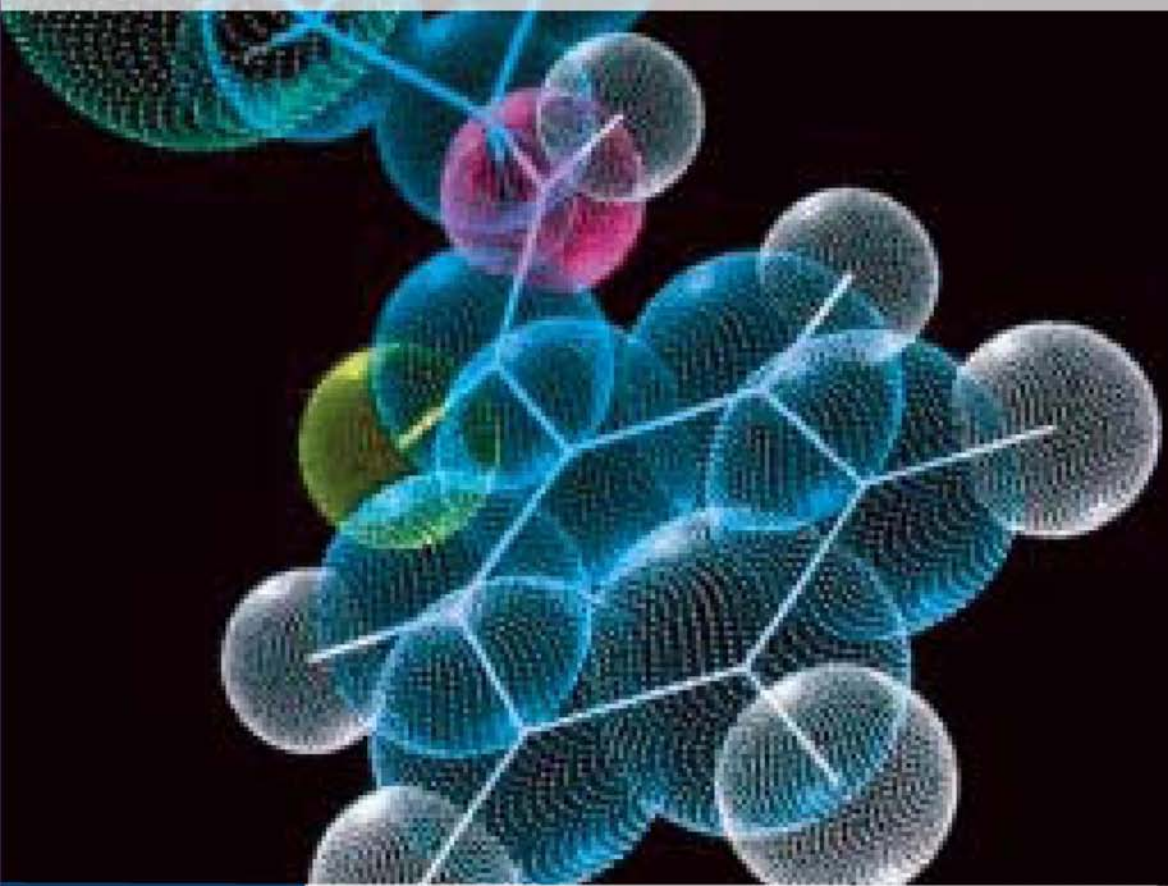
Molecular Biopharmaceutics

Edited by **Bente Steffansen, Birger Brodin and Carsten Uhd Nielsen**



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Molecular Biopharmaceutics

Aspects of drug characterisation, drug delivery and dosage form evaluation

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ULLA pharmacy series

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The ULLA pharmacy series is a new and innovative series of introductory textbooks for postgraduate students and science monographs for practising scientists.

The series is produced by the ULLA Consortium (European University Consortium for Advanced Pharmaceutical Education and Research). The Consortium is a European academic collaboration in research and teaching of the pharmaceutical sciences that is constantly growing and expanding. The Consortium was founded in 1990 and consists of pharmacy departments from leading universities throughout Europe:

- Faculty of Pharmacy, University of Uppsala, Sweden
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- The Faculty of Pharmaceutical Sciences, University of Copenhagen, Denmark
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The titles in this series are primarily aimed at PhD students and will also have global appeal to postgraduate students undertaking masters or diploma courses, undergraduates for specific courses, and practising pharmaceutical scientists.

Further information on the Consortium can be found at www.u-l-l-a.org.

Preface

Molecular Biopharmaceutics concerns physicochemical characterization, membrane transport and bioavailability of mainly small (pro)drug substances/candidates. The book describes experimental and predictive methods, ie from chemical stability, dissolution, passive diffusional and carrier-mediated membrane permeability to biosimulation of oral absorption and bioavailability. These methods are all applied in modern molecular biopharmaceutical science, in industrial preformulation and preclinical pharmaceutical development, as well as suggested in various regulatory guidelines.

The book would not have been written without the experimental laboratory work, done by our 'Drug Transporters in ADME' research group at Faculty of Pharmaceutical Sciences, University of Copenhagen. We therefore wish to thank laboratory technicians Birgitte Eltong, Bettina Dinitzen, and Maria Læssøe Pedersen, who are running the various equipment and cells. We also wish to thank the PhD's that have been running many experiments during their stay in our laboratories, and thereby indirectly contributed to the book: André Huss Eriksson, Rikke Andersen, Luise Kvistgaard Gram, Karina Thorn, Gerda Marie Rist, Sidsel Frølund, Helle Bach Søndergaard, Mie Larsen and Diana Højmark Omkvist.

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Bente Steffansen
Birger Brodin
Carsten Uhd Nielsen
August 2009

About the editors

Carsten Uhd Nielsen (CUN) is Associate Professor of Transporters in ADME at the Faculty of Pharmaceutical Sciences (PHARMA), University of Copenhagen. His research has focused on epithelial drug transport via transporters and the impact of transporters in defining oral bioavailability. Carsten Uhd Nielsen graduated with MSc(Pharm) in 1997 from the Royal Danish School of Pharmacy. After a brief period in industry, in 2001 he obtained his PhD in drug delivery via transporters under the Center of Drug Delivery and Transport. He has served as Programme Director for the MSc in Pharmaceutical Sciences programme at PHARMA and has been on the committee developing the final BSc project in Pharmaceutics. Carsten Uhd Nielsen has furthermore worked with postgraduate teaching as both a PhD advisor and as a member of the PhD Study Board at PHARMA. From 2007 to 2009 he was on part-time leave from PHARMA working on barrier models for Bioneer:FARMA, an affiliation of the biotech company Bioneer.

Birger Brodin, MSc PhD in Biology, graduated from the August Krogh Institute, University of Copenhagen in 1994. After a Carlsberg-granted postdoctoral scholarship, he was employed as Post Doc by the Center for Drug Design and Transport at the Department of Pharmaceutics and Analytical Chemistry, The Faculty of Pharmaceutical Sciences (PHARMA), University of Copenhagen, where he is Associate Professor at present.

Birger Brodin has been working with the biophysics of drug transporters in the 'Drug Transporters in ADME' section at PHARMA since 1998. His main area of research has been peptide transporters, where he has authored a number of scientific papers, reviews and popular science articles. Birger Brodin is an elected member of the Academic Advisory Board, PHARMA, Head of the Cell Culture Facility, PHARMA, Group Leader of the 'Drug Transporters in ADME' section and Course Director of PhD and graduate courses. He is a member of the American Association of Pharmacautical Scientists, The Danish Society for

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Bente Steffansen is Associate Professor in Transporters in ADME at The Faculty of Pharmaceutical Sciences (PHARMA), University of Copenhagen. She graduated with MSc(Pharm) in 1989 from The Royal Danish School of Pharmacy and obtained her PhD under the Danish Research Academy in Ocular Drug Delivery in 1994. During her PhD study she also worked for 1½ years as Research Scientist at The University of Kentucky, USA, and later as Visiting Scientist at University of Uppsala. Her research is focused on studying drug delivery processes, such as transporter-mediated ADME processes, prodrug delivery and biosimulation. Bente Steffansen has more than 50 research publications and is a member of the European Biosim network of excellence. She serves as the Program Director for the Master in Pharmaceutical Regulatory Affairs at PHARMA and supervises many Bachelor, Master and PhD students. She is a member of the Chemical Committee under the National Pharmacopoeia Board.

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Abbreviations

AAPS	American Association of Pharmaceutical Scientists
ABC	ATP-binding cassette
ACAT	advanced CAT (model)
ACE	angiotensin-converting enzyme
ADAM	advanced dissolution, absorption and metabolism (model)
ADME	absorption, distribution, metabolism and elimination
ADP	adenosine disphosphate
AIC	Akaike information criterion
AOA	acycloxyalkoxy
API	active pharmaceutical ingredient
AQ	absorption quotient
ASA	acetyl salicylic acid
ATP	adenosine triphosphate
AUC	area under the curve
AZT	azidothymidine
BCRP	breast cancer-resistance protein
BCS	Biopharmaceutics Classification System
BDDCS	Biopharmaceutics Drug Disposition Classification System
BHPH	bis-(p-hydroxyphenyl)-pyridyl-2-methane
BSA	bovin serum albumin
BSEP	bile salt export pump
CA	coumarinic acid
CAT	compartmental transit and absorption
Caco-2	human colon carcinoma cells
CBER	Center for Biologics Evaluation and Research
CCK	cholecystokinin
CD	candidate drug
CDER	Center for Drug Evaluation and Research
CHN	carbon hydrogen nitrogen
CHO	Chinese hamster ovary
CL	clearance

CNS	central nervous system
CNT	concentrative nucleoside transporter
CV	coefficient of variation
CYP	cytochrome P
DMPK	drug metabolism and pharmacokinetic
DMSO	dimethylsulfoxide
DSC	differential scanning calorimetry
DVS	dynamic vapour sorption
EC	enzyme classification
EMEA	European Medicines Agency
ENT	equilibrative nucleoside transporter
ER	efflux ratio
FA	fraction absorbed
FaSSGF	fasted-state simulated gastric fluid
FaSSIF	fasted-state simulated intestinal fluid
FBP	folate-binding protein
FDA	Food and Drug Administration
FeSSGF	fed-state simulated gastric fluid
FeSSIF	fed-state simulated intestinal fluid
FIP	International Pharmaceutical Federation
5-FU	5-fluorouracil
GABA	γ-aminobutyric acid
GI	gastrointestinal
GITS	gastrointestinal therapeutic system
GLUT	glucose transporter
GO	Gene Ontology
GSE	general solubility equation
GST	glutathione-*S*-transferase
HAT	heteromeric amino acid transporter
HGNC	Human Genome Nomenclature Committee
HMIT	H+-*myo*-inositol
HMM	hidden Markov model
HPLC	high-performance liquid chromatography
HSA	human serum albumin
HTS	high-throughput screening
HUGO	Human Genome Organization

IAMS immobilised phospholipids onto a silica surface
IC_{50} concentration at 50% inhibition
IF intrinsic factor
IR immediate release
IUBMB International Union of Biochemistry and Molecular Biology
iv intravenous
IVIVC *in vitro–in vivo* correlation

LC liquid chromatography
LG lead generation
LO lead optimisation

MCT monocarboxylate transporter
MDCK Madin–Derby canine kidney (cells)
MDR multidrug-resistant/multidrug resistance
MHD 10-hydroxy-carbazepine
MMC migrating motor complex
MPA mycophenolatic acid
MRP multidrug-resistance-associated protein
MS mass spectroscopy
MW molecular weight

NHE Na^+/H^+ exchanger

OAT organic anion transporter
OATP organic anion-transporting polypeptide
OB oral bioavailability
OCT organic cation transporter
OF objective function
OMCA oxymethyl-modified coumarinic acid

PAMPA parallel intraluminal permeability approach
PCA principal component analysis
PEG polyethylene glycol
P-gp P-glycoprotein
Ph Eur *European Pharmacopoeia*
Pi inorganic phosphate
PLS partial least squares
po oral
POT proton-dependent oligopeptide transporter
PSA polar surface area

QSAR quantitative structure–activity relationship
QSPR quantitative structure–property relationship

RBC red blood cell
RFT reduced folate transporter
RP-HPLC reverse-phase HPLC

SAR structure–activity relationship
SLC solute carrier
SLS sodium lauryl sulphate
SMCT sodium-coupled monocarboxylate transporter
SMVT sodium-coupled multivitamin transporter
SNP single nucleotide polymorphism
SPAN sorbitan ester
SQ secretion quotient
SULT sulphotransferase

TC transporter classification
TCDB transporter classification database
TEER transepithelial electrical resistance
TGA thermogravimetric analysis
ThT thiamine transporter
TI target identification
TMS transmembrane segment
TS transition state

UGT uridine diphosphate glucuronosyl transferase
UIR unit impulse response
UR uptake ratio
USP *US Pharmacopoeia*
UV ultraviolet

wt wild-type

XPRD X-ray powder diffraction