

Abstract	iii
Acknowledgment	xiii
1 Introduction	1
1.1 Nanoparticles as carriers	2
1.2 Microfluidic operations for drug processing	5
1.3 Engineering of a microfluidic downstream process	9
1.4 Microfluidic precipitation of carriers	10
2 State of the art	17
2.1 Microfluidics for preparing drug carrier particles	18
2.1.1 Microfluidic devices for particle precipitation	18
2.1.2 Removal of acetone by microfluidic perva-	
poration	28
2.1.3 Separation of microparticles in microflui-	
dic systems	29
	vii

2.1.4	Microfluidic particle sizing	36
2.1.5	Methods used to counter precipitation related fouling	43
2.2	Matrices used to precipitate nanoparticulate carriers	46
2.2.1	Polymers	46
2.2.2	Polylactic acid and derivatives	47
2.2.3	Emulsions	47
2.2.4	Liposomes	48
2.2.5	Solid lipid nanoparticles	49
3	Microfluidic lipid nanoparticle precipitation	51
3.1	Design of the microfluidic precipitation system . .	52
3.1.1	Microfluidic mixer	52
3.1.2	Chip mounting and periphery	56
3.2	Experimental methods	59
3.3	Functional validation of the microfluidic precipitation system	62
3.4	Dispersion characteristics and optimization . . .	66
3.4.1	Characteristics of the precipitated nanoparticles	66
3.4.2	Characteristics of the precipitated micro-particles	69
3.4.3	Optimization of the stream parameters . .	70
3.4.4	Influence of sonication on the particle size	75
4	Removal of acetone in a microfluidic pervaporation chip	77
4.1	Design of the pervaporation chip	78

4.1.1	Mean driving concentration gradient . . .	80
4.1.2	Available membrane area	85
4.1.3	Mass transfer coefficient	87
4.1.4	Comparison of influence factors and final design	93
4.1.5	Validation of the system design consider- ing transport mechanisms in channel . .	98
4.2	Manufacturing of the PDMS pervaporation chip .	99
4.3	Pervaporation experiments	102
4.3.1	Proof-of-concept of the pervaporation chip	104
5	Microfluidic removal of microparticles	107
5.1	Suitability of the membrane for the application . .	108
5.1.1	Calculation of required filter efficiency . .	108
5.1.2	Pore size distribution of track- etched membranes	109
5.2	The design used for microfluidic filtration	112
5.2.1	Diffusion only membrane transport	113
5.2.2	Transport of nanoparticles through nanos- cale pores	114
5.2.3	Loss of nanoparticles on the membrane .	117
5.3	Realizing the filter chip	119
5.3.1	Development of the filter chips	119
5.3.2	Manufacturing the filter chip	119
5.4	Long time protective filtration	124
5.5	Quality of the microfluidic chips	126
6	Online analysis of the change in particle size	133
6.1	Construction of the detection system	135

6.1.1	Construction of the microfluidic chip . . .	135
6.1.2	Optical detection setup	138
6.2	Methods used to analyze the microfluidic detector	142
6.2.1	Dispersions used for system characteriza- tion	142
6.2.2	Software for particle analysis	142
6.2.3	External analysis of samples for comparison	143
6.3	Combination with the microfluidic precipitation setup	145
6.4	Validation and characterization of the detector . .	148
6.5	Application of detector for monitoring of a precipi- tation process	155
6.5.1	Measuring the particle concentration by particle counting	155
6.5.2	Analysis of signals generated by single particles	160
6.6	Summary	171
7	Combination of systems	173
8	Summary and Further Research Potential	179
8.1	Summary	180
8.2	Outlook	182
8.2.1	Precipitation system	182
8.2.2	Pervaporation system	182
8.2.3	Filtration system	183
8.2.4	Detection system	183
8.2.5	Combined systems	184

A Abbreviations	185
B Parameters for pervaporation approximation	187
C Parameters for microparticle filter approximation	191
References	193
Figures	245
Tables	251