# TABLE OF CONTENTS

Abstract i

Abbreviations xi

List of Figures xiii

List of Tables xviii

Chapter - 1

INTRODUCTION 1

1.1 Novel drug delivery systems 1

1.2 Oral controlled release drug delivery systems 2

   1.2.1 Advantages 6

   1.2.2 Disadvantages 6

1.3 Need of controlled oral drug delivery systems 7

1.4 Classification of oral controlled release systems 7

   1.4.1 Dissolution controlled release systems 8

   1.4.2 Diffusion controlled release systems 9

   1.4.3 Dissolution and diffusion controlled systems 9

   1.4.4 Ion exchange resins 10

   1.4.5 pH independent formulations 10

   1.4.6 Osmotically controlled release systems 10

   1.4.7 Altered density controlled release systems 11

   1.4.8 Produgs 11

   1.4.9 Delayed release systems 11

1.5 Matrix type oral controlled drug delivery systems 12

   1.5.1 Advantages of matrix tablets 12

   1.5.2 Disadvantages of matrix tablets 12

   1.5.3 Classification of matrix tablets 13

   1.5.4 Depending on the type of polymer 13

      1.5.4.1 Lipophilic matrices (plastic matrices) 13

      1.5.4.2 Wax matrices 13

      1.5.4.3 Hydrophilic matrices 14

      1.5.4.4 Mineral matrices 14

      1.5.4.5 Biodegradable matrices 14
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5.5 Depending on porosity of matrix</td>
<td>15</td>
</tr>
<tr>
<td>1.6 Introduction to benign prostatic hyperplasia (BPH)</td>
<td>15</td>
</tr>
<tr>
<td>1.6.1 Advice for the management of lower urinary tract Symptoms</td>
<td>17</td>
</tr>
<tr>
<td>1.6.2 Pharmacological classification of Drugs</td>
<td>19</td>
</tr>
<tr>
<td>1.6.2.1 Alpha1 adrenergic blockers</td>
<td>19</td>
</tr>
<tr>
<td>1.6.2.2 5-alfa-reductase inhibitors</td>
<td>19</td>
</tr>
<tr>
<td>1.7 Introduction to cerebrovascular disease</td>
<td>20</td>
</tr>
<tr>
<td>1.7.1 Types of stroke</td>
<td>21</td>
</tr>
<tr>
<td>1.7.1.1 Ischemic stroke</td>
<td>21</td>
</tr>
<tr>
<td>1.7.1.2 Hemorrhagic stroke</td>
<td>22</td>
</tr>
<tr>
<td>1.7.2 Complications</td>
<td>22</td>
</tr>
<tr>
<td>1.7.3 Factors for stroke</td>
<td>23</td>
</tr>
<tr>
<td>1.8 Parkinson’s disease (pd)</td>
<td>23</td>
</tr>
<tr>
<td>1.9 Alzheimer’s disease (ad)</td>
<td>24</td>
</tr>
<tr>
<td>1.10 Need for Alfuzosin extended release tablets</td>
<td>26</td>
</tr>
<tr>
<td>1.11 Need for controlled release dosage form of Citicoline</td>
<td>26</td>
</tr>
</tbody>
</table>

**Chapter – 2**

**LITERATURE REVIEW**

2.1 Past work done on Afuzosin extended release formulation           | 28   |
2.2 Past work done on Afuzosin analytical methods                    | 29   |
2.3 Past work done on Afuzosin Bio analytical methods                | 32   |
2.4 Past work done on Citicoline formulation                         | 33   |
2.5 Past work done on Citicoline analytical methods                  | 33   |
2.6 Past work done on Citicoline tablets Bio analytical methods      | 36   |

**Chapter – 3**

**DRUG – EXCIPIENT PROFILE**

3.1 Drug profile                                                     | 38   |
3.1.1 Alfuzosin hydrochloride                                        | 38   |
3.1.2 Citicoline sodium                                              | 40   |
3.2 Polymer and excipient profiles                                   | 42   |
3.2.1 Guar gum                                                      | 42   |
3.2.2 Hydroxypropyl cellulose                                       | 43   |
3.2.3 Hypromellose 44
3.2.4 Povidone 45
3.2.5 Starch, pregelatinized 46
3.2.6 Ammonio methacrylate Copolymer, Type A (Eudragit RLPO) 47
3.2.7 Ammonio methacrylate Copolymer, Type B (Eudragit RSPO) 48
3.2.8 Microcrystalline cellulose 49
3.2.9 Colloidal silicon dioxide 50
3.2.10 Magnesium stearate 51

Chapter – 4
OBJECTIE AND PLAN OF WORK 52

Chapter – 5
DEVELOPMENT AND EVALUATION OF ALFUZOSIN EXTENDED RELEASE TABLETS 55

5.1 Materials and Equipments 55
5.2 Analytical methods 57
5.2.1 Method development 57

5.2.1.1 Standard calibration curve of Alfuzosin 58
5.2.1.1.1 Preparation of 0.01N HCl 58
5.2.1.1.2 Preparation of standard stock solution 58
5.2.1.1.3 Preparation of standard calibration curve 58

5.2.2 Assay by HPLC 60
5.2.2.1 Method development 60

5.2.2.1.1 Preparation of dilute Orthophosphoric acid 61
5.2.2.1.2 Preparation of buffer 61
5.2.2.1.3 Preparation of mobile phase 61
5.2.2.1.4 Chromatographic conditions 61
5.2.2.1.5 Standard preparation 62
5.2.2.2 Method validation 62

5.3 Pre-formulation 65
5.3.1 Solubility analysis

5.3.2 Compatibility studies
  5.3.2.1 Differential Scanning Calorimetry
  5.3.2.2 Fourier Transform Infra-Red (FT-IR) spectral analysis

5.4 Preparation of Matrix Tablets
  5.4.1 Preparation of matrix tablets containing Alfuzosin

5.5 Evaluation of Tablets
  5.5.1 Evaluation of physical parameters for granules
    5.5.1.1 Flowability
  5.5.2 Evaluation of physical parameters for tablets
    5.5.2.1 Uniformity of Weight
    5.5.2.2 Thickness
    5.5.2.3 Hardness
    5.5.2.4 Friability
  5.5.3 Drug content by HPLC
  5.5.4 Uniformity of drug content test
  5.5.5 In-vitro Dissolution Study (By UV)
    5.5.5.1 Test Solution
  5.5.6 Effect of hardness on dissolution
  5.5.7 Statistical approach to difference and similar Factor
  5.5.8 Kinetic modelling system for In-vitro release
    5.5.8.1 Zero Order
    5.5.8.2 First Order
    5.5.8.3 Erosion model
    5.5.8.4 Korsmeyer-Peppas model
    5.5.8.5 Higuchi’s model

5.6 Stability studies

5.7 Results
  5.7.1 Solubility analysis
  5.7.2 Compatibility studies
    5.7.2.1 Differential scanning calorimetry
5.7.2.2 Fourier Transform Infra-Red (FT-IR) spectral analysis 81
5.7.3 Evaluation of matrix tablets 87
  5.7.3.1 Evaluation of physical parameters for granules 87
    5.7.3.1.1 Flowability 87
  5.7.3.2 Evaluation of physical parameters for tablets 88
    5.7.3.2.1 Physical parameters of tablets 88
  5.7.3.3 Evaluation of chemical parameters for tablets 90
    5.7.3.3.1 Drug content 90
    5.7.3.3.2 In-vitro dissolution study 90
5.7.4 Kinetic modelling system for In-vitro release 95
5.7.5 Stability studies 101
5.8 Discussion 102

Chapter – 6 107
DEVELOPMENT AND EVALUATION OF CITICOLINE CONTROLLED RELEASE TABLETS 107
6.1 Materials and equipments 107
6.2 Analytical methods 109
  6.2.1 Method development 109
    6.2.1.1 Standard calibration curve of Citicoline 110
      6.2.1.1.1 Preparation of pH 6.8 Phosphate buffer 110
    6.2.1.2 Preparation of standard stock solution 110
    6.2.1.3 Preparation of standard calibration curve 110
  6.2.2 Assay by HPLC 112
    6.2.2.1 Method development 112
      6.2.2.1.1 Preparation of dilute acetic acid 112
      6.2.2.1.2 Preparation of Buffer 112
      6.2.2.1.3 Preparation of mobile phase 112
      6.2.2.1.4 Chromatographic conditions 113
      6.2.2.1.5 Standard preparation 113
    6.2.2.2 Method validation 113
6.3 Pre-formulation 115
  6.3.1 Solubility analysis 115
  6.3.2 Compatibility studies 116
    6.3.2.1 Differential Scanning Calorimetry 116
    6.3.2.2 Fourier Transform Infra-Red (FT-IR) spectral Analysis 116

6.4 Preparation of matrix tablets 117
  6.4.1 Preparation of matrix tablets containing Citicoline 117

6.5 Evaluation of tablets 120
  6.5.1 Evaluation of physical parameters for granules 120
    6.5.1.1 Flowability 120
  6.5.2 Evaluation of physical parameters for tablets 121
    6.5.2.1 Uniformity of Weight 121
    6.5.2.2 Thickness 122
    6.5.2.3 Hardness 122
    6.5.2.4 Friability 122
  6.5.3 Drug content by HPLC 123
  6.5.4 In-vitro Dissolution Study (by UV) 123
    6.5.4.1 Test solution 124
    6.5.4.2 Statistical approach to difference and similar Factor 124
  6.5.5 Kinetic modelling system for In-vitro release 125
    6.5.5.1 Zero Order 125
    6.5.5.2 First Order 125
    6.5.5.3 Erosion model 125
    6.5.5.4 Korsmeyer-Peppas model 126
    6.5.5.5 Higuchi’s model 126

6.6 Stability studies 127

6.7 Results 128
  6.7.1 Solubility analysis 128
  6.7.2 Compatibility studies 129
    6.7.2.1 Differential scanning calorimetry 129
    6.7.2.2 Fourier Transform Infra-Red (FT-IR) spectral
Analysis 132

6.7.3 Evaluation of matrix tablets 139
   6.7.3.1 Evaluation of physical parameters for granules 139
   6.7.3.2 Evaluation of physical parameters for tablets 140
   6.7.3.3 Evaluation of chemical parameters for tablets 142
      6.7.3.3.1 Drug content 142
      6.7.3.3.2 In-vitro dissolution study 143

6.7.4 Kinetic modelling system for In-vitro release 146

6.7.5 Stability studies 152

6.8 Discussion 152

Chapter – 7 159

IN-VIVO STUDIES 159

7.1 In-vivo evaluation of Alfuzosin ER tablets 159
   7.1.1 Study design 160
      7.1.1.1 Study objective 160
      7.1.1.2 Study plan 161
   7.1.2 Bio analytical method development 162
      7.1.2.1 Instrumentation and chromatographic conditions 162
      7.1.2.2 Standard calibration curve 162
      7.1.2.3 Precision and accuracy 164
   7.1.3 Sample collection 164
   7.1.4 Sample Preparation 164
   7.1.5 Results and discussion 176

7.2 In-vivo evaluation of Citicoline controlled release matrix tablets 178
   7.2.1 Study design 178
      7.2.1.1 Study objective 178
      7.2.1.2 Study plan 179
   7.2.2 Bio analytical method development 180
      7.2.2.1 Instrumentation and chromatographic conditions 180
      7.2.2.2 Standard calibration curve 180
7.2.3 Sample collection 181
7.2.4 Sample preparation 182
7.2.5 Results and discussion 194

Chapter – 8 195

SUMMARY, CONCLUSION AND RECOMMENDATIONS 195

8.1 Alfuzosin extended release tablets 195
8.2 Citicoline controlled release tablets 199
8.3 Conclusion 202
8.4 Recommendations for Alfuzosin extended release tablets 202
8.5 Recommendations for Citicoline controlled release tablets 203

BIBLIOGRAPHY 205