## CONTENTS

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Name of the topic</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>CHAPTER-1</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>INTRODUCTION</strong></td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.1.1 Characteristics of fast disintegrating systems</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.1.1.1 Simplicity of administration</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.1.1.2 Medicament taste</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.1.1.3 Hygroscopicity</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.1.1.4 Friability</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.1.1.5 Mouth feel</td>
<td>4</td>
</tr>
<tr>
<td>1.1.2</td>
<td>Advantages of fast dissolving drug delivery through sublingual route</td>
<td>4</td>
</tr>
<tr>
<td>1.1.3</td>
<td>Approaches for fast disintegrating tablets</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1.1.3.1 Lyophilization (freeze drying) technique</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1.1.3.2 Tablet molding technique</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1.1.3.3 Spray drying technique</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1.1.3.4 Cotton candy process</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1.1.3.5 Mass extrusion technique</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1.1.3.6 Sublimation technique</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1.1.3.7 Direct compression technique</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1.1.3.7.1 Superdisintegrants</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1.1.3.7.2 Sugar based excipients</td>
<td>10</td>
</tr>
<tr>
<td>1.1.4</td>
<td>Patented technologies</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>1.1.4.1 Zydis technology</td>
<td>11</td>
</tr>
</tbody>
</table>
1.1.4.2 Durasolv technology
1.1.4.3 Orasolv technology
1.1.4.4 Flash dose technology
1.1.4.5 Wow tab technology

1.1.5 Taste masking

1.1.5.1 Taste masking using sweetening agents, flavoring agents and amino acids
1.1.5.2 Taste masking using lipophilic vehicles
1.1.5.3 Taste masking using hydrophilic vehicles
  1.1.5.3.1 Carbohydrates
1.1.5.4 Taste masking using inclusion complexation
1.1.5.5 Taste masking using ion-exchange resins (IERs)
1.1.5.6 Taste masking using miscellaneous approaches
  1.1.5.6.1 Effervescent agent
  1.1.5.6.2 Salt preparation
  1.1.5.6.3 Solid dispersion technique
  1.1.5.6.4 Group modification and pro-drug approach
  1.1.5.6.5 Freeze drying method
  1.1.5.6.6 Wet spherical and continuous melt method

1.1.6 Mechanism of tablet disintegration and water absorption

1.1.6.1 Swelling
1.1.6.2 Wicking
1.1.6.3 Deformation
1.1.6.4 Disintegrating particle/particle repulsive forces.
1.2 Literature review 20
1.3 Need for investigation 32
  1.3.1 Advantages of sublingual route 35
1.4 Drug profile 36
  1.4.1 Zolmitriptan 36
  1.4.2 Rizatriptan benzoate 37
1.5 Polymer profile 39
  1.5.1 Sodium starch glycollate 39
  1.5.2 Croscarmellose sodium 40
  1.5.3 Crospovidone 42
  1.5.4 Microcrystalline cellulose (Avicel pH102) 44
  1.5.5 Mannitol (D-mannitol) 46
  1.5.6 Aspartame 46
  1.5.7 Magnesium stearate 48
1.6 Objectives 49
1.7 Research work plan 49

CHAPTER-2

FORMULATION AND EVALUATION OF ZOLMITRIPTAN

SUBLINGUAL TABLETS

2.1 Experimental methods 51
  2.1.1 Preparation of calibration curve of zolmitriptan in 0.1N hydrochloric acid 51
  2.1.2 Calibration curve of zolmitriptan in mixture of buffer
(pH4.0) and acetonitrile (90:10)

2.1.2.1 Standard and sample zolmitriptan drug solutions preparation

2.1.2.2 λmax determination of zolmitriptan

2.1.2.3 Preparation of mobile phase

2.1.2.4 Preparation of buffer

2.1.2.5 Calibration curve of zolmitriptan

2.2 Preparation of sublingual tablets using direct compression technique

2.3 Evaluation of zolmitriptan sublingual tablets

2.3.1 Evaluation of blends

2.3.1.2 Angle of repose (θ)

2.3.1.3 Bulk density (Dₐ)

2.3.1.4 Tapped density (Dₜ)

2.3.1.5 Carr’s index (Compressibility percentage)

2.3.1.6 Hausner’s Ratio

2.3.2 Determination of physical properties of tablets

2.3.2.1 Appearance

2.3.2.2 Tablet thickness and diameter

2.3.2.3 Weight variation

2.3.2.4 Hardness of tablets

2.3.2.5 Friability

2.3.2.6 Wetting time

2.3.2.7 Disintegration time in vitro

2.3.2.8 Disintegration time in vivo
2.3.2.9 Water absorption ratio 61
2.3.2.10 Dissolution in vitro 62
2.3.2.11 Uniformity of content 62
2.3.3 Characterisation of zolmitriptan sublingual tablets 63
  2.3.3.1 Scanning Electron Microscopy (SEM) studies 63
  2.3.3.2 Differential Scanning Calorimetry (DSC) studies 63
  2.3.3.3 Powder X-Ray Diffractometry (PXRD) studies 64
  2.3.3.4 Fourier Transform Infrared Spectroscopy (FT-IR) studies 64
2.4 Stability studies 64
2.5 Results and Discussion 65
  2.5.1 Calibration curves of zolmitriptan 65
    2.5.1.1 Calibration curve of zolmitriptan in 0.1NHC1 65
    2.5.1.2 Calibration curve of zolmitriptan in mixture of buffer (pH 4.0) and acetonitrile (90:10) 66
  2.5.2 Evaluation of zolmitriptan sublingual tablets 68
    2.5.2.1 Evaluation of blend 68
    2.5.2.2 Evaluation of prepared zolmitriptan sublingual tablets 69
    2.5.2.3 Comparison of dissolution profile for F1, F2 and F3 zolmitriptan formulations containing 2%, 4% and 6% of sodium starch glycollate. 75
    2.5.2.4 Comparison of dissolution of F4, F5 and F6 Zolmitriptan formulations containing 2%, 4% and 6% of croscarmellose Sodium. 76
2.5.2.5 Comparison of dissolution of F7, F8 and F9 Zolmitriptan formulations containing 2%, 4% and 6% of crospovidone

2.5.2.6 Scanning Electron Microscopy (SEM) studies

2.5.2.7 Differential scanning calorimetry (DSC) studies

2.5.2.8 Powder X-Ray diffraction (PXRD) studies

2.5.2.9 Fourier transforms Infrared Spectroscopy (FTIR) studies

2.5.3 Evaluation of stability studies

CHAPTER-3

COMPARATIVE PHARMACOKINETIC STUDIES OF ZOLMITRIPTAN SUBLINGUAL TABLETS

3.1 Introduction

3.1.1 Objective

3.1.2 Compliance of study

3.1.3 Animal Welfare

3.1.3.1 Animal Ethics Committee Approval (IAEC) of institution

3.1.4 Personnel safety precautions

3.2 Material and methods

3.2.1 Details of test item

3.2.2 Identification of test item

3.2.3 Justification of selection of vehicle
3.2.4 Test system 86
3.2.5 Husbandry 86
3.2.6 Selection of test system justification 87
3.2.7 Acclimatization 87
3.2.8 Randomization and grouping 87

3.3 Experimental design 88
3.3.1 Administration of test item 88
3.3.2 Study design 88
3.3.3 Collection of blood samples 90
3.3.4 Dose formulation preparation 90
3.3.5 Route of administration 90
3.3.6 Bio-analysis 90
3.3.7 Evaluation of pharmacokinetic parameters 90

3.3.8 Calibration curve standards and quality control samples preparations

3.3.8.1 Preparation of stock solution of zolmitriptan standard 91
3.3.8.2 Preparation of stock solution of internal standard 91
3.3.8.3 Preparation of zolmitriptan CC spiking solutions 92
3.3.8.4 K2EDTA rabbit plasma (CCs) spiking 93
3.3.8.5 Quality control samples stock dilutions preparation 94
3.3.8.6 Quality control spiking solution of zolmitriptan preparation 95

3.3.8.7 Extraction of zolmitriptan from plasma samples 96

3.3.9 Mass Spectroscopic conditions 97

3.3.10 Evaluation of pharmacokinetic parameters 98

3.4 Results 99

3.4.1 Bio-analysis 99

3.4.2 Pharmacokinetic analysis 111

3.4.2.1 Cmax 111

3.4.2.2 Tmax 111

3.4.2.3 AUC 111

3.4.2.4 T1/2 111

CHAPTER-4

FORMULATION AND EVALUATION OF RIZATRIPTAN SUBLINGUAL TABLETS

4.1 Experimental methods 118

4.1.1 Preparation of standard graph of rizatriptan in water at 282nm 118

4.1.2 Standard graph of rizatriptan benzoate in mixture of buffer (pH3.5) and acetonitrile (80:20) 118

4.1.2.1 Preparation of the standard and sample drug solutions 118

4.1.2.2 λmax determination 119
4.1.2.3 Preparation of mobile phase 119
4.1.2.4 Preparation of buffer 119
4.1.2.5 Preparation of standard graph 119

4.2 Preparation of sublingual tablets using direct compression technique 120

4.3 Evaluation of fast disintegrating sublingual rizatriptan benzoate tablets 123

4.3.1 Evaluation of blends 123
4.3.1.1 Angle of Repose (θ) 123
4.3.1.2 Bulk density (D_b) 123
4.3.1.3 Tapped density (D_t) 124
4.3.1.4 Carr’s Index (Compressibility percentage) 125
4.3.1.5 Hausner’s Ratio 125

4.3.2 Determination of physical properties of tablets 126
4.3.2.1 Appearance 126
4.3.2.2 Tablet thickness and diameter 126
4.3.2.3 Weight variation 126
4.3.2.4 Tablet hardness 127
4.3.2.5 Friability 128
4.3.2.6 Wetting time 128
4.3.2.7 Disintegration time \textit{in vitro} 128
4.3.2.8 Disintegration time \textit{in vivo} 128
4.3.2.9 Water absorption ratio 128
4.3.2.10 Dissolution \textit{in vitro} 129
4.3.2.11 Uniformity of content 130
4.3.3 Characterisation of rizatriptan sublingual tablets 130
   4.3.3.1 Scanning Electron Microscopy (SEM) studies 130
   4.3.3.2 Differential Scanning Calorimetry (DSC) studies 131
   4.3.3.3 Powder X-Ray Diffractometry (PXRD) studies 131
   4.3.3.4 Fourier Transform Infrared Spectroscopy (FT-IR) studies 132

4.4 Stability studies 132

4.5 Results and Discussion 133
   4.5.1 Calibration curves of rizatriptan 133
      4.5.1.1 Preparation of calibration curve of rizatriptan 133
      4.5.1.2 Calibration curve of rizatriptan benzoate in mixture of buffer (pH3.5) and acetonitrile (80:20) 134
   4.5.2 Evaluation of rizatriptan sublingual tablets 137
      4.5.2.1 Evaluation of blend 137
      4.5.2.2 Evaluation of prepared rizatriptan sublingual tablets 138
      4.5.2.3 Comparison of dissolution profile for F1, F2 and F3 rizatriptan formulations containing 2%, 4% and 6% of sodium starch glycollate. 144
      4.5.2.4 Comparison of dissolution of F4, F5 and F6 rizatriptan formulations containing 2%, 4% and 6% of croscarmellose sodium. 145
      4.5.2.5 Comparison of dissolution of F7, F8 and F9 rizatriptan formulations containing 2%, 4% and 6% of crospovidone. 146
4.5.2.6 Scanning Electron Microscopy (SEM) studies 147
4.5.2.7 Differential scanning calorimetry (DSC) studies 148
4.5.2.8 Powder X-Ray diffraction studies (PXRD) 149
4.5.2.9 Fourier Transform Infrared Spectroscopy (FTIR) studies 150
4.5.3 Evaluation of stability studies 151

CHAPTER-5

COMPARATIVE PHARMACOKINETIC STUDIES OF RIZATRIPTAN

SUBLINGUAL TABLETS

5.1 Introduction 152
5.1.1 Objective 152
5.1.2 Study compliance 152
5.1.3 Animal welfare 152
5.1.3.1 Approval of institutional animal Ethics Committee (IAEC) 152
5.1.4 Personnel safety precautions 152
5.2 Material and methods 153
5.2.1 Test item details 153
5.2.2 Identification of test item 154
5.2.3 Justification of selection of vehicle 154
5.2.4 Test system 154
5.2.5 Husbandry 154
5.2.6 Justification of selection of the test system 155
5.2.7 Acclimatization 155
5.2.8 Randomization and grouping 155

5.3 Experimental design 156
5.3.1 Administration of test substance 156
5.3.2 Study design 156
5.3.3 Collection of blood samples 158
5.3.4 Dose formulation preparation 158
5.3.5 Route of administration 158
5.3.6 Bio-analysis 158
5.3.7 Evaluation of pharmacokinetic parameters 158

5.3.8 Calibration Curve (CC) standards and Quality Control (QC) samples preparation 159
5.3.8.1 Preparation of stock solution of rizatriptan standard 159
5.3.8.2 Preparation of stock solution of internal standard 159
5.3.8.3 Preparation of rizatriptan CC spiking solutions 160
5.3.8.4 K2EDTA rabbit plasma (CC standards) spiking 161
5.3.8.5 QC samples stock dilutions preparation 162
5.3.8.6 QC spiking solution of rizatriptan preparation 163
5.3.8.7 Extraction of rizatriptan from plasma samples 165

5.3.9 Chromatographic and Mass Spectrometric conditions 166
5.3.10 Evaluation of pharmacokinetic parameter 167

5.4 Results 167
5.4.1 Bio-analysis 167
5.4.2 Pharmacokinetic analysis

5.4.2.1 Cmax

5.4.2.2 Tmax

5.4.2.3 AUC

5.4.2.4 T1/2