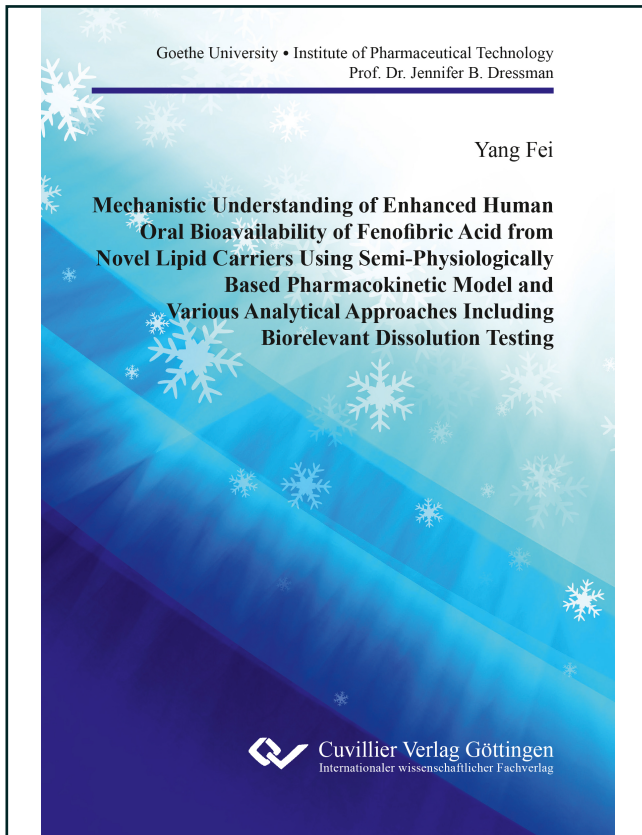




Yang Fei (Autor)

Mechanistic Understanding of Enhanced Human Oral Bioavailability of Fenofibric Acid from Novel Lipid Carriers Using Semi- Physiologically Based Pharmacokinetic Model and Various Analytical Approaches Including Biorelevant Dissolution Testing



<https://cuvillier.de/de/shop/publications/7781>

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

Acknowledgements	V
List of Figures	X
List of Tables	XIV
Abbreviations	XVI
Chapter 1. Introduction	1
1.1 Lipid-based formulation – an overview	1
1.2 Oral Lipid-based formulation with examples.....	1
1.3 The Lipid Formulation Classification System and its application	3
1.4 Potential advantages / disadvantages of lipid formulations	6
1.5 Evaluation of oral lipid-based formulations.....	7
1.5.1 Dispersion	7
1.5.2 Digestion	8
1.5.3 Dissolution	10
1.6 Introduction of PBPK software applied in this research	11
1.6.1 Overview of STELLA [®] software, including establishment of the PBPK model.....	11
1.6.2 Introduction of the Simcyp simulator and its application to evaluating LBFs	13
1.7 Introduction of the LBFs and methodology used for the present dissertation.....	13
Chapter 2. Aims of the thesis	15
2.1 Overall aim of the thesis.....	15
2.2 Aims of Chapter 4.....	15
2.3 Aims of Chapter 5.....	15
Chapter 3. Materials and equipment	16
3.1 Materials	16
3.1.1 Chemicals.....	16
3.1.2 Overview of fenofibrate drug substance	18
3.2 Equipment.....	20



Chapter 4. Study of LBF No.1 – No.7 of fenofibrate	23
4.1 Dispersion and dilution experiments	23
4.1.1 LBFs developed at the Goethe University (No.3 – No.4)	23
4.1.1.1 Choice of lipid-based excipients	23
4.1.1.2 Preparation of fenofibrate lipid formulations	24
4.1.1.3 Media preparation.....	25
4.1.1.4 Dispersion and dilution test set-up of LBF No.2	27
4.1.1.5 Discussion of the dilution results of LBF No.2.....	29
4.1.2 LBFs developed by scientists from Ireland, Switzerland, Greece and Germany (No.5 – No.7)	30
4.1.2.1 Dilution test set-up of LBFs No.5 – No.7	30
4.1.2.2 Results and discussion.....	32
4.2 Solubility experiments.....	34
4.2.1 Literature Data	34
4.2.2 Solubility test set-up and sample preparation	36
4.2.3 Solution preparation and HPLC method (common to the entire thesis)	37
4.2.4 Results and discussion of the solubility tests.....	38
4.3 Dissolution experiments	41
4.3.1 Dissolution testing using USP III apparatus	41
4.3.1.1 Dissolution test set-up	41
4.3.1.2 Results and discussion.....	41
4.3.2 Dissolution testing using USP II apparatus	46
4.3.2.1 Dissolution test set-up	46
4.3.2.2 Results and discussion.....	47
4.3.3 Dissolution experiment using the transfer model	50
4.3.3.1 Dissolution testing set-up of the transfer model.....	50
4.3.3.2 Results and discussion.....	51
4.4 <i>In silico</i> simulation of plasma profiles following oral administration of LBFs	53



4.4.1 STELLA [®] software approach	53
4.4.1.1 Mathematical description of dissolution mechanisms	53
4.4.1.2 Results and discussion.....	57
4.4.2 Simcyp [®] software approach.....	59
4.4.2.1 Description of the Simcyp [®] model parameters	59
4.4.2.2 Results and discussion.....	60
Chapter 5. Study of LBF No.8 – No.11 of fenofibrate.....	65
5.1 Preparation of LBF No.8 – No.11	65
5.2 Fasted state <i>IVISIVC</i> of LBF No.8 – No.11	66
5.2.1 Solubility of fenofibrate in biorelevant dissolution media in the presence of lipid-based excipients	67
5.2.1.1 Solubility test set-up.....	67
5.2.1.2 Results and discussion.....	68
5.2.2 Dissolution studies	69
5.2.2.1 Dissolution test set-up	69
5.2.2.2 Results and discussion.....	70
5.2.2.3 z value estimation	73
5.2.3 STELLA [®] model set-up.....	74
5.2.3.1 Overall description of the model map and assumptions	74
5.2.3.2 Description of the ODEs involved	76
5.2.3.3 Modeling of precipitation process	77
5.2.3.4 Fenofibrate permeability estimation and STELLA [®] intestinal absorption model	79
5.2.4 <i>In vivo</i> clinical study and calculation of PK parameters.....	85
5.2.5 <i>f2</i> approach and simulation outcome using STELLA [®] software.....	87
5.2.6 Comparison of simulated and reported plasma concentration profiles.....	94
5.2.7 Sensitivity analysis of the model parameters for simulation of the fenofibric acid plasma profiles in fasted state.....	95
5.3 Fed state <i>IVISIVC</i> of LBF No.8 – No.11	99



5.3.1 Media preparation	100
5.3.2 Solubility testing and results	101
5.3.3 Dissolution testing and results	102
5.3.4 z value estimation.....	105
5.3.5 Updated model parameters to predict the fed state plasma profiles	105
5.3.6 Prediction of the fed state plasma profiles of fenofibric acid using STELLA [®] software	106
5.3.7 Sensitivity analysis: varying model parameters for response of fenofibric acid plasma profile in the fed state.....	111
5.3.8 Discussion of food effect and comparison of results in fasted and fed state	113
Chapter 6. Summary and outlook	114
6.1 Summary.....	114
6.2 Outlook.....	118
Chapter 7. Deutsche Zusammenfassung (German summary).....	119
Appendix.....	124
References	186
Curriculum vitae.....	195
Publications and presentations	196