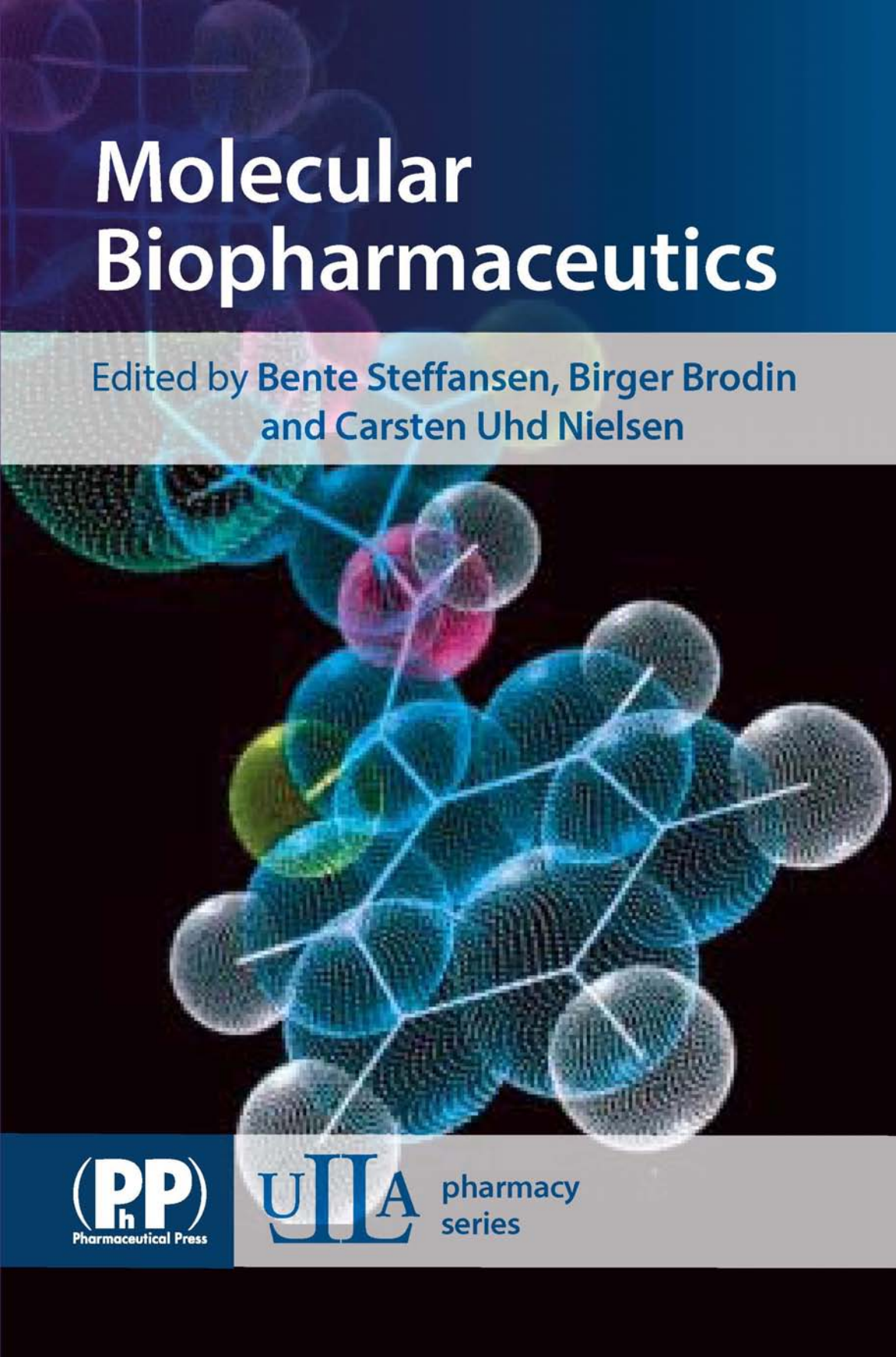


# Molecular Biopharmaceutics

Edited by Bente Steffansen, Birger Brodin  
and Carsten Uhd Nielsen

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# **Molecular Biopharmaceutics**

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# Molecular Biopharmaceutics

Aspects of drug characterisation,  
drug delivery and dosage form evaluation

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# ULLA pharmacy series

## Series Editor-in-Chief

**Professor Anthony C Moffat**, The School of Pharmacy, University of London, UK

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

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Further information on the Consortium can be found at [www.u-l-l-a.org](http://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

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# Abbreviations

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



**xvi** Abbreviations

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

IAMS	immobilised phospholipids onto a silica surface
IC <sub>50</sub>	concentration at 50% inhibition
IF	intrinsic factor
IR	immediate release
IUBMB	International Union of Biochemistry and Molecular Biology
iv	intravenous
IVIVC	<i>in vitro</i> – <i>in vivo</i> 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 <sup>+</sup> /H <sup>+</sup> 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	<i>European Pharmacopoeia</i>
Pi	inorganic phosphate
PLS	partial least squares
po	oral
POT	proton-dependent oligopeptide transporter
PSA	polar surface area

xviii Abbreviations

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	<i>US Pharmacopoeia</i>
UV	ultraviolet
wt	wild-type
XPRD	X-ray powder diffraction