

MULTIPARTICULATE DRUG DELIVERY SYSTEM FOR LIPOPHILIC DRUGS AND MACROMOLECULE DRUGS

Dissertation zur Erlangung des akademischen Grades des
Doktors der Naturwissenschaften

eingereicht im Fachbereich Biologie, Chemie, Pharmazie
der Freien Universität Berlin

vorgelegt von
WENYU DONG
Tianjin, China

Juli 2005

- 1. Gutachter: Prof. Dr. R. Bodmeier**
- 2. Gutachter: Prof. Dr. P. Maincent**

Disputaion am 1. Juli 2005

Acknowledgements

Many thanks to my supervisor, Prof. Dr. Roland Bodmeier, for his patience, kindness and gentleness to me. Deeply thank to his advice, guidance, encouragement and support in my research work through this study. The way he shows me is invaluable for my future work and life.

I would like to thank Martin Körber, Katrin Johannsen, Martin Schulz, Dr. Andrei Dashevsky, Prof. Dr. Jürgen Siepmann, Dr. Florence Lecomte, Dr. Srisagul Sungthongjeen (Toy), Dr. Xiaosong Luan, Oliver Bley, Christine Curbach, Dirk Sticha, Diana Klose, Frauke Kreye, Vivian Lopez, Soravoot Rujivipat, Ildiko Terebesi, Eva Ewest, and all my friends and colleagues in the Kelchstrasse for your kindness, support, constructive discussions and great atmosphere in the group. Special thanks to Angelika Schwarz,

Furthermore, I would like to thank Prof. Dr. Philippe Maincent for evaluating this thesis. I am also very thankful to him, Prof. Dr. H.-H. Borchert, Prof. Dr. Kolodziej and Dr. W. Mehnert as members of my thesis advisor committee.

I sincerely wish to thank Dr. Henrik Saalbach, Prof. Enming Deng and his wife Ziruo Zhu, Dr. Linjie Hu and his wife Wei Liu, Dr. Lixia Yang and her husband Jun Zhang, Wei Chen and his wife Yuhui Hu, Dr. Yuemin Wang and his wife Baoyan Duan, and all of the other Chinese friends in Berlin. I appreciate and cherish your warm friendship, support, encouragement and help.

Special and warmest thanks to Kathy Whitt, Denies Chen, Xin Li, Yunying Wu, Tianyu Chen, Wenhua Li and his wife Qiuning Yang, Xiaoning Miao and Xinan Guo, Huaiyu Mu, Chunyan Lei, Xaiobei Tang, and all the other people in our bible study group and in Chinese church for their love and encouragement.

Finally, I want to thank my wife Xia Teng and my sweet daughter Hanzhe Dong, my parents and my parents in law for their never-ending love and support through the years and their encouragement and confidence in me. Special appreciation to my parents in law for their taking care my daughter all of these years.

Wenyu Dong

CHAPTER 1. INTRODUCTION 8

1. Lipophilic drugs	9
1.1. Solubilization and surfactants	9
1.2. Modification of polymorphs.....	11
1.3. Reduction in particle size	12
1.4. Complexation	15
1.5. Solid solutions/dispersions.....	17
1.5.1. Production methods	17
1.5.2. Carriers	18
1.5.3. Challenges	18
1.6. Enteric microparticles	20
1.6.1. Enteric polymers.....	20
1.6.2. Enteric polymers as carriers for lipophilic drugs.....	21
2. In-situ forming drug delivery systems.....	23
2.1. Parenteral in-situ forming systems	23
2.1.1 In-situ forming implant (ISI)	24
2.1.2. In-situ forming microparticle (ISM)	26
2.2. Oral in-situ forming systems	28
2.2.1. Conventional oral micro-/nanoparticles.....	28
2.2.2. Oral in-situ forming gel	29
2.2.3. Oral in-situ forming microparticles	30
2.3. Heparin oral delivery systems	31
3. PLGA stability in in-situ forming systems	33
3.1. Application of PLGA	33
3.2. PLGA degradation and erosion	34
3.3. PLGA stability	36
4. Research objectives	36
4.1. Development of enteric microparticles	36
4.2. Development of in-situ forming microparticles (ISM).....	36
4.3. PLGA stability in in-situ forming systems	37

CHAPTER 2. MATERIALS AND METHODS 38

1. Materials	38
2. Methods.....	39
2.1. Enteric microparticles	39
2.1.1. Preparation of enteric microparticles.....	39

2.1.2. Viscosity of the aqueous polymer phase	40
2.1.3. Yield of enteric microparticles and encapsulation efficiency of carbamazepine.....	40
2.1.4. Particle size analysis.....	41
2.1.5. Phase separation of enteric polymers and precipitation of drugs.....	41
2.1.6. Determination of coacervation region	41
2.1.7. Scanning electron microscopy.....	41
2.1.8. Differential scanning calorimetry	42
2.1.9. Powder X-ray diffraction.....	42
2.1.10. Compatibility of drugs and enteric polymer	42
2.1.11. Determination of enteric polymer and drugs in polymer-rich/-poor regions	43
2.1.12. Solubility of carbamazepine and ibuprofen in water/ethanol mixtures	43
2.1.13. Partition of carbamazepine between polymer rich/poor regions in coacervate	43
2.1.14. Wettability	44
2.1.15. In vitro drug release studies.....	44
2.1.16. Stability of the microparticles.....	45
2.1.17. In vivo study	45
2.1.17.1. Animal experiments	45
2.1.17.2. Assay of drug and its metabolite in plasma	45
2.1.17.3. Pharmacokinetic analysis.....	46
2.2. In-situ forming microparticles (ISM)	46
2.2.1. Parenteral ISM.....	46
2.2.1.1. Reduction of heparin particle size.....	46
2.2.1.2. Preparation of parenteral ISM.....	46
2.2.1.3. In vitro drug release	47
2.2.1.4. Recovery of heparin.....	47
2.2.2. Oral in-situ forming microparticles	47
2.2.2.1. Preparation of oral ISM	47
2.2.2.2. Particle size distribution and surface zeta potential	48
2.2.2.3. In vitro drug release	48
2.3. PLGA stability in in-situ forming systems	49
2.3.1. Water uptake of organic solvents during storage at 75 % relative humidity	49
2.3.2. Preparation of PLGA solutions, suspensions and lyophilized sponges	49
2.3.3. Determination of the water content	50
2.3.4. Thermal analysis.....	50
2.3.5. Degradation studies of PLGA followed by gel permeation chromatography	50
2.3.6. RP-HPLC assay for stability studies of leuprolide acetate	51
CHAPTER 3. RESULTS AND DISCUSSION.....	52
1. Enteric microparticles	52
1.1. Formation of drug-free enteric microparticles.....	54

1.1.1. Aqueous phase.....	56
1.1.2. Concentration and pH of HPMC solution and type of enteric polymer.....	58
1.1.3. Effect of organic solvent.....	63
1.1.4. Phase diagrams for the characterization of the phase separation of enteric polymers.	63
1.2. Drug-loaded enteric microparticles	65
1.3. Characterization of drug-loaded enteric microparticles	73
1.3.1. Cyclosporin A-loaded enteric microparticles	74
1.3.2. Carbamazepine-loaded enteric microparticles	77
1.3.2.1. In vitro characterization.....	78
1.3.2.2. In vivo study	86
2. In-situ forming microparticles	90
2.1. Parenteral in-situ forming microparticles	90
2.2. Oral in-situ forming microparticles	96
2.2.1. Selection of excipients.....	96
2.2.2. Oral ISM using PLGA.....	97
2.2.3. Oral ISM using Eudragit® RS/RL	102
2.2.4. Oral ISM using blend of PLGA and Eudragit® RS/RL	103
3. Stability of PLGA in in-situ forming systems.....	106
3.1. Polymer organic solution.....	107
3.1.1. Selection of organic solvents for in-situ PLGA systems	108
3.1.2. Water uptake of organic PLGA solvents during storage at 75 % relative humidity ..	109
3.1.3. Effect of solvent type and storage temperature on PLGA stability	110
3.1.4. Effect of water content on PLGA stability in solution	113
3.1.5. Effect of leuprolide acetate on PLGA stability in solution.....	114
3.2. Stability of PLGA in oils and aqueous phases used for in-situ forming microparticles....	115
3.4. Stability of PLGA sponges prepared by lyophilization of PLGA solutions	118
3.5. Stability of leuprolide acetate.....	121
CHAPTER 4. SUMMARY	123
1. Enteric microparticles	123
2. In-situ forming microparticles	124
3. PLGA stability.....	125
ZUSAMMENFASSUNG.....	127
1. Magensaftresistente Mikropartikel	127
2. In-situ Mikropartikel (ISM).....	128

3. PLGA Stabilität.....	129
REFERENCES	131
LIST OF PUBLICATIONS FROM THIS WORK	150
CURRICULUM VITAE.....	151
LIST OF ABBREVIATIONS	152