

Contents

Abstract	i
Contents	v
Acknowledgements	1
1 Introduction	3
1.1 Background	3
1.2 Objective	6
2 Theoretical section	8
2.1 Solid state properties	8
2.1.1 Process-induced transformations	13
2.1.2 Solvent-mediated phase transformations	15
2.2 Solubility and dissolution	16
2.3 Miniaturized assays	19
2.4 Excipient effects on solubility and solid state	21
3 Miniaturized X-ray powder diffraction assay (MixRay) for quantitative kinetic analysis of solvent-mediated phase transformations in pharmaceuticals	27
Summary	27
3.1 Introduction	28
3.2 Materials and Methods	30
3.2.1 Materials	30
3.2.2 Thermal gravimetric analysis (TGA)	31
3.2.3 X-ray powder diffractometry (XRPD)	32
3.2.4 Microscopy	32
3.2.5 Preparation of polymorphic mixtures	32
3.2.6 XRPD data analysis	33
3.2.7 Kinetics of drug concentrations and polymorphic transformation	33
3.3 Results and Discussion	35
3.3.1 Characterization of raw materials	35
3.3.2 XRPD calibration	37
3.3.3 Piroxicam in excipient-solutions and biorelevant medium	38
3.4 Conclusions	43

4 Influence of excipients on solvent-mediated hydrate formation of piroxicam studied by dynamic imaging and fractal analysis	44
Summary	44
4.1 Introduction	45
4.2 Materials and Methods	47
4.2.1 Materials	47
4.2.2 Preparation of solutions	48
4.2.3 Preparation of piroxicam monohydrate	48
4.2.4 Differential scanning calorimetry (DSC)	48
4.2.5 X-ray powder diffraction (XRPD)	49
4.2.6 Raman spectroscopy	49
4.2.7 Solubility and residual solid analysis	50
4.2.8 Microscopy	50
4.2.9 Data analysis	51
4.3 Results	53
4.3.1 Initial characterization of piroxicam	53
4.3.2 Solubility and residual solid analysis of piroxicam in excipient-solutions	54
4.3.3 Dynamic microscopic imaging and fractal dimensions	57
4.4 Discussion	62
4.5 Conclusions	67
5 The quest for exceptional drug solubilization in diluted surfactant solutions and consideration of residual solid state	68
Summary	68
5.1 Introduction	69
5.2 Materials and Methods	70
5.2.1 Materials	70
5.2.2 Sample preparation	71
5.2.3 Solubility and residual solid analysis	71
5.2.4 Correlation and regression analysis	72
5.3 Results and discussion	73
5.3.1 Drug solubilization screening at low surfactant concentration and analysis of residual solid	73
5.3.2 Correlation and regression analysis of solubility enhancement	81
5.4 Conclusions	85
6 A systematic study of molecular interactions of anionic drugs with a dimethylaminoethyl methacrylate copolymer regarding solubility enhancement	87
Summary	87
6.1 Introduction	88
6.2 Materials and Methods	90

6.2.1 Materials	90
6.2.2 Sample preparation	91
6.2.3 Viscosity measurements	91
6.2.4 Solubility and residual solid analysis	91
6.2.5 ¹ H NMR spectroscopy	93
6.2.6 Statistical analysis and molecular modeling	93
6.3 Results	94
6.3.1 Viscosity	94
6.3.2 Solubility and residual solid analysis	95
6.3.3 ¹ H NMR spectroscopy	98
6.4 Discussion	100
6.5 Conclusion	105
7 Unexpected solubility enhancement of drug bases in presence of a dimethylaminoethyl methacrylate copolymer	106
Summary	106
7.1 Introduction	107
7.2 Materials and Methods	109
7.2.1 Materials	109
7.2.2 Sample preparation	110
7.2.3 Solubility and residual solid analysis	110
7.2.4 ¹ H NMR spectroscopy	111
7.3 Results	112
7.3.1 Solubility and residual solid analysis	112
7.3.2 ¹ H NMR spectroscopy	117
7.4 Discussion	118
7.5 Conclusions	120
8 Interactions of dimethylaminoethyl methacrylate copolymer with non-acidic drugs demonstrated high solubilization <i>in vitro</i> and pronounced sustained release <i>in vivo</i>	122
Summary	122
8.1 Introduction	123
8.2 Materials and Methods	125
8.2.1 Materials	125
8.2.2 Sample preparation	126
8.2.3 Solubility and residual solid analysis	127
8.2.4 Precipitation of polymer in presence and absence of APIs	128
8.2.5 Dynamic image analysis	129
8.2.6 <i>In vivo</i> pharmacokinetics after oral administration	130
8.3 Results	132

8.3.1 Solubility and residual solid analysis	132
8.3.2 Precipitation <i>in vitro</i> of EPO with and without API	132
8.3.3 Characterization of the <i>in vitro</i> formulations precipitates of FLP	134
8.3.4 <i>In vivo</i> pharmacokinetics after oral administration	135
8.4 Discussion	138
8.5 Conclusions	141
9 Final remarks and outlook	143
Bibliography	147
List of Abberivations	165
List of Symbols	168
List of Figures	170
List of Tables	172
Curriculum Vitae	174