

**Al-Quds University**

**Deanship of Graduate studies**



**Formulation of Ferrous Gluconate Floating Drug  
Delivery System**

**Hala Othman abdel raheem hj hamad**

**M. Sc. Thesis**

**Jerusalem – Palestine**

**2015 -1437**

# **Formulation of Ferrous Gluconate Floating Drug Delivery System**

**Prepared By:**

**Hala Othman Abdel Raheem Hj Hamad**

**B.Sc. Pharmacy**

**Al-Najah University –Palestine**

**Supervisor: Dr. Tareq Al-Jubeh**

**A thesis Submitted in Partial fulfillment of requirements  
for the degree of Master of pharmaceutical science/  
Deanship of Graduate studies/ Al-Quads University**

**2015 -1437**

Al-Quds University  
Deanship of Graduate Studies  
Master of pharmaceutical science



## Thesis approval

### Formulation of Ferrous Gluconate Floating Drug Delivery System

Prepared by : Hala Othman abdelraheem hj hamad

Registration number: 21112811

Supervisor: Dr. Tareq Al-Jubah

Master thesis submitted and accepted, 22 /12 / 2015, the names and signatures of the examining committee are as follows:

1- Dr. Tareq Al-Jubah      Head of Committee

Signature:

2- Dr. Ahamad Amro      Internal Examiner

Signature:

3- Dr. Numan Malkia      External Examiner

Signature:

Jerusalem – Palestine

2015-1437

## **Dedication**

I am deeply grateful and thankful to my husband and children who inspired, supported and encouraged me to explore the best in me. I thank them for dedication and patience.

I am deeply thankful to my family and husband family for the support and the encouragement they surrounded me with.

## **Declaration**

I certify that this thesis submitted for the degree of master is the result of my own research, except where otherwise acknowledged, and this thesis has not been submitted for the higher degree to any other university or institute.

Signed: .....

Name: Hala Othman abdelraheem hj hamad

Date: 22/12/2015

## **Acknowledgment**

I have no words to express my deepest gratitude to Almighty, compassionate, and supreme Allah, who enabled me to accomplish this work. I also invoke peace for the last prophet of Allah, Muhammad (SAAW), who is forever a torch of guidance for humanity as a whole.

Special appreciation goes to my supervisor, Dr. Tareq Al-Jubah, for his supervision and constant support. His immeasurable help of constructive comments and suggestions throughout the experimental and thesis works have contributed to the success of this research.

I would like to express my appreciation to Al-Quds University for the role it is playing in fulfilling the needs of the Palestinian society and the efforts to upgrade and promote the students to have a share in developing the Palestinian industry through the master program of applied and industrial technology.

I would like to express my sincere thanks to the Palestinian Pharmaceutical Industry, especially Birzeit Pharmaceutical Company and Jerusalem Pharmaceutical Company for their unlimited support in donating materials, providing equipment, laboratories and assistance. My special thanks to the honorable and respected dr. Numan Malkia the head of the quality control department in AlQuds company and to Raghda Hawari and her colleagues from the quality control department In Jerusalem Pharmaceutical Company for their assistance and help in the experimental work.

Finally I take great privilege to express my heartfelt thanks to all the people who have been involved directly or indirectly with the successful completion of this work.

## Table of contents

Declaration .....	I
Acknowledgment .....	II
List of figures: .....	IX
List of Abbreviations: .....	X
Abstract: .....	XII
Part 1 .....	1
1.Introduction: .....	2
1.2. Gastro retentive dosage forms:.....	2
1.2.2-Conventional Oral Dosage forms V.S GRDDS:.....	3
1.2.3 The types of GRDDS: .....	4
1.2.3.1-Low density systems/Floating dosage forms .....	6
a). Effervescent Systems/Gas Generating Systems .....	6
1) Volatile Liquid Containing Systems .....	7
2)Gas Generating Systems .....	7
3) Floating Film Delivery System.....	8
b). Non-Effervescent Systems:.....	8
1.2.3.2 High Density Systems: .....	12
1.2.3.3MucoadhesiveSystems: .....	13
1.2.3.4 Super-porous Hydro-gels : .....	14
<b>1.2.3.5Magnetic systems:</b> .....	14
1.2.3.6 Raft Floating System:.....	15
1.3 Advantages of Gastro retentive Drug Delivery System: .....	15
1.4List of marketed floating dosage form .....	16
1.5 Ideal Drug Candidates For GastroRetentive Drug Delivery System.....	17
1.6Drugs those are unsuitable for Gastroretentive Drug Delivery Systems.....	17
1.7 Factors affecting GastricRetention:.....	17
1.8 Disadvantages of GDDS .....	19
1.9 Drawbacks of the gastro retntive drug deivery systems .....	19
1.10 Anatomy and physiology of the stomach and a description of gastric emptying.....	19
1.10.1Gastric Motility: .....	20
1.10.2 Gastric Emptying Rate: .....	20
1.11 Introductions on Iron:.....	21
1.11.1 Dietary Iron: .....	22
1.11.2 Iron absorption: .....	24

TFR-HFE: Trans ferrin receptor .....	26
1.11.3 Anemia and Iron Deficiency Anemia:.....	27
1.11.3.1 Anemia: .....	27
1.11.3.2 Diagnosis of anemia .....	27
1.11.3.3 Causes of Iron Deficiency: .....	28
1.11.3.4 people at Risk for Iron-Deficiency Anemia .....	29
1.11.3.5 Signs and Symptoms of Anemia .....	29
1.11.3.6 Signs and Symptoms of Iron Deficiency.....	30
1.11.3.7 Tests that used to Diagnose Iron Deficiency Anemia: .....	30
1.11.3.8 Treatment of Iron Deficiency Anemia : .....	31
1.11.3.9 Types of iron salts that used in iron supplement: .....	31
1.12 Iron deficiency anemia in Palestine: .....	34
1.13 Back ground on ferrous gluconate: .....	35
<b>1.13.1 Chemical and Physical Properties:[77]</b> .....	36
Stability: .....	36
Pharmacological Classification: .....	37
Absorption:.....	37
Methods of Manufacturing:.....	37
Formulations/Preparations: .....	37
Part 2 .....	38
2.1 Problem Statements:.....	39
2.2Literature review: .....	41
2.3 Main Objective of the Study: .....	44
2.4 The Specific Objectives of the Study are: .....	44
2.5 Advantage of Floating Gastric Retentive Drug System:[18] .....	45
2.6 Why ferrous gluconate used in our study? .....	47
Part 3 .....	49
Materials and Methods:.....	50
3.1 Materials and Reagents: .....	50
3.2 Tools and Equipment: .....	50
3.3 Spectrophotometric Determination of Iron: .....	51
Table (13) standard solutions preparation for calibration curve .....	52
3.4 Preparation of effervescent floating tablets:.....	53
Wet granulation and direct compression were used to prepare the tablets.....	53
3.4.1 Wet Granulation Method:.....	53



3.4.2 Direct Compression Method: .....	54
3.5 Quality Control Tests of tablets: .....	56
3.5.1 Pre-compression parameter: .....	56
3.5.2 Post-compression parameters: .....	57
3.5.2.1 Shape of Tablets: Compressed tablets were visually examined for their shapes. [104].....	57
3.5.2.2 Tablet Dimensions.....	57
3.5.2.3 Hardness : .....	57
3.5.2.4 Friability test .....	57
3.5.2.5 Weight Variation Test .....	58
3.5.2.6 Buoyancy/ Floating Test: .....	58
3.5.2.7 Swelling Study: .....	58
3.5.2.8 In vitro drug release for the formulation .....	59
3.5.2.9 Drug content uniformity study: .....	59
3.5.3 Stability test for tablet .....	59
3.6 Kinetics of drug release:.....	60
3.7 Mathematical modeling of dissolution rate profile: .....	60
3.7.1 Zero order models .....	61
3.7.2 First order model .....	61
3.7.3 Higuchi Model .....	62
3.7.4 Korsmeyer- Peppas Model.....	62
3.7.5 Hixson Crowell model: .....	63
3.7.6 Selection of Best Model: .....	63
Part 4 .....	65
Results and discussion.....	65
4.1 Spectrophotometric determination of iron : .....	66
4.2 preparation of effervescent floating tablets : .....	69
4.2.1 Wet granulation method's formulas : .....	69
4.2.2 Direct Compression Method: .....	71
4.3 The pre-compression physical properties for the powder for H7:.....	73
4.4 The post- compression physical properties for the tablets (for formula H7): .....	73
4.4.1 Shape of Tablets: .....	73
4.4.2 Dimensions of the tablets: .....	73
4.4.3 Friability test : .....	73
4.4.4 Hardness of the tablet.....	74

4.4.5 Weight variation.....	74
4.4.6 Content Uniformity Test: .....	75
4.4.7 Buoyancy / Floating Test .....	75
4.4.8 Swelling Study: .....	77
4.4.9 The in vitro release study for Ferrous gluconate :( .....	79
4.4.10 In vitro release kinetics data analysis for optimized formula H7 :.....	81
4.4.11 Stability studies : .....	85
<b>2. Assay :</b> .....	86
4.4.11.2 Stability studies for three months : .....	87
Part 5 .....	91
5.1 Conclusion: .....	91
5.2 Appendix: .....	92
5.2.1 Hypromellose: (HPMC K 100.000/HPMCK 4/ HPMC K15):.....	92
5.2.2 Ethyl Cellulose:.....	96
<b>5.2.3 Citric acid :</b> .....	99
5.2.4 Sodium bi carbonate:.....	101
5.2.5 starch: .....	103
5.2.6 Mg stearate : .....	103
5.2.7 Povidine : (PVP K30 ):.....	104
5.2.8 Microcrystalline cellulose: .....	106
5.2.9 Ascorbic Acid : .....	106
5.3 References: .....	108
الملخص.....	114

## List of Tables

Table(1) : Comparison between conventional and Gastroretentive drug delivery system .....	4
Table(2) list of marketed dosage form .....	16
Table (3) drawbacks of gastro retentive drug delivery system.....	19
Table (4) the Estimated Average Requirement and Recommended Dietary Allowance of Iron for Adult Men and Women .....	23
Table (5) definition of anemia according to hemoglobin level : .....	28
Table (6) summarizing the signs and symptoms of iron deficiency anemia : .....	30
Table (7) available oral and parenteral iron preparations: .....	32
Table (8) differences between bivalent and trivalent oral iron preparation. (Santiago 2012).....	33
Table (9) A Chart Summarizing the Iron Supplement Product Marketed in Palestine. ....	34
Table(10) Distribution of Anemia Percentage between Pregnant Beneficiaries in MCH Centers by Type and District, West Bank, Palestine, 2014.....	35
Table (11) Distribution of Anemia Percentage of Postnatal Beneficiaries of MCH Centers by Type and District, West Bank, Palestine, 2014.....	35
Table (12) list of the tools and equipments used in the study: .....	50
Table (13) standard solutions preparation for calibration curve .....	52
Table (14) summary of formula used in wet granulation method .....	54
Table (15) summary of formulas used in direct compression method .....	55
Table (16) the relationship between Angle of repose and powder flow is as follows in.....	56
Table (17) Scale of flowability .....	57
Table (18) the USP acceptable limits for the weight variation.....	58
Table( 19): Various drug transport mechanisms .....	63
Table (20 ) the floating lage time (FLT) and the total floating time (TFT) for all fromulas we studied in both wet granulation and direct compression methods. ....	68
Table (21) Results of Weight Variation Quality Control Test .....	74
Table (22) shows the results of the content uniformity for 6 tablets .....	75
Table (23) Floating time measured for 6 tablet .....	76
The table (24) showses the results for the swelling index for formula H7 .....	77
Table (25) shows the result of the % release of the ferrous from the tablet of formula H7 for 10 hours.....	79
Table (26 ) Mathematical Models used to describe Drug Release Kinetics from various Matrices .....	82
Table(27) for the 5 kintecs modle we studied : .....	82
Table(28): The interperation of diffusion exponent (n) value for release from polymeric film .....	83

Table (29) % release of iron from (6) tablets after one month stability at 30 C/65 %RH...	85
Table(30) % release of Fe from (6) tablet after one month stability at 40 C/75 %RH.....	85
Table (31) shows the result of assay for(10) tablets after one month stability test at both 30C/65 RH and 40C/ 75RH.....	86
Table (32) the hardness results for (6) tablets after one month at 30C/65 RH.....	86
Tablel (33) the Hardness results for (6) tablets after one month stability test at 40 C/75 RH	87
Table(34) shows the %release of iron from (6) tablets up to 10 hours after 3 month stability test at30 C/65 %RH. ....	87
Table (35) shows the % release of iron from (6) tablets up to 10 hours after 3 month stability test at 40 C/75 %RH. ....	88
Table (36): the assay result of (6) tablets after three month at different incubation condition	89
Table( 37) hardness result of (6) tablets after 3 months at 30C/ 65 RH.....	89
Table ( 38) hardness result of (6) tablets after 3 months after 40C/ 75 RH .....	89

## List of figures:

Fig (1):Characteristic representation of plasma concentrations of a conventional immediate release dosage form, a sustained release dosage form, and an idealized zero-order controlled release .....	3
Fig(2)Types of GRDDS .....	6
Fig (3)Volatile Liquid Containing Gastro retentive System .....	7
Fig (4) Gas generating Floating Drug Delivery System.....	8
Fig (5) Hydro-dynamically Balanced System.....	9
Fig(10) High Density Drug Delivery System .....	13
Fig (11) Muco adhesive Drug Delivery System.....	14
Fig (12) raft floating drug delivery system .....	15
<b>Fig (13) The Anatomy of the Human Stomach.....</b>	<b>20</b>
Fig (14) iron absorption and metabolism .....	24
Fig (15) Iron Absorption Mechanism.....	26
Fig (16) stages of floating mechanism in FDDS .....	47
Fig (17) Calibration curve of ferrous gluconate .....	66
Fig (18) Swelling Index with time:.....	78
Fig (19) Dissolution Release Profile of Ferrous Gluconate for Formula (H7).....	81
Fig (20) the best model in which the predicted curve fits the data is koresmeyerpeppas model. ....	84
Fig (21) Release after different incubation conditions .....	88

## **List of Abbreviations:**

API: active product ingredient.

BLT: Buoyancy Lag Time

CO<sub>2</sub> : Carbon Dioxide

CRGRDF: Controlled Release Gastric Retentive Drug Floating system

CDC: Center for Disease Control and Prevention

CBC: Complete Blood Count

CR: Controlled Release

DMT: Divalent Metal Transporter

EAR: Estimated Average Requirement

FLT: Floating Lag Time

FDDES: Floating Drug Delivery System FDA: Food and Drug Administration

GIDS: Gastric Intra Drug Delivery System

GIT: Gastro Intestinal Tract

GRT: Gastric Retention Time

GET: Gastric Emptying Time

GRDDS: Gastric Retentive Drug Delivery System

HPMC: Hydroxyl Propyl Methyl Cellulose

HBS: Hydrodynamic Balanced System

HCL : Hydrochloric acid

HA: Hydroxyl Amine

H<sub>2</sub>SO<sub>4</sub> : Sulfuric acid

ID: Iron Deficiency

KCL: potassium chloride

MMC: Migrating Myo-electric Complex

MCH: Ministry Clinic Health Center

MOH: Ministry of Health

MCC: Micro Crystalline Cellulose

NaHCO<sub>3</sub> : Sodium bicarbonate

PVP: Poly Vinyl PyrrolidoneQT: Quality Control Test

RDA: Recommended Dietary Allowance

RLS: Restless Leg Syndrome

RBC: Red Blood Cells

SR: Sustained Release

TFT: Total Floating Time

UL: Upper Tolerance Level

USP: United States Pharmacopeia

WHO: World Health Organization