2.5	Physiologically Based Pharmacokinetics Modeling and Simulation Basic Steps	281
8.3	Physiologically Based Pharmacokinetics Model in Complex Situations	284
8.3.1	Permeability-Limited Model	284
8.3.2	Physiologically Based Pharmacokinetics Model of the Distribution Process	285
8.3.3	Physiologically Based Pharmacokinetics Model of the Absorption Process	286
8.4	Challenges and Perspectives of the Physiologically Based Pharmacokinetics Model	288
8.4.1	Physiologically Based Pharmacokinetics Modeling Software	288
8.4.2	Acquirement for System Parameters of the Physiologically Based Pharmacokinetics Model	289
8.4.3	Perspectives on Future Research on Physiologically Based Pharmacokinetic Models	290
	References	291
9	Molecular Modeling in Drug Delivery	293
	<i>Jiawen Wang, Yi Yu, and Youyong Li</i>	
9.1	Introduction	294
9.2	Basic Principles of Molecular Dynamic Simulation and Molecular Modeling Methods	300
9.2.1	Basic Principles of Molecular Dynamic Simulation	300
9.2.2	Molecular Modeling	302
9.2.3	Molecular Dynamic Simulations	302
9.3	Molecular Dynamic Simulation of Drug Delivery Strategies with Nanoparticles	303
9.3.1	Carbon-Based Nanomaterials	303
9.3.2	Silicon-Based Nanomaterials	308
9.3.3	Metal-Based Nanomaterials	309
9.3.4	Other Nanoparticles	316
9.3.5	Other Applications of Molecular Dynamic in DDS	317
9.4	Summary	320
	References	321
10	Integration of Dendrimer-Based Delivery Technologies with Computational Pharmaceutics and Their Potential in the Era of Nanomedicine	328
	<i>Karnaker Reddy Tupally, Prasenjit Seal, Preeti Pandey, Rink-Jan Lohman, Sean Smith, Defang Ouyang, and Haredra Parekh</i>	
10.1	Introduction	329
10.2	Dendrimers as Drug/Gene Delivery Systems and Their Pharmaceutical Applications	331

10.2.1	Multifunctional Carrier Systems	331
10.2.2	Solubility Enhancers	338
10.2.3	Permeation Enhancers	343
10.2.4	Drug Delivery Agents	348
10.2.5	Therapeutic Agents	351
10.2.6	Gene Delivery Agents	357
10.2.7	Role and Application of Dendrimers in the COVID-19 Pandemic	362
10.3	Computational Aspects of Dendrimer-Based Drug Delivery and Challenges	363
10.4	Conclusions	367
	References	368
11	Artificial Intelligence and Computational Modeling in Orally Inhaled Drugs	379
	<i>Renjie Li, Hao Miao, Xudong Zhou, Ruiping Zou, and Zhenbo Tong</i>	
11.1	Overview	381
11.2	Chronic Respiratory Diseases and Inhaled Therapy	381
11.2.1	Chronic Respiratory Diseases	381
11.2.2	Inhaled Therapy	381
11.2.3	Inhalers	382
11.3	Introduction of Computational Methods	383
11.3.1	Computational Fluid Dynamics Modeling	383
11.3.2	Physiologically Based Pharmacokinetic Modeling	383
11.3.3	Artificial Intelligence	384
11.3.4	Verification and Validation of Computational Models	385
11.4	Applications in R&D of Inhalers and Drug Formulations	386
11.4.1	Nebulizer Development	386
11.4.2	pMDI Development	386
11.4.3	SMI Development	387
11.4.4	DPI Development	387
11.4.5	Inhaled Drug Formulations	388
11.5	Applications in the Evaluation of Inhaled Drug Efficacy	389
11.5.1	Prediction of Drug Deposition	389
11.5.2	PBPK Modeling of Inhaled Drug Dissolution and Absorption	393
11.6	Applications in the Management of Chronic Respiratory Diseases	394
11.6.1	Inhaler-based Electronic Monitoring Devices	394
11.6.2	Improvement in Adherence	395
11.6.3	Measurement of Inhalation Parameters	395
11.6.4	Predictive Models for Acute Exacerbations	397
11.7	Challenges and Future	397
11.8	Conclusions	399
	References	399

12	Digital Formulation Development Using 3D Printing Technology: AI and Modeling	408
	<i>Timothy Tracy, Lei Wu, Senping Cheng, and Xiaoling Li</i>	
12.1	Introduction	409
12.2	3D Printing Methods in the Formulation of Pharmaceuticals	411
12.2.1	Extrusion-based Methods	411
12.2.2	Powder-Based Methods	414
12.2.3	Liquid-Based Methods	414
12.2.4	Sheet Lamination-Based Methods	414
12.3	Novel Tablet Structures Possible with 3D Printing	415
12.3.1	Unique Tablet External Geometries	415
12.3.2	Unique Tablet Internal Geometries	415
12.4	Artificial Intelligence in Formulation Development Using 3D Printing	416
12.4.1	Excipient Selection	416
12.4.2	Formulation Development using 3D Printing	417
12.4.3	Mathematical Modeling in Formulation Development Using 3D Printing	423
12.4.4	Predicting Printability	423
12.4.5	Predicting Dissolution Profiles	424
12.5	3D Printing Formulation by Design	430
12.5.1	3D Printing Formulation by the Design (3DFbD [®]) Approach	430
12.5.2	Contribution of 3DFbD [®] to Quality by Design	431
12.6	Summary	432
	References	433
13	A Review on Research and Application of Expert Systems on Drug Formulation and Process Design	437
	<i>Ruofei Du and Yu Zhang</i>	
13.1	Introduction	437
13.2	The Structure of ES	438
13.2.1	Database	439
13.2.2	Rule Base	443
13.2.3	Inference Engine	445
13.2.4	User Interface	447
13.3	Applications	449
13.3.1	SeDeM	453
13.3.2	Typical ESs in TCM Research	458
13.4	Discussions	466
	References	468
14	Application of PBPK Modeling in Formulation Development	474
	<i>Bo Liu and Xue Li</i>	
14.1	Introduction	475
14.2	Pharmacokinetic (PK) Software for Modeling	476

14.2.1	Quantitative Structure-Activity/Property Relationship (QSAR/QSPR) Modeling	476
14.2.2	<i>De Novo</i> Drug Design and Synthesis Planning	477
14.2.3	Drug Formulation Design Using Molecular Dynamic (MD) Simulation	477
14.2.4	Drug Formulation Design with Physiologically Based Pharmacokinetic Modeling	478
14.3	Modeling Mechanisms for Different Types of Dosage Forms	479
14.3.1	Models for Oral Solid Dosage Forms	480
14.3.2	Inhalation Model	482
14.3.3	Dermal Model	483
14.3.4	Long-acting Injection Model	484
14.3.5	Limitations and Improvements	488
14.4	Summary and Conclusion	489
	References	490
15	Multiscale Models for Tablet Manufacturing Process Development	493
	<i>Xizhong Chen, Kai Liu, LiGe Wang, Liang Li, and Zheng-Hong Luo</i>	
15.1	Introduction	494
15.2	Tablet Manufacturing	496
15.3	Computational Modeling	499
15.4	Case Studies	506
15.4.1	Diamond Pilot Plant at the University of Sheffield	506
15.4.2	Simulation of a Continuous Direct Compression Process	508
15.5	Summary and Outlook	513
	References	514
16	Machine Learning as a Part of Pharmaceutical Product Development	517
	<i>Johan Bøtker, Jukka Rantanen, and Anders Ø. Madsen</i>	
16.1	Introduction	518
16.2	Pharmaceutical Materials Science	519
16.2.1	Examples of Pharmaceutically Relevant Databases	520
16.2.2	Simulation	523
16.3	Product Design	524
16.4	Processing of Pharmaceuticals	526
16.4.1	Process Data and Predictive Models	526
16.4.2	Process Analytics as a Source of Data	527
16.4.3	Aspects Related to Production Systems for Personalized Pharmaceuticals	529
16.5	Analytical Chemistry in a Pharmaceutical Setting	529
16.6	Concluding Remarks	530
	References	531

17	Big Data Analysis of Patents and Their Applications in Biomedical Research and Development	533
	<i>Jiaqi Xu, Jialu Yuan, Hong Cai, and Yuanjia Hu</i>	
17.1	Introduction	534
17.1.1	Status of Patent Data Utilization	534
17.1.2	Utility of Patent Data for Biomedical Research	535
17.1.3	Conceptual Framework	535
17.2	Patent Landscape Analysis	536
17.2.1	Data Collection and Standardization	536
17.2.2	Brief Bibliometric Analysis	537
17.2.3	Standards of Patent Landscaping	537
17.2.4	Patent Retrieval Database	539
17.3	Mining Chemical Information from Patents	540
17.3.1	Chemical Information in Patents	541
17.3.2	Methods in Chemical Information Data Mining	541
17.3.3	Patent Chemical Information Database	545
17.3.4	Comparison of Popular OCSR Tools	545
17.4	Mining Biological Information from Patents	546
17.4.1	Biological Information in Patents	546
17.4.2	Methods in Biological Sequence Data Mining	546
17.4.3	Patent Biological Information Databases	550
17.4.4	Patent Antibody Sequence Data Mining — A Case Study	552
17.5	Mining Pharmaceutics Information from Patents	553
17.5.1	Studies of Pharmaceutics Patent Analysis	554
17.5.2	Methods in Pharmaceutics Information Data Mining	554
17.6	Practical Operations and Related Issues	556
17.6.1	Patent Retrieval Database Operation	556
17.6.2	Chemical Information Database Operation	560
17.6.3	Biological Information Database Operation	561
17.6.4	Database Issues	566
17.6.5	Workflow of Biomedical Patent Analysis	568
17.7	Outlook	568
	References	569
18	Model-informed Drug Development (MIDD) Regarding Regulatory Requirements and Thinking	574
	<i>Wei Wang, Yuzhu Wang, and Defang Ouyang</i>	
18.1	Driving Forces Toward MIDD	576
18.2	Regulatory Guidance on Modeling Methods	578
18.2.1	E-R Models or PK/PD Models	578
18.2.2	Pop-PK Model	579

18.2.3	PBPK Model	580
18.2.4	CFD and Other Modeling Techniques	581
18.3	Evolving Thinking on MIDD	582
18.3.1	PBPK Modeling for <i>In Vivo</i> Study Waiver	582
18.3.2	PK-Related Modeling for Reducing BE Study Burden	585
18.3.3	Applications of Machine Learning and Other Statistical Models	586
18.3.4	Efforts from Regulatory Agencies Toward Promoting MIDD Applications	587
18.4	The Advancement of Pharmacometrics in China	588
18.5	Summary	589
	References	589

<i>Index</i>	593
---------------------	------------

List of Contributors

Johan Bøtker Department of Pharmacy, University of Copenhagen, København, Denmark

Alex Bunker Drug Research Program, Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland

Hong Cai State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

Zeying Cao Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Center for Pharmaceutical Research, Shanghai, China

Xizhong Chen Department of Chemical Engineering, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai, China

and

Department of Chemical and Biological Engineering, University of Sheffield, Sheffield, UK

Senping Cheng Triastek, Inc., Nanjing, Jiangsu, China

Jie Dong Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan, P. R. China

Ruihu Du Clinical Pharmacology and Pharmacometrics Office, Drug Clinical Trial Center, Peking University Third Hospital, Beijing, China

Ruofei Du Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

and

Engineering Research Center of Modern Preparation Technology of Traditional Chinese Medicine, Ministry of Education, Shanghai, China

Kai Ge Jiangsu Province Hi-Tech Key Laboratory for Biomedical Research, School of Chemistry and Chemical Engineering, Southeast University, Nanjing, China

Jiawei Hu School of Chemistry and Chemical Engineering, University of Surrey, Guildford, UK

Yuanjia Hu State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

Chenxi Huang Lingang Laboratory, Shanghai, China

Yuanhui Ji Jiangsu Province Hi-Tech Key Laboratory for Biomedical Research, School of Chemistry and Chemical Engineering, Southeast University, Nanjing, China

Josef Kehrein Drug Research Program, Division of Pharmaceutical Biosciences, Faculty of Pharmacy, University of Helsinki, Helsinki, Finland

and

Soft Matter Chemistry, Department of Chemistry, Faculty of Science, University of Helsinki, Helsinki, Finland

Liang Li Department of Chemical Engineering, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai, China

Renjie Li Department of Chemical and Biological Engineering, Monash University, Clayton, Australia

and

Monash Suzhou Research Institute, Suzhou, China

Youyong Li Macao Institute of Materials Science and Engineering, Macau University of Science and Technology, Taipa 999078, Macau SAR, China

and

Institute of Functional Nano & Soft Materials (FUNSOM), Soochow University, 199 Ren'ai Road, Suzhou, 215123, Jiangsu, China

Xiaoling Li Triastek, Inc., Nanjing, Jiangsu, China

and

Department of Pharmaceutics and Medicinal Chemistry, Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, CA, USA

Xue Li Yinghan Pharmaceutical Technology (Shanghai) Co. Ltd., Shanghai, China

Bo Liu Department of Pharmaceutical Engineering, School of Chemical Engineering and Pharmacy, Wuhan Institute of Technology, Wuhan, China

Dongyang Liu Clinical Pharmacology and Pharmacometrics Office, Drug Clinical Trial Center, Peking University Third Hospital, Beijing, China

Kai Liu Department of Chemical and Biological Engineering, University of Sheffield, Sheffield, UK

Rink-Jan Lohman School of Pharmacy, The University of Queensland, Woolloongabba, Australia

Zheng-Hong Luo Department of Chemical Engineering, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai, China

Anders Ø. Madsen Department of Pharmacy, University of Copenhagen, København, Denmark

Hao Miao Department of Chemical and Biological Engineering, Monash University, Clayton, Australia

and

Monash Suzhou Research Institute, Suzhou, China

Defang Ouyang State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China

and

Department of Public Health and Medicinal Administration, Faculty of Health Sciences (FHS), University of Macau, Macau, China

Preeti Pandey School of Pharmacy, The University of Queensland, Woolloongabba, Australia

Haredra Parekh School of Pharmacy, The University of Queensland, Woolloongabba, Australia

Raphael Paus Department of Biochemical and Chemical Engineering, Laboratory of Thermodynamics, TU Dortmund, Dortmund, Germany

Jukka Rantanen Department of Pharmacy, University of Copenhagen, København, Denmark

Gabriele Sadowski Department of Biochemical and Chemical Engineering, Laboratory of Thermodynamics, TU Dortmund, Dortmund, Germany

Prasenjit Seal Aerosol Physics Laboratory, Physics Unit, Faculty of Engineering and Natural Sciences, Tampere University, Tampere, Finland

Sean Smith National Computational Infrastructure, Australian National University, Canberra, Australia

Zhenbo Tong School of Energy and Environment, Southeast University, Nanjing, China
and

Southeast University-Monash University Joint Research Institute, Suzhou, China

Timothy Tracy Triastek, Inc., Nanjing, Jiangsu, China

and

Tracy Consultants, LLC, Huntsville, AL, USA

Karnaker Reddy Tupally School of Pharmacy, The University of Queensland, Woolloongabba, Australia

Jiawen Wang Macao Institute of Materials Science and Engineering, Macau University of Science and Technology, Taipa 999078, Macau SAR, China

and

Institute of Functional Nano & Soft Materials (FUNSOM), Soochow University, 199 Ren'ai Road, Suzhou, 215123, Jiangsu, China

LiGe Wang Department of Smart Manufacturing and Engineering Software, Shandong University, Jinan, China

Nannan Wang State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China

Wei Wang State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China

Yuzhu Wang Office of Biostatistics and Clinical Pharmacology, Center for Drug Evaluation, National Medical Products Administration, Beijing, China

Chuan-Yu Wu School of Chemistry and Chemical Engineering, University of Surrey, Guildford, UK

Lei Wu Triastek, Inc., Nanjing, Jiangsu, China

Li Wu Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Center for Pharmaceutical Research, Shanghai, China

Tiqiao Xiao Shanghai Synchrotron Radiation Facility, Shanghai Institute of Applied Physics, Chinese Academy of Sciences, Shanghai, China

Jiaqi Xu State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

Zhuyifan Ye State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China

and

Faculty of Applied Sciences, Macao Polytechnic University, Macao, China

Xianzhen Yin Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Center for Pharmaceutical Research, Shanghai, China

and

Lingang Laboratory, Shanghai, China

Peter York Institute of Pharmaceutical Innovation, University of Bradford, Bradford, UK

Yi Yu Institute of Functional Nano & Soft Materials (FUNSOM), Soochow University, 199 Ren'ai Road, Suzhou, 215123, Jiangsu, China

Jialu Yuan State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

Jiwen Zhang Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Center for Pharmaceutical Research, Shanghai, China

Ling Zhang School of Chemistry and Chemical Engineering, University of Surrey, Guildford, UK

Yu Zhang Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

and

Engineering Research Center of Modern Preparation Technology of Traditional Chinese Medicine, Ministry of Education, Shanghai, China

Zheng Zhang Jiangsu Province Hi-Tech Key Laboratory for Biomedical Research,
School of Chemistry and Chemical Engineering, Southeast University, Nanjing, China

Hao Zhong State Key Laboratory of Quality Research in Chinese Medicine, Institute of
Chinese Medical Sciences (ICMS), University of Macau, Macau, China

Xudong Zhou Department of Chemical and Biological Engineering, Monash University,
Clayton, Australia

and

Monash Suzhou Research Institute, Suzhou, China

Ruiping Zou Department of Chemical and Biological Engineering, Monash University,
Clayton, Australia

and

ARC Hub for Computational Particle Technology, Monash University, Clayton,
Australia

Preface

It is with great pleasure that we present the second edition of our book, *Exploring Computational Pharmaceutics – AI and Modeling in Pharma 4.0*. This book builds upon the foundation laid by our previous work, *Computational Pharmaceutics: Application of Molecular Modeling in Drug Delivery*, published by the Wiley Press in 2015.

The pharmaceutical industry is in a constant state of evolution, presenting new daily challenges and opportunities. With the advent of Pharma 4.0 and the increasing importance of artificial intelligence and modeling in drug discovery and development, we felt it was necessary to update our previous work to reflect these changes.

In this book, we explore the latest advancements in computational pharmaceutics, including the use of AI and machine learning in drug formulation, the application of multi-scale modeling in drug delivery, and the integration of these technologies into the drug development process. We hope that this book will serve as a valuable resource for scientists, students, and professionals in the field of pharmaceutics.

We would like to express our gratitude to our collaborators who have contributed to this book, as well as to the Wiley Press for their continued support. We hope that this book will inspire further research and innovation in the field of computational pharmaceutics, and we look forward to seeing the impact that these technologies will have on the future of drug discovery and development.

29 March 2024

Defang Ouyang
University of Macau, Macau, China

1

Introduction to Computational Pharmaceutics

Nannan Wang¹, Wei Wang¹, Hao Zhong¹, and Defang Ouyang^{1,2}

¹State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macau, China

²Department of Public Health and Medicinal Administration, Faculty of Health Sciences (FHS), University of Macau, Macau, China

Acronyms

3D	three-dimensional
ADME	absorption, distribution, metabolism, and excretion
AI	artificial intelligence
ANDA	abbreviated new drug application
CFD	computational fluid dynamics
DDS	drug delivery systems
DEM	discrete element method
FDA	food and drug administration
ISPE	the international society for pharmaceutical engineering
MD	molecular dynamics

MDI	pressurized metered dose inhaler
MIDD	model-informed drug development
NDA	new drug application
NME	new molecular entity
PBPK	physiologically based pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
QM	quantum mechanics
R&D	research and development

1.1 Current Pharmaceutical Research

Modern pharmaceutics, closely related to novel dosage forms and drug delivery systems (DDSs), has experienced a dramatic transformation over the past 70 years. In 1952, the development of the first 12-hour drug release formulation with Spansule[®] technology by Smith Kline & French initiated the history of modern pharmaceutics [1]. The progress of modern pharmaceutics made during the past 70 years could be divided into two generations [2, 3]. During the first generation (1950s–1980s), physical pharmacy, developed by combining the basic principles of physical chemistry with pharmacy, mainly focused on building the controlled-release preparations. During this period, drug delivery technologies were developed rapidly and achieved great success in clinical application, including oral sustained-release preparations, transdermal patch (Scop[®]) [4], and pressurized metered dose inhaler (MDI) [5]. The attention of the second generation (1980s–2010s) was dedicated to the development of advanced drug delivery systems. In the second generation of drug delivery technologies, several advanced approaches were widely investigated, including nanotechnology-based drug delivery systems, self-regulated drug delivery systems, and long-term depot formulations. However, due to biological barriers of the human body, the introduction of clinical formulations was significantly hindered and success rates were limited [6].

Nowadays, there is an obvious gap between the input of research and development (R&D) and the output of new molecular entities (NMEs). The costs of NMEs are growing significantly at an average rate of 13.4% per year [7]. However, the success rate of NMEs in clinical trials is merely about 10%. Research in 2007 involving 68 approved drugs reveals that it takes 15 years [8] and up to 2558 million dollars on average to bring a single NME to market [9]. As shown in Figure 1.1, only 37 NMEs were approved by the US Food and Drug Administration (FDA) in 2022 and the annual approval number remains at 20–50 compounds a year during the past 30 years despite the exponentially increasing resources invested, a phenomenon known as “Eroom’s law” [10]. Moreover, the current pharmaceutical products exhibit a far from optimal performance in clinical practice due to their low solubility, poor stability, and poor targeting effect. Theoretically, developing a novel formulation only costs a tiny fraction of the billions spent on each NME, and it only takes 3–4 years overall, which pushed many pharmaceutical companies to advanced drug delivery systems.

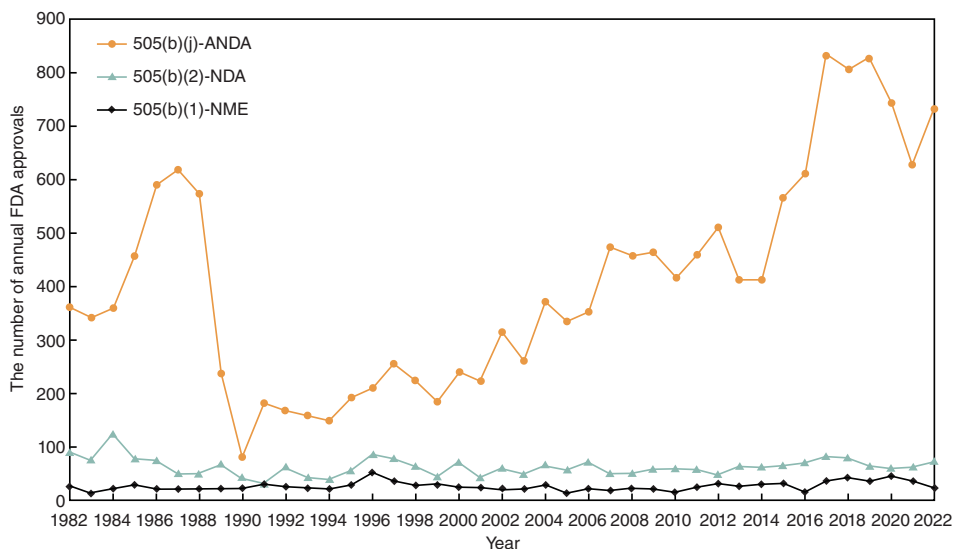


Figure 1.1 The number of annual FDA approvals: (1) 505(b)(1)-NME: the approval of new molecular entities under section 505(b)(1); (2) 505(b)(2)-NDA: the approval of modified new drugs under section 505(b)(2), including new active ingredient, new dosage form, new combination, new formulation, or new indication; (3) 505(b)(j)-ANDA: the approval of abbreviated new drug applications under section 505(b)(j).

Academic research in pharmaceuticals has achieved remarkable progress in the past 40 years. As shown in Figure 1.2a, a total of 141,523 papers were published in pharmaceutical SCI journals with an impact factor above 1 between 1980 and 2022, showing a stable increase trend. The publication number in 2022 has reached up to 8420, almost 5.5 times higher than that in 1980 (1523). However, the clinical success rate (the ratio of marketed drug products to clinical trials) of advanced drug delivery systems was even lower than that of NMEs (10%) [11]. The main reason is that traditional R&D of pharmaceutical formulations still relies on the inefficient trial-and-error pattern, which lacks the focus and understanding of the multiscale interactions between the drug delivery system and the biological system.

The challenges of the high cost, long period, and low success rate bring about a question, that is, how to improve the efficiency of R&D of drug products. The current low efficiency of drug formulation development should be attributed to the conflict between the pharmaceutical principles and the traditional drug formulation development paradigm. Pharmaceutical research is essentially a multi-objective optimization task in the high-dimensional space consisting of material properties and process parameters. It has been estimated that the dimensionality of the space for formulation development can be as high as 10^{25} – 10^{30} [12]. It is highly inefficient to perform trial-and-error tests in such a high-dimensional space. A straightforward idea is that knowing the basic principles in drug formulations in advance of production and testing should be cheaper than the endless trial-and-error tests relying on the favor of Lady Luck. Integrating the understanding of both products and processes into the design of drugs to improve their qualities is also encouraged in the philosophy of Quality by Design promoted by the US Food and Drug Administration.

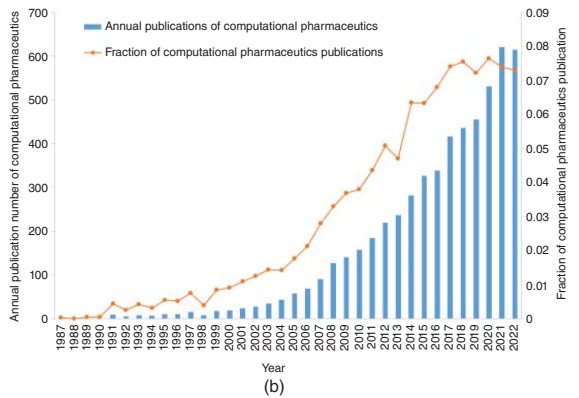
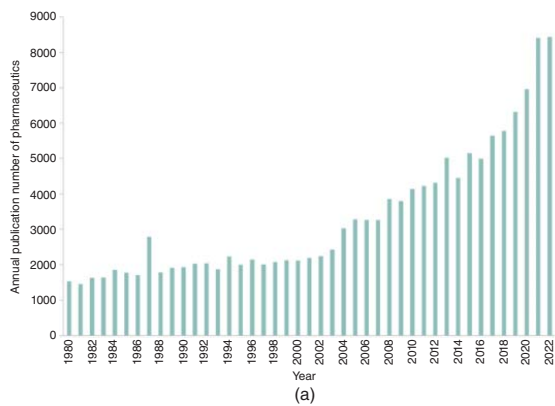


Figure 1.2 (a) The annual publication number of pharmaceuticals from 1980 to 2022. (b) The annual publication number of computational pharmaceuticals and the fraction it represents out of all pharmaceuticals publications. The number of publications of computational pharmaceuticals in the year from 1987 to 1990 are 1, 0, 1, and 1, respectively.

1.2 What is Computational Pharmaceutics?

Over the past decade, leaps in computing power are powering digital transformation in all sectors, and the pharmaceutical industry is no exception. The incorporation of artificial intelligence (AI) and multiscale modeling in drug formulation development has led to the emergence of a novel field known as “Computational Pharmaceutics” [12]. As shown in Figure 1.3, distinguished from conventional “screen-verify-re-screen” formulation development procedures, computational pharmaceutics emphasizes the computer-driven “understand-design-verify-optimize” formulation design paradigm [13]. By leveraging modeling and simulation tools to comprehensively comprehend the mechanisms of drug delivery, coupled with the potent design and optimization algorithms of AI, the concept of Quality by Design is being well implemented in computational pharmaceutics. This approach is expected to not only enhance the effectiveness of drug formulation development but also facilitate the objective-oriented and personalized drug development.

The commonly used tools in computational pharmaceutics include machine learning or AI, quantum mechanics (QM), molecular dynamics (MD) simulation, mathematical modeling, process simulation, and physiologically based pharmacokinetic (PBPK) modeling. By training models on existing data, machine learning or AI algorithms can uncover the underlying relationships and make predictions for new scenarios. QM uses the spatial electron density of molecules and functions of quantum chemistry to precisely calculate molecular properties and changes in chemical reactions. MD simulation is based on the potential energy within and between molecules and Newton’s laws of motion to simulate and analyze the dynamic change in structures of the molecules and the constituted system. Mathematical modeling uses mathematical equations to describe macroscopic processes. Mathematical equations are the base of many types of simulations; however, the term “mathematical modeling” is usually accompanied by simulations of dissolution

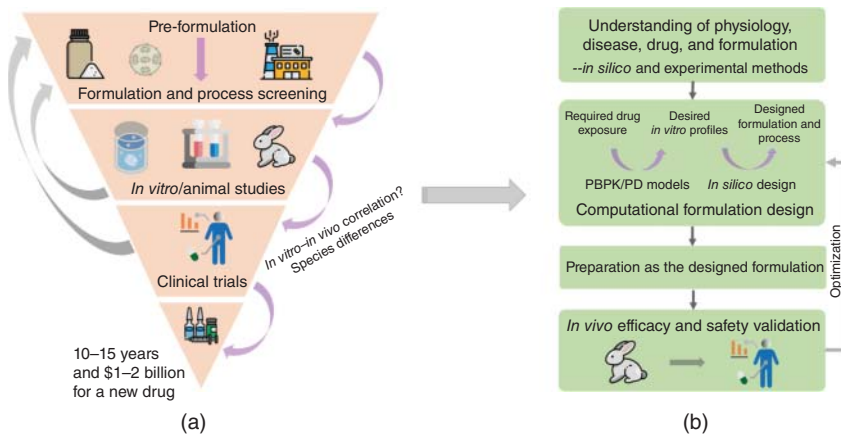


Figure 1.3 Pharmaceutical formulation development paradigm shift prompted by computational pharmaceutics. (a) Conventional drug formulation development procedures: “screen-verify-re-screen” and (b) computer-driven drug formulation design framework: “understand-design-verify-optimize.”

and precipitation. Process simulation is to simulate the change in materials during the drug process in the manufacturing pipelines, and the involved techniques include computational fluid dynamics (CFD), discrete element method (DEM), and automatic monitoring systems trained from data with statistical algorithms. PBPK is a method of using a set of differential equations involving pharmaceutical and physiological parameters to simulate the pharmacokinetics of drug administration. Besides, if the pharmacokinetic/pharmacodynamic (PK/PD) relationship is known, PBPK/PD modeling is also possible.

Nowadays, research about computational pharmaceutics is increasingly getting popular. Using the same strategy as in the article [12] and searching the publications in the Web of Sciences up to the year 2022, 5547 papers were found. Among these publications, 85.2% (4724) of them are research articles, while review papers occupy 10.1% (590) and other types take around 5%. The number of publications per year is shown in Figure 1.2b. In the past decades, both the annual publication number for the field of computational pharmaceutics and its fraction in all pharmaceutics publications present rapid increases, especially from the year 2000. The number of publications in 2022 has exceeded 600.

These investigations present a landscape of the applications with computational pharmaceutics, as shown in Figure 1.4. The picture is that all stages of drug development can involve modeling technologies. AI or machine learning delves into the relationship underlying the data; thus, it can be used in nearly all situations only if the data is properly collected. QM and MD simulations are microscopic investigation techniques used to study the mechanisms of biomolecules, drug molecules, excipients, and their interactions. When faced with problems on a larger scale, QM and MD are not applicable because their calculation precision is too high, and the computation power of current machines does not support the simulation of too large systems. In such cases, methods based on mathematical modeling have to be used. The available mathematical equations cover processes like solid dissolution, molecule diffusion, flow of fluid or powder, particle collision, and ADME (absorption, distribution, metabolism, excretion) of drugs. These equations correspond to special problems in the stages of formulation development, product process, and clinics.

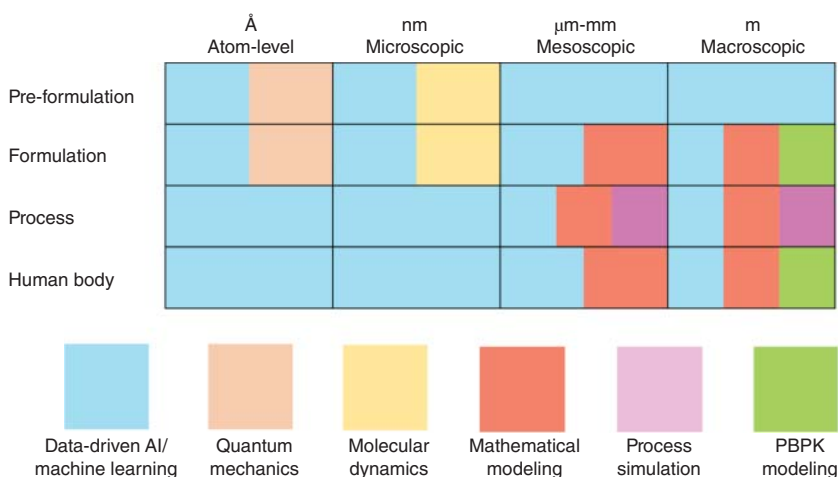


Figure 1.4 Multi-level modeling techniques in computational pharmaceutics.