Table of Content

Dedication I
Acknowledgment II
Abstract III
Table of Content IV
List of Figure X
List of Tablet XII
Abbreviation XV

1 Introduction

1.1 Biopharmaceutical Aspects on Oral ER Formulations 2
1.2 Oral Controlled Release Systems 4
1.2.1 Diffusion Controlled System 5
1.2.2 Dissolution Controlled Systems 8
1.2.3 Diffusion and Dissolution Controlled Release System 9
1.2.4 Methods Using Ion Exchange Resins 9
1.2.5 Methods Using Osmotic Pressure 10
1.2.6 pH - Independent Formulations 10
1.2.7 Altered Density Formulations 11
1.3 Matrix Tablet 11
1.3.1 Hydrophilic Matrix Tablet 12
1.3.1.1 Hydroxypropyl Methylcellulose (HPMC) 13
1.3.2 Fat-wax Matrix Tablet 13
1.3.3 Plastic Matrix Tablet (hydrophobic matrices) 14
1.4 Quality by Design (QbD) 15
1.4.1 Quality Risk Management (QRM) 15
1.4.2 Quality Target Product Profile (QTPP) 16
1.4.3 Critical Quality Attributes (CQA) 17
1.4.4 Critical Process Parameter (CPP) 17
1.4.5 Design Space 18
1.4.6 Control Strategy 20
4.5.4 Initial Formulation Trial with Wet Granulation 55
4.5.5 Design batches of Zidovudine ER Matrix Tablets 57
4.5.6 In-vitro Drug release study 59
4.5.7 In-vivo Drug release study 59
4.5.8 Composition of Drug Product 63
4.5.9 Initial Manufacturing Process 64
4.5.10 Manufacturing Process optimization 64
4.6 Final Composition and Process 74
4.7 Scale up of Optimized Formulation 76
4.7.1 Study of compression Parameters Throughout Compression Run 78
4.7.2 Stability Study 79
4.7.3 Multimedia Dissolution of Scale up Batch 79
4.7.4 In-vitro Drug Release of Scale up Batch 80
5 Result and Discussion
5.1 Characterization of Drug and Excipients 80
5.1.1 Characterization of Drug 81
5.1.2 Assay 81
5.1.3 Microscopy 81
5.1.4 Infrared Spectrum 81
5.1.5 Powder X-Ray Diffractometry 81
5.1.6 Differential Scanning Calorimetry 81
5.1.7 Water Vapor Sorption Analysis 82
5.1.8 Stress Stability of Zidovudine 82
5.1.9 Characterization of Excipients 82
5.2 Characterization of Innovators (Reference) Drug Product 82
5.3 API Excipient Compatibility 82
5.4 Formulation Development 83
5.4.2 Design batches of Zidovudine ER Matrix Tablets 83
5.4.3 In-vivo Drug release study 83
5.4.4 Manufacturing Process optimization 85
5.5 Final Composition and Process 88
7.8.10 Critical Material Attributes 130
7.8.11 Critical Process Parameters 134
7.9 Final Composition and Process 145
7.10 Scale up of Optimized Formulation 147
7.11 Final Risk Assessment 152
8 Result and Discussion
8.1 Characterization of Drug and Excipients
8.1.1 Characterization of Drug 152
8.1.2 Assay 152
8.1.3 Microscopy 152
8.1.4 Infrared Spectrum 152
8.1.5 Powder X-Ray Diffractometry 152
8.1.6 Differential Scanning Calorimetry 152
8.1.7 Thermo-Gravimetric Analysis (TGA) 153
8.1.8 Water Vapor Sorption Analysis 153
8.1.9 Stress Stability of API 153
8.2 Characterization of Innovators (Reference) Drug Product 153
8.2 Characterization of Innovators (Reference) Drug Product 155
8.2.2 Decoding of Innovator Drug Product 155
8.2.3 Stability Innovator Drug Product 155
8.3. API Excipient Compatibility 156
8.4 Formulation Development 156
8.4.1 Initial Concept 156
8.4.2 Critical Material Attributes 157
8.4.3 Critical Process Parameters 158
8.4.4 Scale up of Optimized Formulation 161
8.4.5 Final Risk Assessment 161
9 Summary and Conclusion
9.1 Summary 162
9.2 Conclusion 164
10 Appendix 166