

Contents

ABSTRACT	I
-----------------------	----------

CONTENTS	V
-----------------------	----------

ACKNOWLEDGMENTS	VIII
------------------------------	-------------

INTRODUCTION	1
---------------------------	----------

1.1 BACKGROUND	1
1.2 OBJECTIVES	6

THEORETICAL SECTION	9
----------------------------------	----------

2.1 AMORPHOUS SOLID DISPERSIONS	9
2.1.1 GENERAL CONSIDERATION.....	9
2.1.2 THE AMORPHOUS FORM.....	12
2.1.3 MANUFACTURING TECHNIQUES.....	16
2.1.4 ANALYTICS.....	17
2.1.5 BIOPHARMACEUTICAL IMPLICATIONS.....	23
2.2 HOT MELT EXTRUSION	25
2.2.1 PROCESS.....	25
2.2.2 RESTRICTIONS AND BENEFITS.....	28
2.2.3 EXCIPIENT SELECTION.....	29
2.3 CO-FORMER IN AMORPHOUS SOLID DISPERSIONS	32
2.3.1 GENERAL CONSIDERATIONS.....	32
2.3.2 APPLICATION OF CO-FORMERS IN POLYMERIC AMORPHOUS DRUG FORMULATIONS.....	36

MODIFIED POLYMER MATRIX IN PHARMACEUTICAL HOT MELT EXTRUSION BY MOLECULAR INTERACTIONS WITH A CARBOXYLIC CO-FORMER	38
---	-----------

3.1 INTRODUCTION	39
3.2 MATERIALS AND METHODS	40
3.2.1 MATERIALS.....	40
3.2.2 METHODS.....	41
3.3 RESULTS AND DISCUSSION	44
3.3.1 MOLECULAR CONSIDERATIONS FOR POLYMER AND CO-FORMER SELECTION.....	44
3.3.2 MODIFIED POLYMERIC MATRIX.....	45
3.3.3 FORMULATION OF A MODEL DRUG IN THE MODIFIED POLYMER MATRIX.....	49
3.4 CONCLUSIONS	55

<u>POLYELECTROLYTES IN HOT MELT EXTRUSION: A COMBINED SOLVENT-BASED AND INTERACTING ADDITIVE TECHNIQUE FOR SOLID DISPERSIONS</u>	57
4.1 INTRODUCTION	58
4.2 MATERIALS AND METHODS	60
4.2.1 MATERIALS	60
4.2.2 METHODS	60
4.3 RESULTS AND DISCUSSION	62
4.3.1 AMINO ACIDS AS ADDITIVES	62
4.3.2 ADDITIVES OTHER THAN AMINO ACIDS	68
4.4 CONCLUSION	73
4.5 SUPPORTING INFORMATION	74
4.5.1 POWDER X-RAY DIFFRACTION PATTERNS	74
4.5.2 HOT STAGE MICROSCOPY AND HOT STATE FTIR	76
<u>OPPORTUNITIES FOR SUCCESSFUL STABILIZATION OF POOR GLASS-FORMING DRUGS: A STABILITY-BASED COMPARISON OF MESOPOROUS SILICA VERSUS HOT MELT EXTRUSION TECHNOLOGIES</u>	77
5.1 INTRODUCTION	78
5.2 MATERIALS AND METHODS	80
5.2.1 MATERIALS	80
5.2.2 METHODS	80
5.3 RESULTS	83
5.3.1 MACRO- AND MICROSCOPIC CHANGES	83
5.3.2 SOLID-STATE STABILITY OF THE AMORPHOUS FORM	85
5.3.3 STABILITY OF THE SUPERSATURATED STATE IN FASSIF	89
5.4 DISCUSSION	90
5.5 CONCLUSION	93
<u>IN VIVO PERFORMANCE OF INNOVATIVE POLYELECTROLYTE MATRICES FOR HOT MELT EXTRUSION OF AMORPHOUS DRUG SYSTEMS</u>	94
6.1 INTRODUCTION	95
6.2 MATERIALS AND METHODS	96
6.2.1 MATERIALS	96
6.2.2 METHODS	97
6.3 RESULTS	100
6.3.1 MOLECULAR DYNAMICS SIMULATION	100
6.3.2 SOLID-STATE ANALYTICS	101
6.3.3 BIORELEVANT <i>IN VITRO</i> DISSOLUTION STUDY	104
6.3.4 <i>IN VIVO</i> RAT STUDY	106
6.4 DISCUSSION	107
6.5 CONCLUSION	110
<u>FINAL REMARKS AND OUTLOOK</u>	111

<u>BIBLIOGRAPHY</u>	<u>114</u>
<u>LIST OF ABBREVIATIONS.....</u>	<u>135</u>
<u>LIST OF FIGURES</u>	<u>137</u>
<u>LIST OF TABLES</u>	<u>140</u>
<u>LIST OF SYMBOLS.....</u>	<u>141</u>