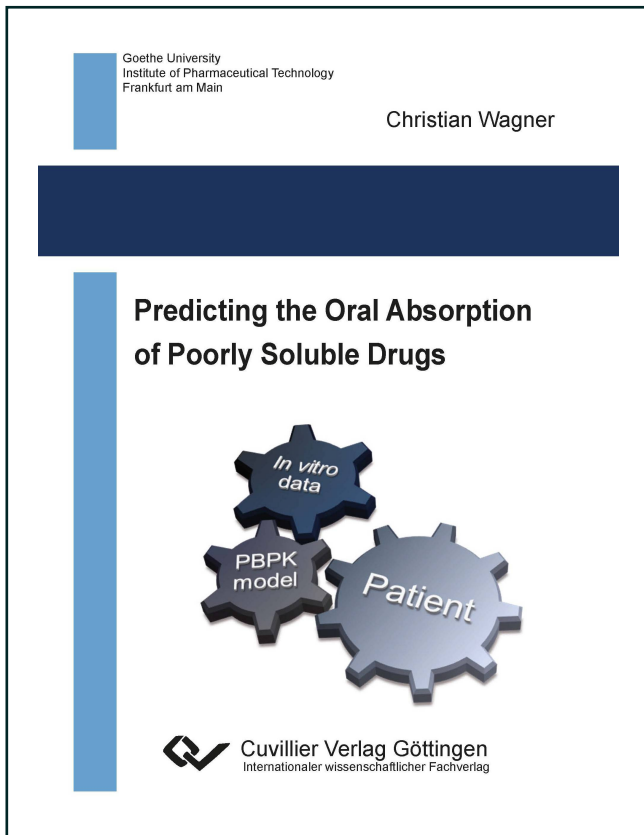




Christian Wagner (Autor)

Predicting the Oral Absorption of Poorly Soluble Drugs



<https://cuvillier.de/de/shop/publications/6557>

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>



Acknowledgements

Table of Contents

List of Abbreviations

1.	Introduction	1
1.1.	Classification of Poorly Soluble Drugs	2
1.1.1.	<i>The Biopharmaceutics Classification Scheme (BCS)</i>	2
1.1.2.	<i>The Biopharmaceutics Drug Disposition Classification Scheme (BDDCS)</i>	3
1.2.	Intraluminal Events in the Context of Oral Absorption and Factors that Limit the Bioavailability of Orally Administered Drugs	4
1.2.1.	<i>Solubility, Dissolution, and Precipitation</i>	6
1.2.2.	<i>Complexation, Degradation</i>	9
1.2.3.	<i>Permeability Considerations</i>	9
1.2.4.	<i>Site-Specific Absorption</i>	10
1.2.5.	<i>Exotransport</i>	10
1.2.6.	<i>First Pass Metabolism</i>	10
1.3.	Current Methods for Predicting the Permeability of Drugs	11
1.3.1.	<i>Jejunal Perfusion Experiments</i>	11
1.3.2.	<i>In Vitro Techniques for Predicting the Intestinal Permeability of a Drug</i>	12
1.3.2.1.	<i>Parallel Artificial Membrane Permeability Assay (PAMPA)</i>	12
1.3.2.2.	<i>Surface Activity Profiling (SAP)</i>	12
1.3.2.3.	<i>Estimation Using Physicochemical Drug Properties</i>	13
1.3.2.4.	<i>Caco 2 Cell Assay</i>	13
1.3.2.5.	<i>HT-29 Cell Assay</i>	14
1.3.2.6.	<i>MDCK II Cell Assay</i>	14
1.3.2.7.	<i>LLC-PK1 Cell Assay</i>	14



1.4.	Current Methods for Predicting the Release Characteristics of Drug Products	15
1.4.1.	<i>Compendial Dissolution Methods</i>	15
1.4.1.1.	<i>Compendial Dissolution Media</i>	15
1.4.1.2.	<i>Compendial Dissolution Apparatus</i>	16
1.4.2.	<i>Biorelevant Dissolution Testing</i>	17
1.5.	Mathematical Description of Dissolution and Release	22
1.5.1.	<i>Fick's Diffusion Law and Noyes-Whitney Kinetics</i>	22
1.5.2.	<i>Zero Order Dissolution Kinetics</i>	23
1.5.3.	<i>First Order Dissolution Kinetics</i>	24
1.5.4.	<i>Weibull Distribution</i>	25
1.5.5.	<i>Higuchi Model</i>	26
1.5.6.	<i>Korsmeyer-Peppas Kinetics</i>	27
1.5.7.	<i>Dissolution Kinetics in Swellable, Erodible Matrices</i>	28
1.6.	Effect of Food on Drug Absorption	28
1.6.1.	<i>Physiological Changes in Response to Meal Ingestion</i>	28
1.6.2.	<i>Possible Effects of Food on the Performance of a Drug or Drug Formulation</i>	30
1.6.2.1.	<i>Gastric Conditions</i>	30
1.6.2.2.	<i>Small Intestinal Conditions</i>	31
1.6.2.3.	<i>Further Considerations for Food Effects</i>	31
1.6.3.	<i>Prediction of Food Effects</i>	32
1.6.3.1.	<i>BCS-Based Predictions</i>	32
1.6.3.2.	<i>Dissolution Studies</i>	33
1.6.3.3.	<i>Preclinical Studies</i>	33
1.6.3.4.	<i>Combining Laboratory and Pharmacokinetic Data</i>	33
1.7.	Physiologically Based Pharmacokinetic (PBPK) Modeling	33
1.8.	Aim of the Thesis and Issues Addressed in this Work	40



2.	Results and Discussion	41
2.1.	Combining Dissolution Testing and PBPK Modeling for Establishing <i>in Vitro</i> – <i>in Silico</i> – <i>in Vivo</i> Correlations (IVISIVC) – Advantages and Limitations	41
2.1.1.	<i>Establishing IVISIVC – Neutral Drugs</i>	44
2.1.2.	<i>Establishing IVISIVC – Weakly Acidic Drugs</i>	46
2.1.3.	<i>Establishing IVISIVC – Weakly Basic Drugs</i>	56
2.1.3.1.	<i>Theoretical Models for Simulating Drug Precipitation</i>	57
2.1.3.2.	<i>In Vitro Models for Simulating Drug Precipitation</i>	58
2.1.4.	<i>What is the Benefit of Coupling Dissolution Results with PBPK Models? A Statement of How to Establish IVISIVC</i>	63
2.2.	PBPK Models to Predict the Pharmacokinetics of Poorly Soluble Drugs – A Guide to Appropriate Model Selection	68
2.2.1.	<i>From 2001 to Now – The Evolution of the STELLA[®] PBPK Model</i>	68
2.2.2.	<i>A Comparison of the STELLA[®]-Based Model with Commercial PBPK Models: Advantages and Limitations</i>	74
2.2.3.	<i>Which PBPK Model Covers My Situation Best?</i>	79
2.2.4.	<i>Regulatory Applications of PBPK Modeling</i>	82
3.	Summary and Outlook	86
4.	German Summary (Deutsche Zusammenfassung)	89
5.	References	94
6.	Publications	118
6.1.	Publication List	118
6.1.1.	<i>Peer-Reviewed Papers</i>	118
6.1.2.	<i>Review Articles</i>	118
6.1.3.	<i>Book Chapter</i>	118
6.1.4.	<i>Poster Presentations</i>	119



6.2.	Personal Contributions to Peer-Reviewed Papers and Book Chapter	121
6.3.	Original Publications (Peer-Reviewed Papers and Book Chapter)	122
6.3.1.	<i>Biorelevant in Vitro Dissolution Testing of Products Containing Micronized or Nanosized Fenofibrate with a View to Predicting Plasma Profiles</i>	122
6.3.2.	<i>Predicting the Oral Absorption of a Poorly Soluble, Poorly Permeable Weak Base using Biorelevant Dissolution and Transfer Model Tests Coupled with a Physiologically Based Pharmacokinetic Model</i>	130
6.3.3.	<i>Utilizing in Vitro and PBPK Tools to Link ADME Characteristics to Plasma Profiles: Case Example Nifedipine Immediate Release Formulation</i>	142
6.3.4.	<i>In Vitro – in Silico Tools to Predict Pharmacokinetics of Poorly Soluble Drug Compounds. Chapter 12 in: Predictive ADMET: Integrated Approaches in Drug Discovery and Development</i>	157
7.	Curriculum Vitae	195
8.	Academic Teachers	201