



Adela Kalivoda (Autor)

Solubility enhancement of poorly water-soluble drugs by solid dispersion

a comparison of two manufacturing methods

Adela Kalivoda

Solubility enhancement of poorly water-soluble drugs by solid dispersion

a comparison of two manufacturing methods



Cuvillier Verlag Göttingen
Internationaler wissenschaftlicher Fachverlag

<https://cuvillier.de/de/shop/publications/6097>

Copyright:

Cuvillier Verlag, Inhaberin Annette Jentsch-Cuvillier, Nonnenstieg 8, 37075 Göttingen, Germany

Telefon: +49 (0)551 54724-0, E-Mail: info@cuvillier.de, Website: <https://cuvillier.de>



Contents

1	Introduction	1
1.1	Solubility enhancement of poorly soluble drugs	1
1.1.1	Methods of solubility enhancement	1
1.2	Solid dispersions	2
1.2.1	Definition and historical background	2
1.2.2	Methods of manufacture	4
1.2.3	Proposed mechanisms of drug dissolution from solid dispersion systems	4
1.3	Ultrasound-assisted compaction technique	5
1.3.1	Introduction	5
1.3.2	Effects of ultrasound-assisted compaction technique on the material . .	7
1.3.3	Application of ultrasound-assisted compaction technique in the phar- maceutical sector	7
1.4	Hot-melt extrusion	9
1.4.1	Introduction	9
1.4.2	Application of polymeric blends as carriers in hot-melt extrusion . . .	10
1.5	Manufacture of solid dispersions using the applied drugs	11
1.5.1	Solid dispersions with fenofibrate	11
1.5.2	Solid dispersions with felodipine	11
1.5.3	Solid dispersions with oxeglitazar	12
2	Outline and aims of this work	13
3	Results and discussion	15
3.1	Ultrasound-assisted compaction technique	15
3.1.1	Introduction and objectives	15
3.1.2	Developing a design of experiments	16
3.1.3	Ultrasound-assisted compaction of pure polymers	18
3.1.4	Reproducibility of results	21
3.1.5	Ultrasound-assisted compaction of fenofibrate and various polymeric carriers	23
3.1.6	Effect of the polymer on the dissolution profile	27
3.1.7	Evaluation of the equipment	28
3.2	Solubility enhancement of fenofibrate via hot-melt extrusion	30
3.2.1	Introduction and objectives	30
3.2.2	Hot-melt extrusion of fenofibrate with single polymeric carriers	31
3.2.3	Milling of the extrudates	40

3.2.4	Content uniformity of the extrudates	43
3.2.5	Influence of the die diameter on pellet size and release characteristics .	44
3.2.6	Hot-melt extrusion of fenofibrate with mixtures of polymeric carriers .	45
3.2.7	Effect of an additional polymer in the dissolution medium on the supersaturation stability of fenofibrate extrudate	54
3.2.8	Storage stability of fenofibrate extrudates	55
3.3	Solubility enhancement of oxeglitazar via hot-melt extrusion	62
3.3.1	Introduction and objectives	62
3.3.2	Hot-melt extrusion of oxeglitazar with single polymeric carriers	63
3.3.3	Hot-melt extrusion of oxeglitazar with mixtures of polymeric carriers .	67
3.3.4	Variation of the COP:HPMC ratio in oxeglitazar extrudates	72
3.3.5	24 h dissolution profiles of oxeglitazar extrudates	75
3.3.6	Addition of a disintegrant to oxeglitazar extrudates	77
3.3.7	Surface morphology of oxeglitazar extrudates	79
3.3.8	Storage stability of oxeglitazar extrudates	81
3.4	Solubility enhancement of felodipine via hot-melt extrusion	83
3.4.1	Introduction and objectives	83
3.4.2	Hot-melt extrusion of felodipine with single polymeric carriers	83
3.4.3	Hot-melt extrusion of felodipine with mixtures of polymeric carriers .	86
3.4.4	24 h dissolution profiles of felodipine extrudates	89
3.5	Evaluation of results	91
3.5.1	Influence of the drug content on the release characteristics	91
3.5.2	Comparison of hot-melt extruded formulations	92
3.5.3	Comparison of the applied manufacturing methods	96
3.5.4	Comparison to untreated physical mixtures	99
3.5.5	Comparison to marketed solid dosage forms	102
3.5.6	Comparison to other available methods for solid dispersion preparation	104
4	Summary	108
5	Zusammenfassung	110
6	Experimental part	112
6.1	Materials	112
6.1.1	Active pharmaceutical ingredients	112
6.1.2	Polymeric carriers	113
6.1.3	Other	115
6.2	Methods	115
6.2.1	Manufacturing methods	115
6.2.1.1	Preparation of physical mixtures	115
6.2.1.2	Design of experiments	117
6.2.1.3	Ultrasound-assisted compaction technique	119
6.2.1.4	Hot-melt extrusion	121
6.2.1.5	Milling	121



6.2.2	Analytical methods	123
6.2.2.1	Stability testing	123
6.2.2.2	Saturation concentration	123
6.2.2.3	Dissolution studies	123
6.2.2.4	High pressure liquid chromatography	125
6.2.2.5	Differential scanning calorimetry	127
6.2.2.6	X-ray diffraction	127
6.2.2.7	Particle size analysis	127
6.2.2.8	Karl-Fischer titration	127
6.2.2.9	Scanning electron microscopy	127
6.2.2.10	Content uniformity of extrudates	128
7	Appendix	129
A	Characterization of extrudates	129
A.1	Dissolution profiles of fenofibrate extrudates	129
A.2	Dissolution profiles of oxeglitazar extrudates	134
A.3	Pellet sizes of extrudates	135
A.4	AUC values for manufactured formulations	136
A.5	XRD patterns of felodipine extrudates	137
A.6	XRD patterns of fenofibrate extrudates	139
A.7	XRD patterns of oxeglitazar extrudates	142
A.8	DSC thermograms of single components	144
A.9	DSC thermograms of felodipine extrudates	146
A.10	DSC thermograms of fenofibrate extrudates	149
A.11	DSC thermograms of oxeglitazar extrudates	153
A.12	Surface morphology of oxeglitazar extrudates	156
B	Dissolution profiles of physical mixtures	157
B.1	Felodipine	157
B.2	Fenofibrate	158
B.3	Oxeglitazar	159
C	Limits of detection	160
C.1	X-ray diffraction	160
C.2	Differential scanning calorimetry	165
D	Characterization of applied drugs	168
D.1	Solubility	168
D.2	Surface morphology of oxeglitazar	168
	Bibliography	169
	List of Publications	178
	Danksagung	179