



Anna Christine Petereit (Autor)

Prediction of biological membrane penetration of poorly soluble drugs using surface activity profiling

Goethe University • Institute of Pharmaceutical Technology
Prof. Dr. Jennifer B. Dressman

Anna Christine Petereit

**Prediction of biological
membrane penetration of
poorly soluble drugs
using surface activity profiling**

 Cuvillier Verlag Göttingen
Internationaler wissenschaftlicher Fachverlag

<https://cuvillier.de/de/shop/publications/6120>

Copyright:

Cuvillier Verlag, Inhaberin Annette Jentzsch-Cuvillier, Nonnenstieg 8, 37075 Göttingen,
Germany

Telefon: +49 (0)551 54724-0, E-Mail: info@cuvillier.de, Website: <https://cuvillier.de>

TABLE OF CONTENTS

1	INTRODUCTION	1
1.1	New chemical entities (NCE-Discovery)	1
1.2	ADME-Properties	5
1.2.1	Absorption	6
1.2.2	Distribution	6
1.2.3	Metabolism	7
1.2.4	Elimination	8
1.3	Solubility	8
1.4	Transport across lipid bilayers (intestinal/brain)	12
1.4.1	Morphological aspects of intestinal drug absorption	12
1.4.2	Mechanisms of intestinal transport	14
1.4.3	Mechanisms of blood brain barrier penetration	17
1.5	In vitro models for prediction of membrane penetration	21
1.5.1	Octanol/water partition coefficients	22
1.5.2	Polar surface area	23
1.5.3	Lipinski's rules of five	23
1.5.4	Parallel artificial membrane permeation assay	24
1.5.5	Caco-2 cells	25
1.5.6	Biopharmaceutical Classification System	25
1.5.7	Biopharmaceutical Drug Disposition Classification System	27
1.5.8	Summary of established methods	28
1.6	The air/water interface - a model for the lipid bilayer	29
1.7	Surface tension and amphiphilicity	30
1.7.1	Surface tension measurement	33
1.7.2	Thermodynamic characterization	34
2	AIM OF THIS STUDY	39
3	MATERIALS AND METHODS	41
3.1	Standard materials	41
3.1.1	Standard chemicals	41
3.1.2	Standard equipment	42
3.2	Standard media	43
3.2.1	Buffer solution to simulate the small intestine	43
3.2.2	Buffer solution to simulate the blood pH 7.4	44
3.3	Organic solvents	45
3.3.1	Chemical structure of organic solvents	45
3.4	Substance used as test set for oral absorption	46
3.4.1	Surface active compounds	46
3.4.2	Chemical structure	48
3.4.3	Physicochemical and pharmacokinetic properties of the test set compounds	53

3.5 Substances used as a test set for blood brain barrier penetration	55	
3.5.1 Physicochemical properties of the test set compounds for blood brain barrier penetration studies	55	
3.5.2 Pharmacokinetic data and log bb of the test set compounds	57	
3.6 Sample preparation for surface tension measurements	59	
3.6.1 Preparation of aqueous stock solutions of test set compounds by the traditional 'shake-flask' method	59	
3.6.2 Preparation of organic solvent in buffer solution for intrinsic surface activity determination	60	
3.6.3 Preparations of non-aqueous stock solutions of the test set compounds	61	
3.6.4 Sample preparation after pre-dissolving in organic solvent	61	
3.6.5 Preparation of micelle vehicle solution	63	
3.6.6 Preparation of drug stock solution for surface activity profiling in micelle solutions	63	
3.6.7 Sample preparation for the test set compounds in micelle vehicle solutions	63	
3.6.8 Preparations of stock solutions for blood brain barrier measurements	64	
3.6.9 Sample preparation for blood brain barrier SAP measurements	65	
3.7 Surface tension measurement	65	
3.7.1 Delta-8 tensiometer	65	
3.7.2 Measurement principle	66	
3.7.3 Calibration and Quality Control Test	68	
3.7.4 Surface tension measurement of aqueous drug solutions	68	
3.7.5 Surface tension measurement of the drugs pre-dissolved in organic solvents	68	
3.7.6 Surface tension measurements using drugs dissolved in micellar solutions	69	
3.7.7 Surface tension measurements for blood brain barrier penetration	69	
3.7.8 Surface activity profiling (SAP)	69	
3.7.9 Profile analysis – calculation of physicochemical parameters	71	
3.7.10 Surface activity profiling - micelle vehicle	74	
3.8 Statistics	76	
4 RESULTS AND DISCUSSION		77
4.1 Surface activity profiling of poorly soluble compounds for the prediction of oral absorption	77	
4.1.1 Solubility determination	77	
4.1.2 Surface tension measurement from aqueous buffer solution	80	
4.1.3 Surface activity profiling in the presence of organic solvents	87	
4.1.4 SAP parameter after solubility enhancement with organic solvents	98	
4.1.5 Correlation of maximum surface pressure and oral drug absorption	102	
4.1.6 Utilization of solvent mixture in buffer	108	
4.1.7 Conclusion from various sample preparation	116	
4.1.8 Using micelle solution for surface activity measurements	117	
4.1.9 Development of a sample preparation scheme for absorption screening	124	
4.2 SAP as a prediction method of oral drug absorption	125	
4.3 Comparison of different <i>in vitro</i> models for the prediction of oral drug absorption	129	
4.4 Surface activity profiling of compounds for blood brain barrier prediction	133	
4.4.1 Surface tension measurements	133	
4.4.2 Surface activity profiling parameter	137	
4.4.3 Physiological Effects influencing Blood Brain Barrier Penetration	143	
4.4.4 Conclusion: SAP as a prediction model for blood brain barrier penetration	145	
5 SUMMARY	147	

6	GERMAN SUMMARY	151
7	APPENDIX	157
7.1	Surface activity profiling for the prediction of oral drug absorption	157
7.1.1	Surface activity profiling from aqueous media	157
7.1.2	Surface activity profiling from DMSO/buffer mixture	160
7.1.3	Surface activity profiling from DMF/buffer mixture	163
7.1.4	Surface activity profiling from DMSO/DMF-buffer mixture	166
7.1.5	Surface activity profiling from DMA/buffer mixture	169
7.1.6	Surface activity profiling from NMP/buffer mixture	172
7.2	Surface activity profiling for Blood Brain Barrier-Test set in aqueous buffer solution	175
8	REFERENCES	177
9	CURRICULUM VITAE	183