Solubility and Bioavailability Enhancement of Mosapride Citrate

A thesis submitted in the partial fulfillment of the requirements for the Master Degree in Pharmaceutical Sciences (Drug technology) by

Mahmoud Abdelmonem Badawy

Bachelor of Pharmaceutical Sciences, 2006, Ain Shams University

Research and development section head, Pharmed Healthcare for

pharmaceutical industries

Under the supervision of

Prof. Dr. Omaima Ahmed Amin Sammour

Professor and Head of Department of Pharmaceutics and Industrial
Phamarcy

Faculty of Pharmacy, Ain Shams University

Dr. Amany Osama Kamel

Associate Professor of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University

Ain Shams University
Faculty of Pharmacy
Department of Pharmaceutics and Industrial Pharmacy 2014

Acknowledgment

First of any acknowledgment goes to God (Allah) for his innumerable blessings and his guidance for me to the right path.

I would like to express my deepest appreciation and sincere gratitude to *Professor Dr. Omaima Ahmed Amin Sammour*, Professor and Head of Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, for her instructive supervision, kind help and generous attitude throughout the development of this work.

I offer my sincerest gratitude to *Dr. Amany Osama Kamel*, Associate Professor of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, who has supported me throughout my thesis with her patience and knowledge and provided me extensive personal and professional guidance and taught me a great deal about both scientific research and life in general. One simply could not wish for a better or friendlier supervisor.

I would especially like to thank *Dr. Hussein ElSawalhy*, R&D consultant at EGPI, who made me understand pharmaceutics and biopharmaceutics and taught me more than I could ever give his credit for him.

I

I also like to thank all my colleagues in Egyptian Group for Pharmaceutical industries (EGPI) and Pharmed Healthcare for pharmaceutical industries for their valuable help, support and encouragement.

Finally I would like to express my deepest thanks to my parents and my dear wife for their patience throughout the whole work carried out in this thesis.

List of Contents

| Item | Page |
|--|------|
| List of Abbreviations | VII |
| List of Tables | IX |
| List of Figures | XIII |
| Abstract | XX |
| General Introduction | 1 |
| Scope of work | 15 |
| Chapter I: Preparation of mosapride citrate tablets using liquisolid technique | |
| Introduction | 16 |
| Experimental | 24 |
| Methodology | 27 |
| Determination of λ_{max} of MC in distilled water, 0.1N HCl, acetate buffer pH 5 and simulated intestinal fluid | 27 |
| Construction of the calibration curve of MC in distilled water, 0.1N HCl, acetate buffer pH 5 and simulated intestinal fluid | 27 |
| Preformulation study | 27 |
| Solubility studies | 29 |
| Experimental design | 29 |
| Preparation of MC liquisolid systems | 31 |
| Evaluation of the flow properties of the prepared liquisolid systems | 33 |
| Compression of the prepared liquisolid systems into tablets | 34 |

| Item | Page | |
|--|------|--|
| Evaluation of the prepared MC liquisolid tablets | 35 | |
| Stability study | 39 | |
| Data analysis | 40 | |
| Results and Discussion | 41 | |
| Determination of λ_{max} of MC | 41 | |
| Calibration curve of MC in distilled water, 0.1N HCl, acetate buffer pH 5 and simulated intestinal fluid | 43 | |
| Preformulation study | 48 | |
| Physical appearance | 48 | |
| Differential Scanning Calorimetry (DSC) | 48 | |
| X-ray diffraction | 51 | |
| Infra red (IR) absorption spectroscopy | | |
| Solubility studies | 58 | |
| Evaluation of the flow properties of the prepared liquisolid systems | 59 | |
| Evaluation of the prepared MC liquisolid tablets | 60 | |
| Physical appearance | 60 | |
| Uniformity of content and weight | 61 | |
| Tablet friability | 61 | |
| Tablet crushing strength (hardness) | | |
| Tablet disintegration time | | |
| Dissolution studies | 64 | |
| Differential scanning calorimetry (DSC) | 95 | |
| X-ray diffraction (XRD) | 96 | |

| Item | Page |
|---|------|
| Stability study | 99 |
| Conclusions | 102 |
| Chapter II: Preparation of mosapride citrate tablets using complexation technique | |
| Introduction | 104 |
| Experimental | 119 |
| Methodology | 121 |
| Construction of standard calibration curve of MC in phosphate buffer of Ph 6.8 | 121 |
| Phase solubility studies | 121 |
| Experimental design | 122 |
| Preparation of MC-CD inclusion systems | 124 |
| Physicochemical characterization of MC-CD inclusion systems | 125 |
| In-vitro dissolution studies | 125 |
| Preparation of MC-CD inclusion complexes tablets | 126 |
| Evaluation of the prepared MC-CD inclusion complexes tablets | 127 |
| Stability study | 127 |
| Data analysis | 128 |
| Results and Discussion | 129 |
| Calibration curve of MC in phosphate buffer pH 6.8 | 129 |
| Phase solubility studies | 130 |
| Physicochemical characterization of MC-CD inclusion systems | 136 |

| Item | Page |
|---|------|
| Differntial scanning calorimetry studies | 136 |
| X-ray diffraction studies | 141 |
| Forier transform Infra- red analysis | 146 |
| In-vitro dissolution studies | 152 |
| Evaluation of the prepared MC-CD (CX-15) inclusion complexes tablets | 180 |
| Stability study | 185 |
| Conclusions | 188 |
| Chapter III: Bioavailability and pharmacokinetic study of mosapride citrate tablets in healthy human volunteers | |
| Introduction | 190 |
| Experimental | 192 |
| Methodology | |
| LC-MS/MS assay of MC in human plasma | |
| Pharmacokinetic study in healthy volunteers | 196 |
| Results and Discussion | 200 |
| Conclusions | 215 |
| Summery | 216 |
| References | 220 |
| Ethical committee | |
| Publications | |
| الملخص العربي | |

List of Abbreviations

| APT | Active pharmaceutical ingredient |
|---------|---|
| ASD | Amorphous solid dispersion |
| ANOVA | Analysis of variance |
| AUC | Area under the curve |
| BCS | Biopharmaceutical classification system |
| BP | British pharmacopeia |
| CD | Cyclodextrin |
| CE | Complexation Efficiency |
| CI% | Carr's index |
| DSC | Differential scanning calorimetry |
| DR | Dissolution rate |
| FaSSIF | Fasted State Simulated Intestinal Fluid |
| FDA | Food and drug administration |
| FeSSIF | Fed state simulated intestinal fluid |
| FTIR | Fourier transform Infra red |
| GERD | Gastro-oesophageal reflux disease |
| GI | Gastro intestinal |
| GIT | Gastro intestinal tract |
| НР-ß-СD | Hydroxypropyl betacyclodextrin |
| HR | Hausner's ratio |
| IR | Immediate release |

| IR | Infrared |
|---------|---|
| IS | internal standard |
| D.C | Direct compression |
| Lf | Load factor |
| L-HPC21 | Low substituted hydroxyl propyl cellulose |
| M- β-CD | Methyl β-cyclodextrin |
| MC | Mosapride citrate |
| MRT | Mean residence time |
| MTBE | Methyl-t-butyl-ether |
| PEG | Poly ethylene glycol |
| PVP | Polyvinyl pyrrolidone |
| SD | Standard deviation |
| SGF | Simulated gastric fluid |
| USP | United states pharmacopeia |
| UV | Ultra violet |
| XRD | X-ray diffractometery |

List of Tables

| Table no. | Table Name | Page |
|-----------|---|------|
| 1 | Factors and levels used in the factorial design | 30 |
| 2 | Formulae of different liquisolid systems used in the factorial design | 31 |
| 3 | Formulation characteristics of the prepared liquisolid systems | 32 |
| 4 | Relation between concentration of MC and absorbance at 271 nm in distilled water | 44 |
| 5 | Relation between concentration of MC and absorbance at 291 nm in 0.1 N HCl pH 1.2 applying second order derivative | 45 |
| 6 | Relation between concentration of MC and absorbance at 291 nm in acetate buffer pH 5 applying seond order derivative | 46 |
| 7 | Relation between concentration of MC and absorbance at 291 nm in simulated intestinal fluid pH 6.5 applying second order derivative | 47 |
| 8 | Equilibrium solubility of MC in different solvents at 25°C | 58 |
| 9 | Flowability results of different liquisolid systems | 60 |
| 10 | Results of quality control tests of the liquisolid tablets | 63 |
| 11 | Dissolution results of liquisolid tablets prepared using Avicel PH102, pure drug and marketed tablets in 500 ml 0.1N HCl | 66 |

| Table no. | Table Name | Page |
|-----------|---|------|
| 12 | Dissolution results of liquisolid tablets prepared using Mannitol , pure drug and marketed tablets in 500 ml 0.1 N HCl | 68 |
| 13 | Dissolution results of liquisolid tablets prepared using Lactose D.C, pure drug and marketed tablets in 500 ml 0.1 N HCl | 70 |
| 14 | Dissolution results of LS-2, LS-4 and marketed tablets in 500 ml and 300 ml 0.1N HCl | 80 |
| 15 | Dissolution results of LS-2, LS-4, and market tablets in 500 ml 0.1 N HCl and acetate buffer | 84 |
| 16 | Transfer model results of LS-4, pure drug & marketed tablets using fasted state biorelevant media | 91 |
| 17 | Transfer model results of LS-4, pure drug & marketed tablets using fed state biorelevant media | 93 |
| 18 | Dissolution results of fresh and aged MC tablets LS-4 in 0.1 N HCl | 100 |
| 19 | Factors and levels used in the factorial design | 123 |
| 20 | Formulae of different inclusion systems used in the factorial design | 123 |
| 21 | Quantitative formulation of selected inclusion complex in a tablet dosage form | 127 |
| 22 | Relation between concentration of MC and absorbance at 291 nm in phosphate buffer pH 6.8 applying second order derivative | 129 |
| 23 | Data of phase solubility diagrams of MC with different CDs | 134 |

| Table no. | Table Name | Page |
|-----------|---|------|
| 24 | Percentage of MC dissolved from MC-β-CD systems in 500 ml 0.1N HCl | 156 |
| 25 | Percentage of MC dissolved from MC-HP-β-CD systems in 500 ml 0.1N HCl | 158 |
| 26 | Percentage of MC dissolved from MC-M-β-CD system in 500 ml 0.1N HCl | 160 |
| 27 | Percentage of MC dissolved from MC-β-CD systems in phosphate buffer pH6.8 | 166 |
| 28 | Percentage of MC dissolved from MC-HP-β-CD systems in phosphate buffer of pH 6.8 | 168 |
| 29 | Percentage of MC dissolved from MC-M-β-CD systems in phosphate buffer of pH 6.8 | 170 |
| 30 | Percentage of MC dissolved from the optimum MC complexes in 300 ml 0.1N HCl | 175 |
| 31 | Transfer model results of optimum formulae, pure drug & marketed tablets using fasted state biorelevant media | 178 |
| 32 | Evaluation results of tablets prepared from CX-15 formulae | 182 |
| 33 | Dissolution of compressed tablet of mosapride- cyclodextrin inclusion complex | 183 |
| 34 | Dissolution results of aged CX-15 tablets | 186 |
| 35 | Relation between MC concentration and the peak area ratio of MC/IS in spiked human plasma | 202 |
| 36 | Recovery data of MC from spiked human plasma | 204 |

| Table no. | Table Name | Page |
|-----------|--|------|
| 37 | Within-day precision of the LC-MS/MS method for MC determination in human plasma | 205 |
| 38 | Inter-day precision and linearity of the LC-MS/MS method for ACV determination in human plasma | 206 |
| 39 | Mean plasma concentrations time data of MC from different formulae after oral administration | 208 |
| 40 | Pharmacokinetic parameters of MC after oral administration of different formulae | 211 |

List of Figures

| Figure no. | Figure Name | Page |
|------------|---|------|
| 1 | Biopharmaceutics classification system (BCS) and viable formulation options based on the BCS | 4 |
| 2 | Schematic presentation for preparation of liquisolid systems | 22 |
| 3 | Experimental set-up of Transfer model | 38 |
| 4 | Ultraviolet-spectrum of MC in distilled water | 41 |
| 5 | Ultraviolet-spectrum of MC a) before and b) after applying second derivative in 0.1 N HCl pH 1.2 | 42 |
| 6 | UltraViolet-spectrum of MC a) before and b) after applying second derivative in acetate buffer pH 5 | 42 |
| 7 | UltraViolet-spectrum of MC a) before and b) after applying second derivative in simulated intestinal fluid pH 6.8 | 43 |
| 8 | Calibration curve of MC in distilled water at 271 nm | 45 |
| 9 | Calibration curve of MC in 0.1 N HCl pH 1.2 at 291 nm applying second order derivative | 46 |
| 10 | Calibration curve of MC in acetate buffer pH 5 at 291 nm applying second order derivative | 47 |
| 11 | Calibration curve of MC in simulated intestinal fluid pH 6.8 at 291 nm applying second order derivative | 48 |

| Figure no. | Figure Name | Page |
|------------|---|------|
| 12 | DSC thermograms of (A) MC (B) Avicel PH 102 (C) MC : Avicel PH 102 1:1 physical mixture (D) Mannitol (E) MC : Mannitol 1:1 physical mixture (F) Lactose D.C (G) MC : Lactose D.C 1:1 physical mixture (H) Aerosil 200 (I) MC : Aerosil 200 1:1 physical mixture | 50 |
| 13 | X-Ray diffraction pattern of (A) MC (B) Avicel PH102 (C) MC: Avicel 1:1 Physical mixture | 52 |
| 14 | X-Ray diffraction pattern of (A) MC (B) Mannitol (B) (C) MC: Mannitol 1:1 Physical mixture | 53 |
| 15 | X-Ray diffraction pattern of (A) MC (B) Lactose D.C (C) MC: Lactose D.C 1:1 Physical mixture | 54 |
| 16 | X-Ray diffraction pattern of (A) MC (B) Aerosil 200 (C) MC: Aerosil 200 1:1 Physical mixture | 55 |
| 17 | Infrared spectra of: (A)MC (B) Avicel PH 102 (C) MC: Avicel PH 102 1:1 physical mixture (D) Mannitol (E) MC: Mannitol 1:1 physical mixture (F) Lactose D.C (G) MC: Lactose D.C 1:1 physical mixture (H) Aerosil 200 (I) MC: Aerosil 200 1:1 physical mixture | 57 |
| 18 | Dissolution profiles of liquisolid tablets prepared using Avicel PH102, pure drug and marketed tablets in 500 ml 0.1 N HCl | 67 |
| 19 | Dissolution profiles of liquisolid tablets prepared using Mannitol, pure drug and marketed tablets in 500 ml 0.1 N HCl | 69 |