

Formulation and Evaluation of Certain Gastroretentive Systems

Thesis

Presented By

**Mohamed Hassan Hany Kamel Hassan
AbouGhaly**

For The Partial Fulfillment of the Master Degree in
Pharmaceutical Sciences
“PHARMACEUTICS”

Under The Supervision of

Prof. Dr. Saadya A. Tayel

*Professor of Pharmaceutics and Industrial Pharmacy
Faculty of Pharmacy
Cairo University*

Prof. Dr. Mohamed A. El-Nabarawy

*Professor of Pharmaceutics and Industrial Pharmacy
Faculty of Pharmacy
Cairo University*

Prof. Dr. Hanan H. El-Laithy

*Professor of Pharmaceutics and Industrial Pharmacy
Faculty of Pharmacy
Cairo University*

**DEPARTMENT OF PHARMACEUTICS
FACULTY OF PHARMACY
CAIRO UNIVERSITY
(2009)**

بسم الله الرحمن الرحيم

"الحمد لله الذى
هدانا لهذا و ما كنا
لنهتدى لولا أن هدانا
الله"

"صدق الله العظيم"

سورة الأعراف ٤٣

ACKNOWLEDGMENT

Praise is to ALLAH, the most merciful and most gracious, by the help of whom this work has been done.

First of all, I would like to express my heartily appreciation and sincere gratitude to my supervisor Prof. Dr. Saadya A. Tayel, Professor of pharmaceuticals, faculty of Pharmacy, Cairo University, for her patient guidance, encouragement, support and excellent advice throughout this study.

I am also profoundly grateful to Prof. Dr. Mohamed A. ElNabarawy, Professor of pharmaceuticals, faculty of Pharmacy, Cairo University, for his encouragement, supervision and sincere support, his successful instructions, useful suggestions, indispensable help are very much appreciated.

I would like also to express my deepest sense of gratitude to Prof. Dr. Hanan H. ELlaithy, Professor of pharmaceuticals, faculty of Pharmacy, Cairo University, who offered me kindly great help by her fruitful supervision, research guidance and valuable advice.

*I am also grateful to the staff members of the Centre of Applied Research and Advanced Studies (CARAS), faculty of Pharmacy, Cairo University, for their great help in the *in vivo* work in this thesis.*

I am sincerely grateful to my parents, sister and the rest of my family for their great help, continuous support and encouragement, and endless love through the duration of this study.

I would like to extend my deep thanks to all my professors and colleagues in the department of pharmaceuticals for their continuous support and encouragement.

To all of you, thank you.

Contents

List of Tables and Figures

List of Tables

List of Figures

<i>Abstract</i>	I
GENERAL INTRODUCTION	1
Gastrointestinal tract physiology and considerations	1
Factors affecting gastric retention time	4
Effect of density of the dosage form	4
Effect of food	6
Effect of biological factors.....	8
Effect of size and shape of the dosage form	9
Effect of posture	9
Gastroretentive Dosage Forms	11
Classification.....	11
High Density Systems.....	11
Low Density Systems	12
Non effervescent Floating Drug Delivery Systems	12
1. Hydrodynamically balanced systems (HBS)	12
2. Microballoons	13
3. Low density foam powder	13
Effervescent Floating Drug Delivery Systems.....	14
1. Raft forming systems	14
2. Effervescent Floatin Drug Delivery Systems	15
Expandable Systems	17
Swellable systems.....	18
Unfoldable systems	19
Superporous Hydrogels	20

Mucoadhesive or bioadhesive systems	21
Magnetic systems.....	23
Advantages of Gastroretentive Dosage Forms.....	24
Sustained drug delivery	24
Site-Specific drug delivery	25
Pharmacokinetic Advantages.....	26
Pharmacodynamic Advantages.....	27
Famotidine	28
Chemical structure and physical properties	28
Class, Dosing and Mechanism of Action.....	29
Bioavailability, Metabolism and Elimination of Famotidine	30
<i>Scope of Work</i>	31
<i>Chapter 1</i>	33
<i>Formulation and In-vitro Evaluation of Famotidine Floating Matrix Tablets</i>	33
INTRODUCTION.....	33
EXPERIMENTAL	36
Materials	36
Equipment.....	36
Methodology.....	37
I- U.V. Scanning of Famotidine in HCl	37
II- Determination of Procedural Constant of Famotidine in HCl using U.V. spectrophotometer	37
III- Formulation and <i>In-vitro</i> Evaluation of Famotidine Floating Tablets	38

1- Compatibility of Famotidine with Different Pharmaceutical Excipients.....	38
(a) Differential Scanning Calorimetry (DSC).....	38
(b) Fourier-transform Infrared Spectroscopy (FT-IR)	39
2- Formulation of Famotidine Floating Single Layer tablets	39
3- Preparation of Famotidine Floating tablets	43
4- <i>In-vitro</i> Evaluation of the Prepared Floating tablets	43
a. Floating Lag time and Floating Duration.....	43
b. Weight Variation	43
c. Thickness	44
d. Diameter	44
e. Content Uniformity	44
f. Friability	44
g. Hardness	44
h. Swelling (Water Uptake) and Erosion Behavior.....	44
i. <i>In-vitro</i> release studies.....	45
5- Optimization of Famotidine Floating Tablets	45
a. Use of Polymer Combinations	45
b. Use of Compritol.....	46
c. Preparation of Double and Triple Layer Tablets.....	47
6- Kinetic Study of the Release Data of Famotidine Floating Tablets.....	51
RESULTS AND DISCUSSION	52
I- U.V. Scanning of Famotidine in HCl	52
II- Determination of Procedural Constant of Famotidine in HCl using U.V. spectrophotometer.....	52
III- Formulation and In-vitro Evaluation of Famotidine Floating Tablets	54
1- Compatibility of Famotidine with Different Pharmaceutical Excipients	54

(a) Differential Scanning Calorimetry (DSC)	54
(b) Fourier-transform Infrared Spectroscopy (FT-IR).....	64
2- <i>In-vitro</i> Evaluation of the Prepared Floating tablets	77
a. Floating Lag time (FLT) and Floating Duration	77
b. Weight variation.....	79
c. Thickness	79
d. Diameter.....	79
e. Content uniformity.....	79
f. Friability.....	80
g. Hardness.....	80
h. Swelling (Water Uptake) and Erosion Behavior	92
i. <i>In-vitro</i> release studies	100
3- Kinetic study of the Release Data of Famotidine Floating Tablets.	143
CONCLUSION	156
 <i>Chapter 2</i>	160
<i>Formulation and In-vitro Evaluation of Oil-Loaded Famotidine Multiparticulate Systems</i>	160
INTRODUCTION.....	163
EXPERIMENTAL	167
Materials	167
Equipment.....	168
Methodology.....	168
Formulation and <i>In-vitro</i> Evaluation of Famotidine Floating Emulsion Gel Beads	168
1. Preparation of Famotidine Floating Emulsion Gel Beads	168
2. <i>In-vitro</i> Evaluation of the Prepared Famotidine Floating Emulsion Gel Beads.....	174

a. Oil leakage and shape.....	174
b. Buoyancy.....	174
c. Drug content.....	174
d. <i>In-vitro</i> release studies.....	175
3. Optimization of the Prepared Emulsion Gel Beads.....	175
a. Addition of Hydroxypropylmethyl Cellulose	175
b. Wax incorporated emulsion gel beads	176
c. Coating of the emulsion gel beads	177
1. Spray coating.....	177
2. Dip coating.....	178
3. Coacervation by temperature change.....	178
4. Oil-in-oil solvent evaporation method.....	179
4. Preparation of Oil-loaded Chitosan beads and Chitosan Alginate Multilayer beads.....	180
RESULTS AND DISCUSSION	183
1. In-vitro Evaluation of the Prepared Famotidine Emulsion Gel Beads.....	183
a. Oil leakage and Shape	183
b. Buoyancy	184
c. Drug Content	185
d. <i>In-vitro</i> Release studies	189
2. Evaluation of the Optimized Emulsion Gel Beads.....	193
a. Addition of Hydroxypropylmethyl Cellulose	193
b. Wax incorporated Emulsion Gel Beads	195
c. Coating of the Emulsion Gel Beads	197
1. Spray Coating.....	197
2. Dip Coating.....	199
3. Coacervation by temperature change	201
4. Oil-in-oil solvent evaporation method.....	201

3. Evaluation of the Prepared Oil-loaded Chitosan beads and Chitosan Alginate Multilayer beads	203
CONCLUSION	205
<i>Chapter 3</i>	207
<i>In-vivo Performance of Famotidine Gastroretentive System</i>	207
INTRODUCTION	207
EXPERIMENTAL	210
Famotidine Floating Tablet chosen for the <i>in-vivo</i> Performance Study..	210
Study Design	210
Selection of Subjects	211
1. Inclusion criteria	211
2. Exclusion criteria	212
3. Number of Subjects	212
4. Procedure	212
Handling of Samples	212
Assay Method Description	213
1. Description of the Compound	213
2. Description of the Analytical Method	214
Assay Method Validation	219
1. Selectivity	219
2. Linearity and Linear Working Range	219
3. Intra-Day Accuracy and Precision	220
4. Inter-Day Reproducibility	220
5. Freeze and Thaw Stability in Human Plasma	220
Analysis of the pharmacokinetic parameters	220
Statistical analysis of the data	222

RESULTS AND DISCUSSION	223
Clinical Observations.....	223
Assay Method Validation	223
1. Selectivity	223
2. Linearity and Linear Working Range	226
3. Intra-Day Accuracy and Precision	227
4. Inter-Day Reproducibility	229
5. Freeze and Thaw Stability in Human Plasma	229
Plasma Concentration -Time Data.....	230
Assessment of Pharmacokinetic Parameters	239
CONCLUSION	248
<i>References</i>	249
<i>Arabic Summary</i>	264

List of Tables and Figures

List of Tables

Table 1: Composition of tablets containing different grades of HPMC..	40
Table 2: Composition of tablets containing Polyox, Sodium alginate and Carbopol.....	41
Table 3: Composition of tablets containing different gums.	42
Table 4: Composition of tablets containing combination of polymers....	46
Table 5: Composition of tablets containing Compritol.	47
Table 6: Composition of 100mg tablets, double and triple layer tablets.	49
Table 7: Relationship between concentration of Famotidine in 0.1 N HCl and absorbance at $\lambda_{\max}$ 265 nm.....	53
Table 8: Floating duration, Floating lag time (FLT), weight variation, thickness, diameter, content uniformity, friability and hardness of HPMC K100M, HPMC K15M, HPMC K4M, and Polyox based Famotidine floating tablet formulae.....	81
Table 9: Floating duration, Floating lag time (FLT), weight variation, thickness, diameter, content uniformity, friability and hardness of sodium alginate, guar gum, xanthan gum and Carbopol based Famotidine floating tablet formulae.	83
Table 10: Floating duration, Floating lag time (FLT), weight variation, content uniformity and hardness of Compritol containing and polymer combination based Famotidine floating tablet formulae.	85
Table 11: Floating duration, Floating lag time (FLT), weight variation, content uniformity, friability and hardness of 100 mg, double and triple layer Famotidine floating tablet formulae. (#Not Determined).....	86
Table 12: Percent swelling or weight gain by Famotidine floating tablet formulations in 0.1N HCl (pH 1.2).....	94
Table 13: Percent erosion or weight loss by Famotidine floating tablet formulations in 0.1N HCl (pH 1.2).....	95

Table 14: <i>In-vitro</i> Dissolution of Famotidine from market product (Servipep®) in 0.1 N HCl (pH 1.2) at 37°C.....	101
Table 15: <i>In-vitro</i> Release of Famotidine from Hydroxypropylmethyl cellulose K100M based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	105
Table 16: <i>In-vitro</i> Release of Famotidine from Hydroxypropylmethyl cellulose K15M based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.....	107
Table 17: <i>In-vitro</i> Release of Famotidine from Hydroxypropylmethyl cellulose K4M based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.....	109
Table 18: ANOVA test for Q6hr of HPMC based tablets.	110
Table 19: <i>In-vitro</i> Release of Famotidine from Carbopol based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.....	111
Table 20: ANOVA test for Q6hr of Carbopol based tablets.....	112
Table 21: <i>In-vitro</i> Release of Famotidine from Polyox based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	113
Table 22: ANOVA test for Q6hr of Polyox based tablets.	114
Table 23: <i>In-vitro</i> Release of Famotidine from guar gum based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.....	115
Table 24: ANOVA test for Q6hr of guar gum based tablets.	116
Table 25: <i>In-vitro</i> Release of Famotidine from Xanthan gum based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.....	117
Table 26: ANOVA test for Q6hr of xanthan gum based tablets.....	118
Table 27: <i>In-vitro</i> Release of Famotidine from sodium alginate based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.....	119
Table 28: ANOVA test for Q6hr of sodium alginate based tablets.....	120
Table 29: ANOVA test for Q6hr of all single layer tablets.	120

Table 30: <i>In-vitro</i> Release of Famotidine from polymer combination based Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	122
Table 31: ANOVA test for Q6hr of binary mixture tablets.	123
Table 32: <i>In-vitro</i> Release of Famotidine from Famotidine floating tablet formulae containing 2% Compritol in 0.1 N HCl (pH 1.2) at 37°C.	124
Table 33: ANOVA test for Q6hr of tablets containing 2% Compritol.	125
Table 34: <i>In-vitro</i> Release of Famotidine from Hydroxypropylmethyl cellulose K100M based Famotidine floating tablet formulae containing 5 and 10% Compritol in 0.1 N HCl (pH 1.2) at 37°C.	126
Table 35: <i>In-vitro</i> Release of Famotidine from Polyox based Famotidine floating tablet formulae containing 5 and 10% Compritol in 0.1 N HCl (pH 1.2) at 37°C.	128
Table 36: ANOVA test for Q6hr of all tablets containing Compritol.	129
Table 37: ANOVA test for Q6hr of single layer tablets and tablets containing Compritol.	129
Table 38: <i>In-vitro</i> Release of Famotidine from 100mg tablets and double layer Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	130
Table 39: ANOVA test for Q6hr of 100mg tablets and double layer tablets.	132
Table 40: <i>In-vitro</i> Release of Famotidine from Hydroxypropylmethyl cellulose K4M triple layer Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	135
Table 41: <i>In-vitro</i> Release of Famotidine from Polyox triple layer Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	137
Table 42: <i>In-vitro</i> Release of Famotidine from different Hydroxypropylmethyl cellulose K4M based triple layer Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	139

Table 43: ANOVA test for Q6hr of HPMC based triple layer tablets...	140
Table 44: <i>In-vitro</i> Release of Famotidine from different Polyox based triple layer Famotidine floating tablet formulae in 0.1 N HCl (pH 1.2) at 37°C.	141
Table 45: ANOVA test for Q6hr of Polyox based triple layer tablets...	142
Table 46: Kinetic Parameters of Famotidine Release Data from single layer tablets according to Zero order, First order Kinetics and Higuchi Model.	145
Table 47: Kinetic Parameters of Famotidine Release Data from compritol containing and binary mixture tablets according to Zero order, First order Kinetics and Higuchi Model.	146
Table 48: Kinetic Parameters of Famotidine Release Data from 100mg tablets, double and triple layer tablets according to Zero order, First order Kinetics and Higuchi Model.	147
Table 49: Fitting of Famotidine Release Data to Korsmeyer–Peppas model from single layer tablets.	153
Table 50: Fitting of Famotidine Release Data to Korsmeyer–Peppas model from compritol containing and binary mixture tablets.	154
Table 51: Fitting of Famotidine Release Data to Korsmeyer–Peppas model from 100 mg, double and triple layer tablets.	155
Table 52: Composition of Famotidine Floating Emulsion Gel Beads...	170
Table 53: Composition of Famotidine Floating Emulsion Gel Beads expressed as weights dissolved in 50 ml solution.	172
Table 54: Composition of Famotidine Emulsion Gel Beads containing HPMC (in mg).	176
Table 55: Composition of Spray Coated Famotidine Emulsion Gel Beads.	178
Table 56: Composition of Famotidine Emulsion Gel Beads coated by oil-in-oil solvent evaporation method.	180