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Formulation of Ferrous Gluconate Floating Drug Delivery System

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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.

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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

List of Tables

List of figures:

List of Abbreviations:

API: active product ingredient.

BLT: Buoyancy Lag Time

CO_2 : 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

FDDS: Floating Drug Delivery SystemFDA: 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_2SO_4 : 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

$NaHCO_3$: 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

Abstract:

According to WHO, iron deficiency anemia is the most common form of malnutrition in the world. Common forms of iron supplement available in the market show low bioavailability due to the poor absorption of iron in the GIT, mainly because iron has a narrow absorption window in the GIT "in the upper part of the intestine" and because of its oxidation in the intestine so decreasing its absorption. Other problems with iron supplements include its widespread side effects mainly constipation due to its accumulation in the lower GIT. These problems can be solved by using a form of iron that is better absorbed, and to maximize the localization of iron at the absorption site at the upper part of the GIT.

The main goal of this study was to formulate a Gastroretentive drug delivery system (GRDDS) of ferrous gluconate, which is intended to stay for a long time period in the stomach, meanwhile releasing the iron in a controlled manner to be absorbed in the upper part of the intestine for at least 10 hrs.

Tablets were prepared by using swellable polymers having different viscosity properties: HPMC k4M, HPMC k15M and HPMC k100Mand ethyl cellulose as a floating enhancer. Sodium bicarbonate and citric acid were used as gas generating compounds. Varying percentages of the mentioned excipients were used and the desired tablets were prepared by either wet granulation or direct compression methods. . The choice of the best formula manufacturing method was based on the performance of compressed tablet in terms of buoyancy and drug release. Floating properties of the tablets, dissolution tests, swelling properties and physical properties of tablets; weight variation, friability, hardness were done. Physical properties of the powder were also tested, mainly the compressibility index

and angle of repose. The kinetics of the release for the chosen formula was elucidated by the DDsolver program.

The effect of polymer viscosity properties on the buoyancy properties were tested ,we found that the total floating time is decreased by decreasing the viscosity of swellable polymer .

The results showed that the direct compression method was more suitable in the production of a floating tablet which exhibited a sustained release pattern, using the polymer with the best viscosity properties HPMC k100M with a finely tuned amount of ethyl cellulose and sodium bicarbonate. The formula "H7"wich containing HPMC 100 M could allow the entrance of enough water to initiate gas generation and floating but at the same time, formed a coherent gel that entrapped the gas to from floating and permitted a sustain release of ferrous ions, This chosen formula showed a floating lag time of 40 seconds and total floating time up to 24 hour, with gradual release of ferrous gluconate up to 10 hours. All tablet and powder physical properties were in agreement with the official requirements of the USP.

The analysis of the release kinetics showed an agreement with korsemeyer-Peppas model of release, which describes the release from swellable polymeric matrices. The swelling studies indicated initial swelling of the matrix then erosion. Both the kinetics analysis and swelling index analysis may be interpreted by the conclusion that the mechanism of release is diffusion coupled by erosion.

We conclude that such successful GRDDS of iron gluconate can be helpful in increasing the bioavailability of iron. Further in vivo studies on human volunteers are recommended in the future.

Part 1

Introduction

1. Introduction:

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve and maintain therapeutic concentration within range and to show pharmacological action with minimum incidence of adverse effects. To achieve this goal one should maintain dosing frequency and suitable route of administration [1].

There are many kinds of route of administration, rectal ,nasal, parenteral , topical, vaginal, ocular and the most desired route is the oral route because of ease of administration, more flexibility in designing, ease of production and low cost[2].

It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [3]. Control of location of a drug delivery system, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem, in a specific region of the GI tract offers several advantages. These considerations have led to the development of oral controlled-release (CR) dosage forms possessing gastric retention capabilities[4].

Numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. It is evident from the recent scientific and patent literature that there is an increased interest in novel oral controlled release dosage forms that are designed to be retained in the upper gastrointestinal tract (GIT) for a prolonged and predictable period of time .[5].

1.2. Gastro retentive dosage forms:

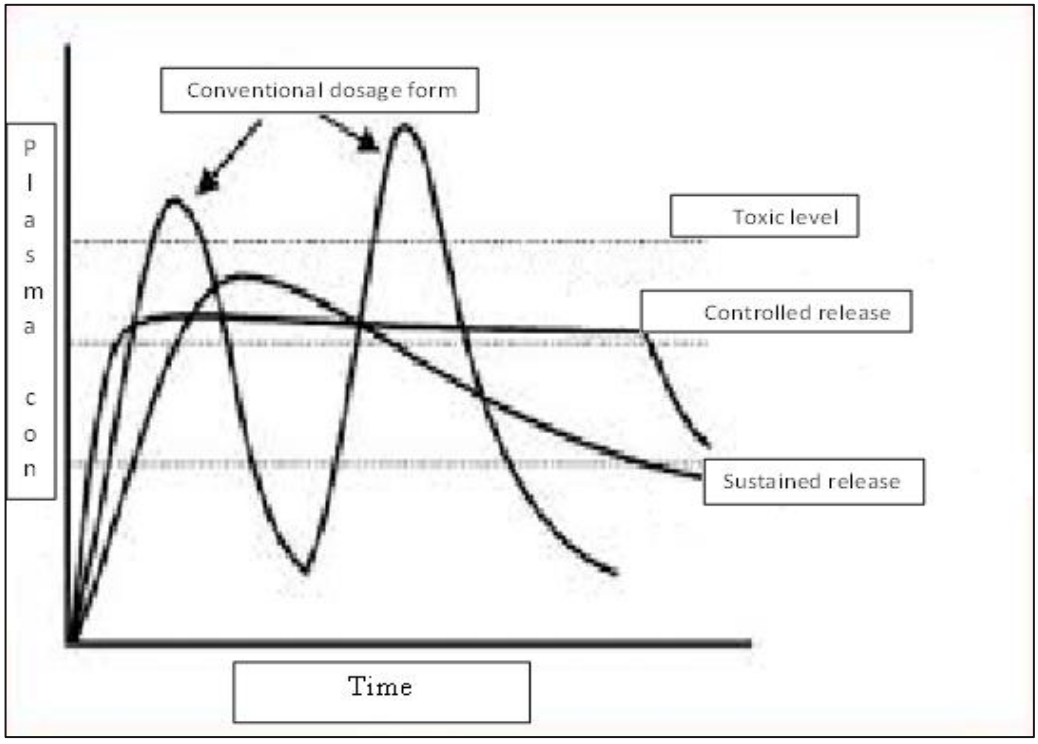
Are defined as the forms which are designed to be retained in the gastric region for prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus ensuring its optimal bioavailability. [6].

This technology has generated enormous attention over the last few decades owing to its potential application to improve oral delivery of some important drugs for which prolonged gastroretention can greatly improve their oral bioavailability[7]

1.2.2-Conventional Oral Dosage forms V.S GRDDS:

In conventional dosage forms, there is no precise control over the release of drug as the administered dose of drug enters the systemic circulation. The minimum effective concentration of drug in the blood plasma is not achieved with frequent administration of a single dose of a drug because of fluctuations in the plasma drug concentration. As it shows in fig(1) Conventional oral controlled dosage forms suffer from mainly two adversities[8]; The short gastric retention time (GRT) and unpredictable gastric emptying time (GET).. These problems can be overwhelmed by altering the gastric emptying. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.[9].

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 dosage form [10]



Table(1) : Comparison between conventional and Gastroretentive drug delivery system [11]

Conventional drug delivery system	Gastro retentive drug delivery system
More side effect	Less side effect
Patient compliance is less due to Taking medication frequently during the day .	Improves patient compliance as drug is taken once daily
Less gastric retention time	Improve gastric retention time
Not appropriate for delivery of drugs with narrow absorption window in small intestine region.	Appropriate for delivery of drugs with narrow absorption window in small Intestinal region
Not much beneficial for drugs Exhibit local action in the stomach.	Beneficial for drugs exhibit local action in the stomach .
Not suitable for Drugs that Degrade in the colon .	Suitable for drugs that degrade in the colon .
Not suitable for drugs having rapid absorption through GIT	Suitable for drugs having rapid absorption through GIT
No risk of dose dumping	High risk of dose dumping.

1.2.3 The types of GRDDS:

Gastroretentive can be achieved by physiological, pharmacological and pharmaceutical method :[12]

The Physiological approach: Uses natural materials or fat derivatives such as Triethanolamine myristate which stimulate the duodenal receptors to slow gastric emptying.

Or the use of large amounts of volume filling polymer such Polycarbophil will also slow gastric emptying. The Pharmacological approach: It involves the co administration or incorporation of a drug for delaying gastric emptying e.g. Loperamide.

The previous approaches are not used because of toxicity problem while -Pharmaceutical approach :are delivery systems which designed to be retained in the stomach for extended time periods these system includes many types and forms as listed below and as it shows in figure (2):[9]

1**. Low Density systems/Floating Dosage Forms**

A. Effervescent Systems/Gas Generating Systems:

1) Volatile Liquid Containing System.

2) Gas Generating System .

3) Floating Film Delivery System .

B. Non-Effervescent Systems:

1- Hydrodynamically Balanced System .

2-Microballons/hallow Microsphere System .

3-Intragastric FDDS.

4-Swelling or Expanding System.

5-Alginate Beads System .

2. High Density Systems

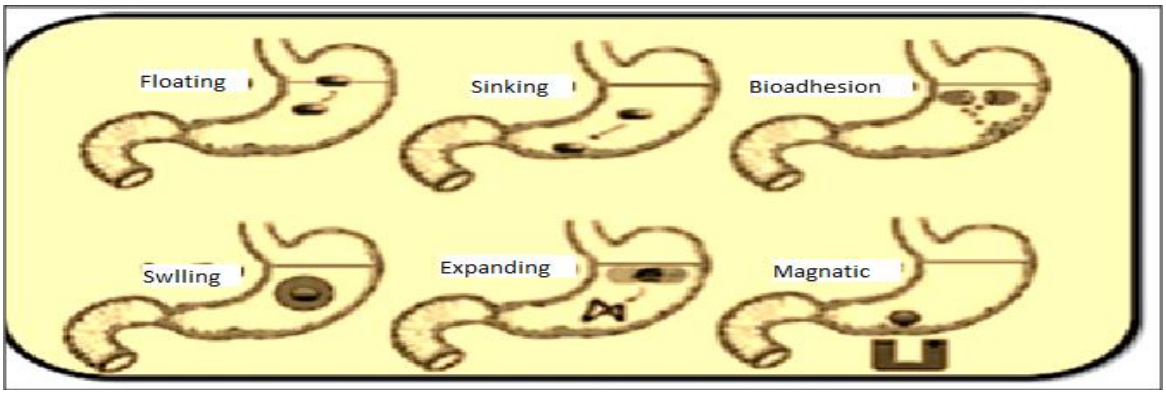
3.MucoadhesiveSystems

4.SuperporousHydrogels Systems.

5. Magnetic Systems

6. Raft Floating System:

Fig(2)Types of GRDDS[9]



1.2.3.1-Low density systems/Floating dosage forms:[13]

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. These Delivery Systems are desirable for drugs with an absorption window in the stomach or in the upper small intestine. This type of delivery system is of great value for drugs which get absorbed from upper part of the stomach .[14].

These systems have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged time periods and the drug is released slowly from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration

The major requirements for a floating drug delivery system are: It should release contents slowly to serve as a reservoir. It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).and It must form a cohesive gel barrier.

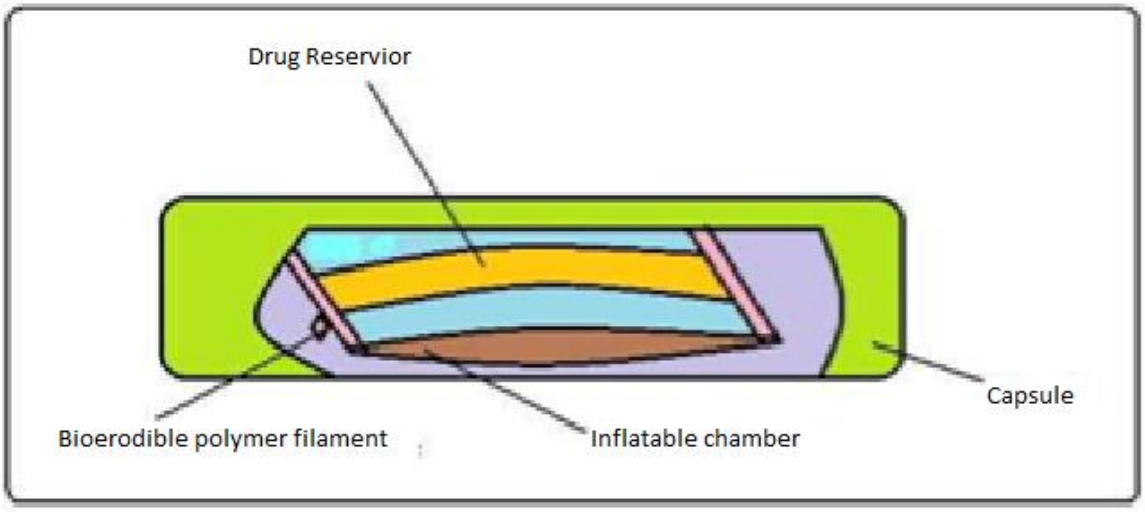
a). Effervescent Systems/Gas Generating Systems :

A drug delivery system can be made to float in the stomach by incorporating a floatation chamber, which may be filled with vacuum, air or inert gas. The gas in the floatation

chamber can be introduced either by the volatilization of an organic solvent or by the effervescent reaction between organic acids and bicarbonate salts. [9]

1) Volatile Liquid Containing Systems: These have an inflatable chamber which contains a liquid e.g. Ether, Cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach .as it shows in figure(3) These systems are somatically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid[15]

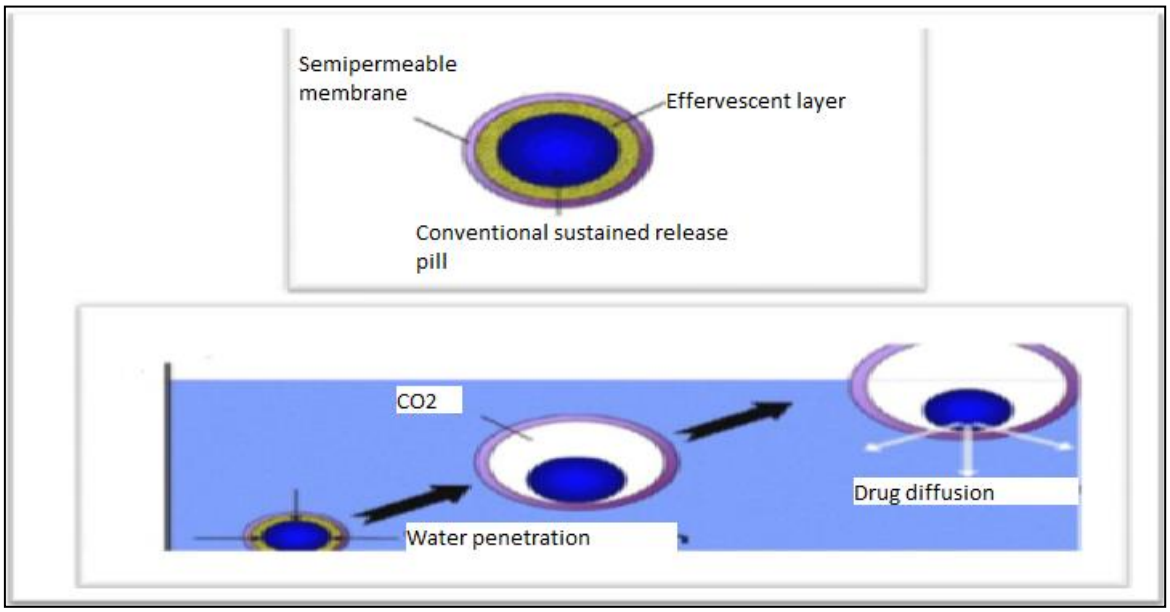
Fig (3)Volatile Liquid Containing Gastro retentive System



[16]

2)Gas Generating Systems: These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2 , which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float as it shows in figure (4) .

Fig (4) Gas generating Floating Drug Delivery System



[13]

A multiple unit type of floating pills, which generate CO2, have also been developed. The system consists of a sustained release (SR) pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swell able membrane layer.[15]

3) Floating Film Delivery System: A drug loaded thin filmstrip filled into capsule is typically designed for oral drug delivery. Floating film offers advantages as, preparation of film is very simple, time saving, economically beneficial and chances of cross contamination are very low, also handling of film is very easy as compared with microspheres.

b). Non-Effervescent Systems**:**

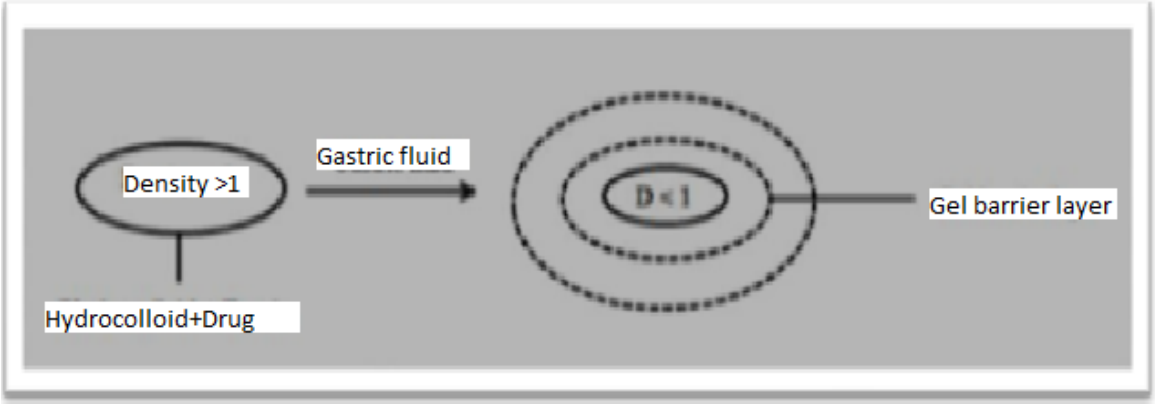
Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients most commonly used in these systems include hydroxypropyl methylcellulose (HPMC)

polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates .[13]

This system can be further divided into the flowing sub-types:

1. ***HydrodynamicallyBalanced Systems***: The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period as it shows in figure (5). Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. [13]

Fig (5) Hydro-dynamically Balanced System



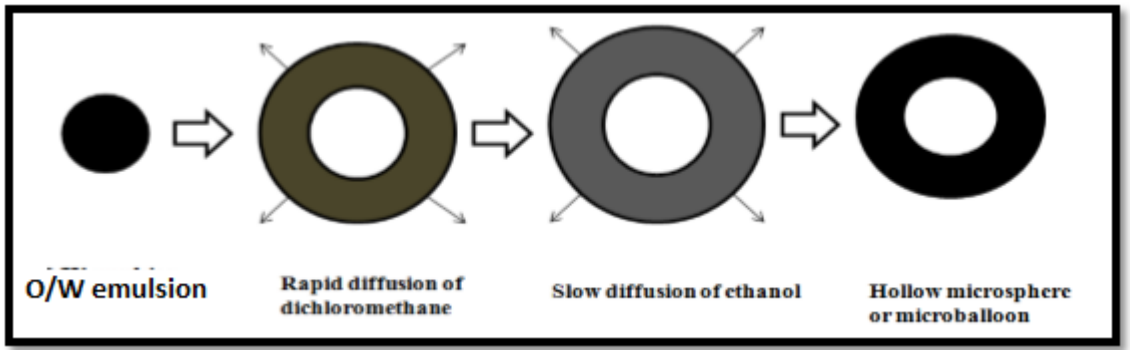
[13]

2. ***Microballoons / Hollow microspheres***: is loaded with drugs ,prepared by simple solvent evaporation or solvent diffusion/evaporation methods as it shows in figure (6) to prolong the gastric retention time (GRT) of the dosage form.

Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation.

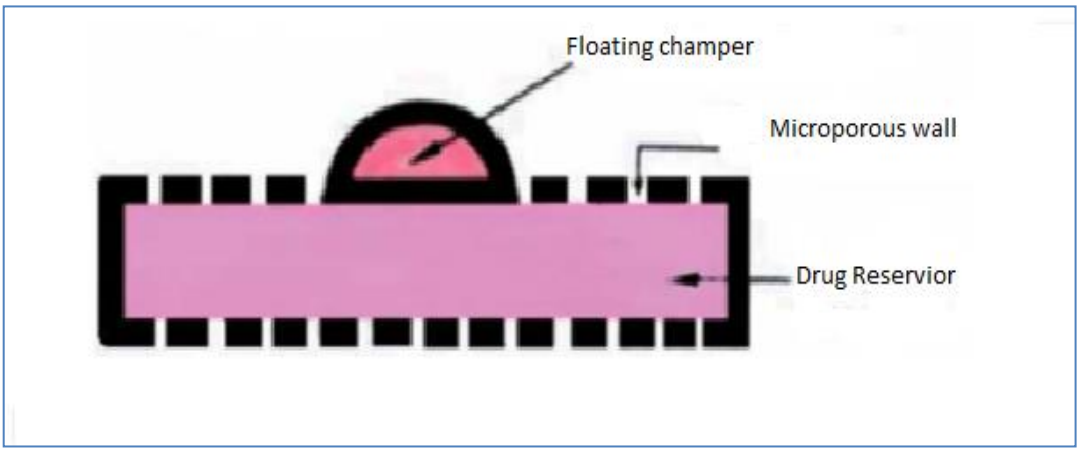
The microballoons floats continuously over the surface of an acidic dissolution media containing surfactant for >12 hours .[13, 17]

Fig (6)Microballoons / Hollow microspheres drug delivery system[13]



.3- **Intragastric FDDS**: the drug reservoir is encapsulated inside a micro porous compartment with halls along its top and bottom walls as it show in figure (7). The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the undissolved drug. In the stomach, the floatation chamber causes it to float in the gastric fluid. Fluids enter through the halls , dissolve the drug, and carry the drug solutes out from the delivery system for continuous transport to the intestine for absorption[9].

Fig (7) Intra Gastric Floating Gastrointestinal Drug Delivery Device[18]



4) **Swelling or Expanding Systems***:*

If a dosage form is bigger than the pyloric sphincter it will withstand the gastric transit. But the dosage form must be small to be swallowed.

There are three configuration features required:

1-A small size for swallowing,

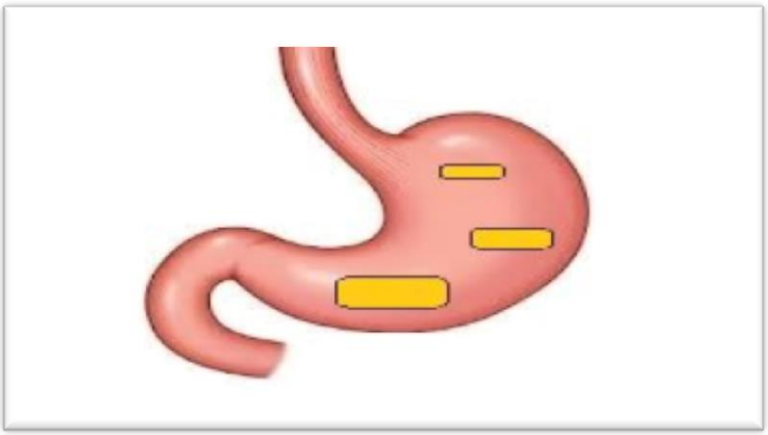
2-An expanded form for gastroretention

3-Finally a small form for evacuation[14]

After swallowing these systems swell to an extent that prevents their exit from the stomach through the pylorus. As it show in figure (8) These systems are also called as "Plug type systems", since they have tendency to remain logged at the pyloric sphincter[19]

When polymers come in contact with gastric fluid, the polymer imbibes water and swells. The swelling of these polymers is due to presence of physical-chemical cross links in the hydrophilic polymer network.[20]

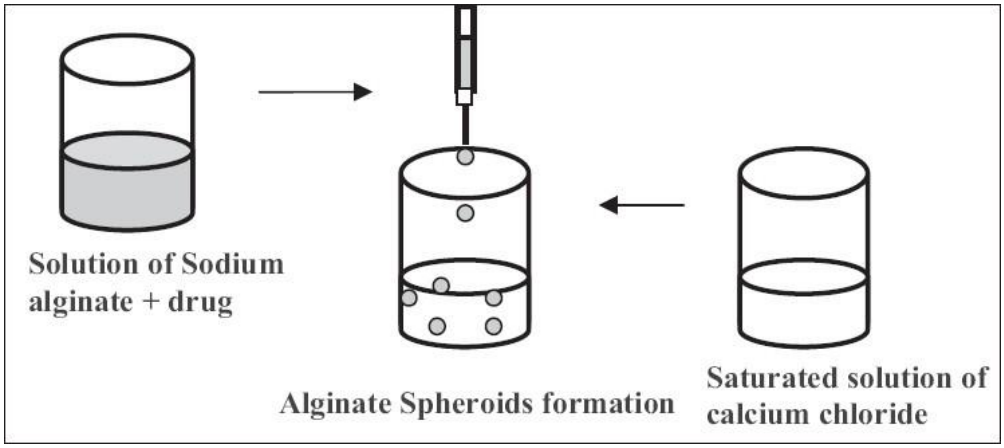
Fig (8)Swelling (Expandable) Drug Delivery System[11]



5)***Alginate Beads System***: Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate as it shows in figure (9). The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40C° for 24 h, leading to the

formation of a porous system, which can maintain a floating force for over 12 h. These floating beads gave a prolonged residence time of more than 5.5 hours.[9]

Fig (9) the formulation process of Na alginate drug delivery system[21]

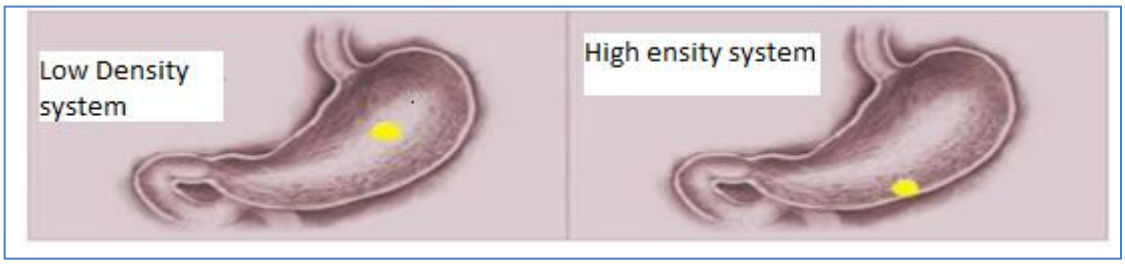


1.2.3.2 High Density Systems:

These systems have density higher than the stomach fluid (1.004 g/cm^3). It would be at least 1.50 g/cm^3[22]

These systems are able to withstand peristaltic movement and retained in the stomach in the Pyloric Antrum for several hours[20] These systems can be manufacture by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder[19] but this system has major drawback that has many technical problems, and cannot stand the vigorous and continuous contraction of the stomach leading to high probability to be evacuated from the stomach rabidly .

Fig(10) High Density Drug Delivery System [17]

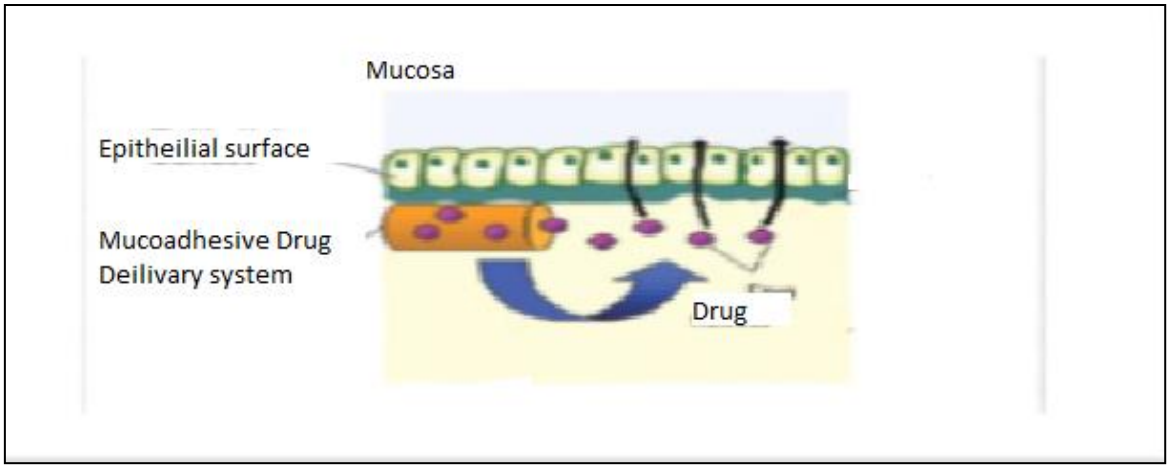


1.2.3.3MucoadhesiveSystems:

Bioadhesive drug delivery systems are used to localize a delivery device within the human to enhance the drug absorption in a site-specific manner as it shows in figure (11). In this approach, various Bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach[23] .They increase the GRT of the dosage forms. The basis of micro adhesion is that a dosage form can stick to the mucosal surface by different mechanisms that can be summarized :[24, 25].In the wetting theory, which is based on the ability of Bioadhesive polymers to spread and develop intimate contact with the mucous layers. Or the diffusion theory, which proposes physical entanglement of mucin strands with the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate. Or the absorption theory, suggests that bioa-dhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding. And. The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material.

Major drawback of this system is gastric muco adhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong contraction forces of the stomach wall

Fig (11) Muco adhesive Drug Delivery System[13]



1.2.3.4 **Super-porous Hydro-gels :**

Super porous hydro gels, With an average pore of size less than 100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores[26].

Super-porous hydro-gels must possess following properties in order to act as gastric retention device, Initial size should be small enough for easy swallowing. The Swelling should be fast enough to overcome gastric emptying. The Size of swollen hydro gel should be large enough to be retained in the stomach. And the Swollen hydro gel should be strong enough to withstand contraction pressure, abrasion and shear forces in stomach.

Among a number of polymers tested, polyanions with a high charge density are highly recommended .[9].

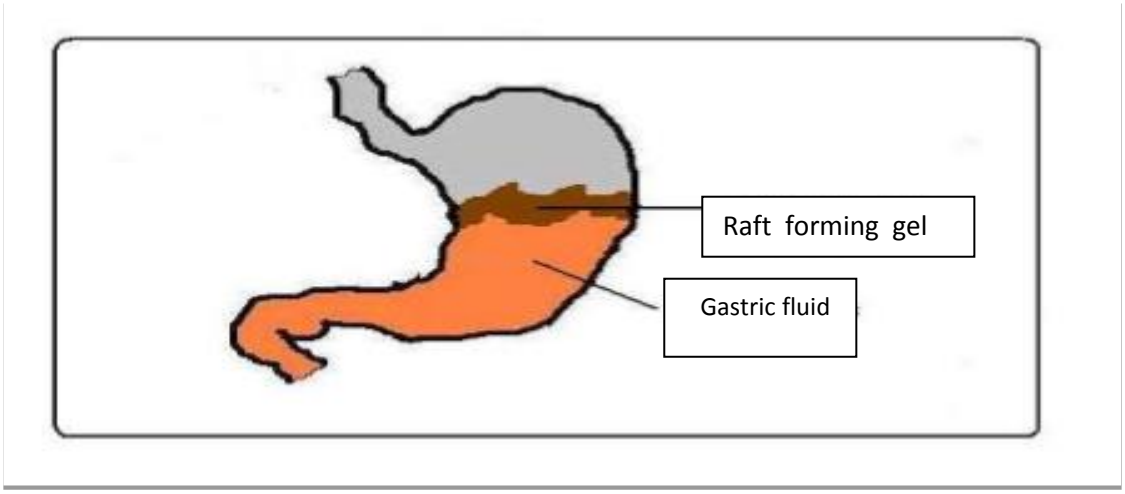
1.2.3.5Magnetic systems:

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet like (ultra-fine ferrite (ã-Fe2O3)),[5] and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance[5]

1.2.3.6 Raft Floating System:

Raft forming systems incorporates alginate gels[27].The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids as it shows in figure (12), where in each portion of the liquid swells forming a continuous layer called a raft .This raft floats on gastric fluids because of low bulk density created by the formation of CO2. A patent assigned to Reckitt and Colman Products Ltd., describes the treatment of Helicobacter pylori (H. Pylori) infections in the GIT a raft forming formulation. [28]

Fig (12) raft floating drug delivery system[29]



1.3 Advantages of Gastro retentive Drug Delivery System:

Extended release dosage form with prolonged residence time in stomach is highly desirable for drugs that are: locally active in stomach, have an absorption window in the stomach or in the upper small intestine, which are unstable in the intestinal or colonic environment or which have low solubility at high pH values[19, 30]

Advantages of GRDDS can be summarized as:[12]

1). Avoiding patient compliance problems by reducing the frequency administration time of the tablets to once daily .

2). Patients use less dose of drug: so this help in

i) Minimize or eliminate local side effects hence they are useful in the treatment of disorders related to stomach and small intestine (e.g. eradication of *Helicobacter pylori*).

ii) Minimize or eliminate systemic side effects thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.

iii) Obtain less potentiating or reduction in drug activity with chronic use.

iv) Minimize drug accumulation with chronic dosing.

3.) The Gastroretentive systems are advantageous for drugs absorbed through the stomach. e.g. Ferrous salts, antacids and the reduction of fluctuation in drug level.[2],.

4.) Reduced fluctuation of drug concentrations: Continuous input of the drug following controlled release Gastroretentive delivery produces systemic drug concentrations within a narrower range compared to the immediate release oral dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent side effects that are associated with peak concentrations can be prevented.

5.) When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response[2]

1.4 List of marketed floating dosage form:[31, 32]

Table(2) list of marketed dosage form

Brand name	AP	Dosageform	Company/country
Modapar®	Levodopa, benserazide	Floating controlled release capsule	RocheProducts/USA
Prolopa®	Levodopa, benserazide	Floating controlled release capsule	RocheProducts/USA
Valrelease®	Diazepam	Floating capsule	Hoffmann-LaRoche/USA
Liquid Gavison	Aluminiumhydroxide, Magnesiumcarbonate	Effervescentfloatingliquid alginate preparation	GlaxoSmithKline/INDIA
Topalkan®	Aluminium-Magnesium antacid	Floatingliquid alginatepreparation	PierreFabre Drug/FRANCE
AlmagateFlatcoat	Aluminium-Magnesium antacid	Floatingdosage form	PierreFabre Drug/FRANCE
Conviron®	Ferrous sulfate	Colloidal gel formingFDDS	Ranbaxy/INDIA
Cifran®	Ciprofloxacin	Gas-generatingfloatingtablets	Ranbaxy/INDIA
Oflin OD	Ofloxacin	Gas-generatingfloatingtablets	Ranbaxy/INDIA
Cytotec®	Misoprostal	Bilayerfloating capsule	Pharmacia/USA

1.5 Ideal Drug Candidates For GastroRetentive Drug Delivery System:[13]

In general, appropriate candidates for CRGRDF are molecules that have poor colonic or lower small intestine absorption but are characterized by better absorption properties at the upper parts of the GIT:

1) Narrow absorption window in GItract, e.g., riboflavin and levodopa

2) Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements, chlordiazepoxide , cinnarazine and ferrouse salts

3) Drugs that act locally in the stomach, e.g., antacids , misoprostol and drug treat H.pylori

4) Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole

5) Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

6) Drugs that have efflux pumbes in the lower intestin .

1.6Drugs those are unsuitable for Gastroretentive Drug Delivery Systems:[13]

1. Drugs that have very limited acid solubility e.g. phenytoin.

2. Drugs that suffer instability in the gastric environment e.g. erythromycin.

3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

1.7 Factors affecting GastricRetention:

1.7.1 Physiological factors:

- Size of dosage form: Dosage forms having diameter greater than the diameter of pyloric sphincter escape from gastric emptying and remain within gastric region[16]. Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT[33]

- Shape of dosage form: Round or Ring shaped dosage form are considered better in comparison to other shapes.[16]

- Density: Location of the particular gastro retentive dosage form in gastric region depends on density of the system. Those with low density tend to float on the gastric fluid surface while high density systems sink to bottom of stomach.[16]

1.7.2 Biological Factors: :

- Age: Geriatric patients show a longer gastric retention time, while the neonates and children have low gastric retention time, in comparison to a normal adult.[16] Elderly people, especially those over 70 years old, have a significantly longer GRT[15]

- Gender: Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface[15]

- Caloric content : GRT can be increased by four to ten hours with a meal that is high in proteins and fats[15]

- Fed or Unfed state:Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer[15]

- Feed frequency: The gastric retension time can be increased by over 400 minutes when a successive meals are given compared with a single meal due to the low frequency of the migrating myoelectric complex(MMC)[15].

- :Nature of meal – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release[15].

- Posture :[34] conducted a comparative study in humans, the floating and non-floating systems behaved differently in the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remaineaway from the pylorus region .

- Concomitant drug administration: Administration of certain drugs along with gastric motility enhancers (metoclopramide, cisapride) or depressants (atropine), greatly affect gastric retention time and hence absorption of stomach specific absorbing drugs[16]

- Disease state: Gastro retentive time is altered during the various gastric diseases like Crohn's disease etc.[16]

1.8 Disadvantages of GDDS:[35]

1). Gastric retention is influenced by many factors such as gastric motility, pH and presence of food, and mucus turnover. These factors are never constant and hence the buoyancy cannot be predicted.

2.) Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

1.9 Drawbacks of the gastro retntive drug deivery systems:[36]

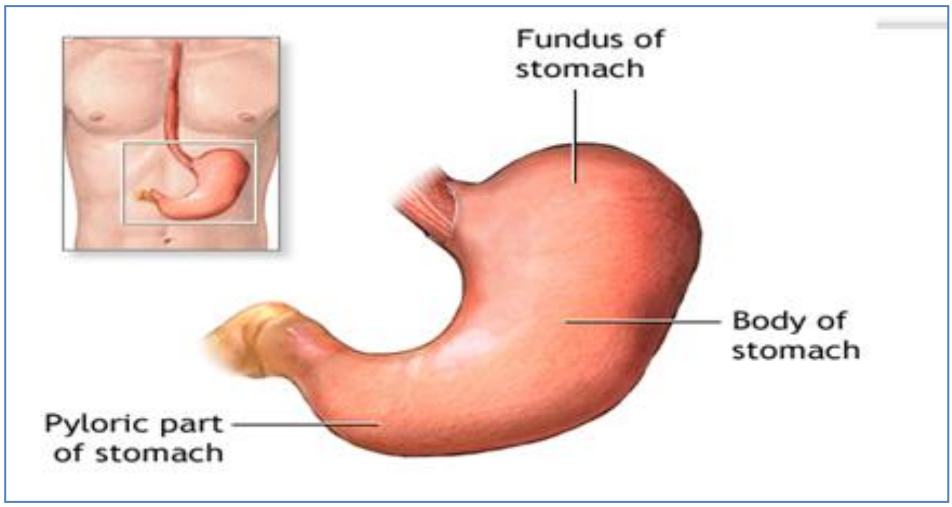
Table (3) drawbacks of gastro retentive drug delivery system

Technology	Drawbacks
High density systems	Cannot be manufactured with large amount of drug due to technical problems. Till date no such system is available in the market.
Floating systems	Highly depends on the fed state of stomach; higher level of fluid is required in gastric region
Expandable systems	Storage troubles due to hydrolysable, biodegradable polymers. Difficult to manufacture and not economical.
Mucoadhesive systems	Efficiency can be reduced in rapid turnover of mucus. Might bind to other mucosal lining like esophagus
Magnetic systems	Might compromise with patient compliance.

1.10 Anatomy and physiology of the stomach and a description of gastric emptying:

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub-mucosa are thrown up into distinct folds called Rugae.[15].

Fig (13) The Anatomy of the Human Stomach[37]



1.10.1 Gastric Motility:

Gastric motility is controlled by a complex set of neural and hormonal signals. Nervous control originates from the enteric nervous system as well as parasympathetic (predominantly Vagus nerve) and sympathetic systems. A large battery of hormones has been shown to influence gastric motility ;both gastrin and Cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility likely are a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals. Liquid readily passes through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing the pyloric gatekeeper. The gastric volume is important for dissolution of the dosage form in vivo. The resting volume of the stomach is 25-50 ml.The pH of fasting stomach is 1.2-.2.0 and in fed conditions 2.0-6.0.[38]

1.10.2 Gastric Emptying Rate:

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive mylo electric cycle or migrating mylo electric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.[39]

1.) Phase I (Basal phase): lasts from 40 to 60 minutes with rare contractions.

2.) Phase II (Pre burst phase): lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3.) Phase III (burst phase): lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4.) Phase IV: lasts for 0 to 5 minutes and occur between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[40]

Major studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

1.11 Introductions on Iron:

Iron is a mineral that can be found in plants, animals, soil, air, water, and rocks.

But iron is also an essential micronutrient. This means that the body does not produce the nutrient; it has to be gotten from food. Micronutrient means that the body only requires tiny amounts of it to function normally. [41]

1.11.1 Dietary Iron:

Iron is present in Diets 10% to 15% Heme iron (from meat) and 85% to 90% Nonheme iron (from meat and plant sources). The bioavailability of iron, which is the amount of iron present in food that is absorbed, is lower for non hemeiron than for heme iron. (Food and Administration 2001)

Nonheme dietary iron requires the acidic environment of the stomach to be solubilized. Absorption of nonheme iron is inhibited when gastric pH is increased and when iron forms insoluble complexes with compounds found in plants, such as phytates and polyphenols. The bioavailability of nonheme iron also will be reduced in the presence of other minerals such as zinc and calcium. The bioavailability of nonheme iron from a mixed diet is decreased twofold by the presence of these inhibitors.

Ascorbic acid (vitamin C) and other organic acids increase nonheme iron absorption. Absorption of heme iron occurs via a mechanism independent of that for nonheme iron. The bioavailability of heme iron is about 25%; that of nonheme iron varies from 10%-5% in a mixed diet . The estimated overall bioavailability of iron from a typical diet is 18%[42].

The estimated average requirement and recommended dietary allowance of iron for adult men and women is summarized in the following table (4) in which:

Table (4) the Estimated Average Requirement and Recommended Dietary Allowance of Iron for Adult Men and Women

	EAR(mg)	**RDA(mg)**	**UL(mg)**
Men, age (year)			
19-30	6	8	45
31-50	6	8	45
50-70	6	8	45
>70	6	8	45
Women			
Nonpregnant			
Non lactating			
Age (year)			
19-30	8.1	18	45
31-50	8.1	18	45
50-70	5	8	45
>70	5	8	45
Pregnant age(years)			
19-30	22	27	45
31-50	22	27	45
Lactating Age(year)			
19-30	6.5	9	45
30-50	6.5	9	45

EAR: means estimated average requirement

RDA: means recommended dietary allowance

UL: means upper tolerable level. [42]

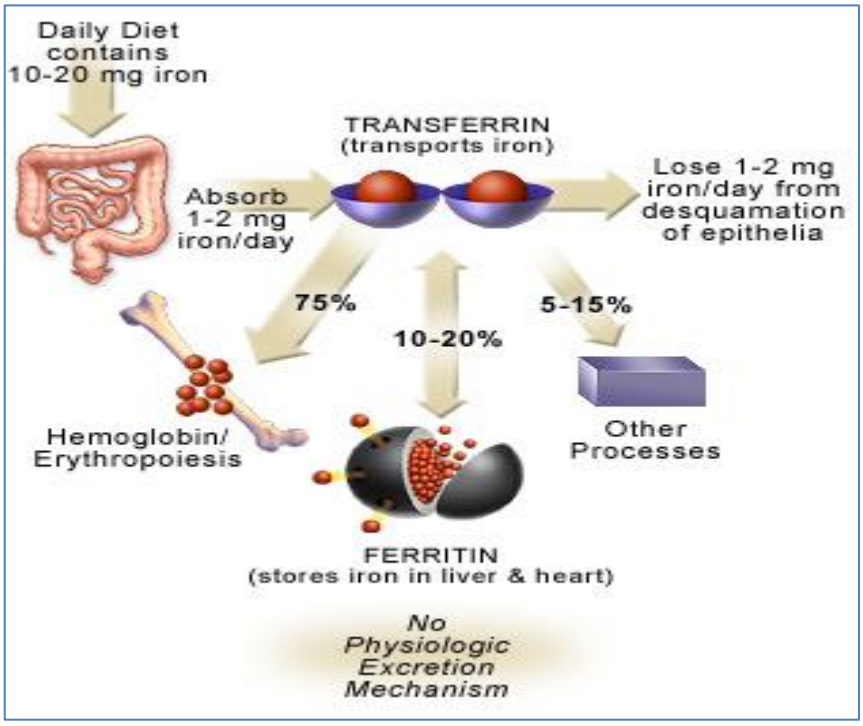
1.11.2 Iron absorption:

The digestive system is set up to maximize absorption; there is no regulation of the amounts of substances absorbed into the body. A notable exception is iron, in which daily dietary absorption is regulated so that it matches daily iron loss.

The reason that absorption must be carefully regulated is that the body does not possess a physiological mechanism for regularly eliminating iron from the body.

Iron plays a dichotomous role in almost all living organisms as it possesses features of both an essential nutrient and a potential toxin [43, 44]. Iron is a central component of vital proteins such as the enzymes involved in deoxy nucleotide synthesis, the citric acid cycle, drug metabolism and mitochondrial electron transport [45]. Among all the iron-containing proteins, hemoglobin, the oxygen transport molecule in circulating red blood cells (RBCs), is the one most abundantly expressed. Consequently, absolute or functional iron deficiency (ID) is associated with insufficient availability of iron for hemoglobin synthesis and thus results in anemia. However, too much iron in the body can be extremely toxic to tissues because it promotes the formation of free radicals[46].

Fig (14) iron absorption and metabolism[47]

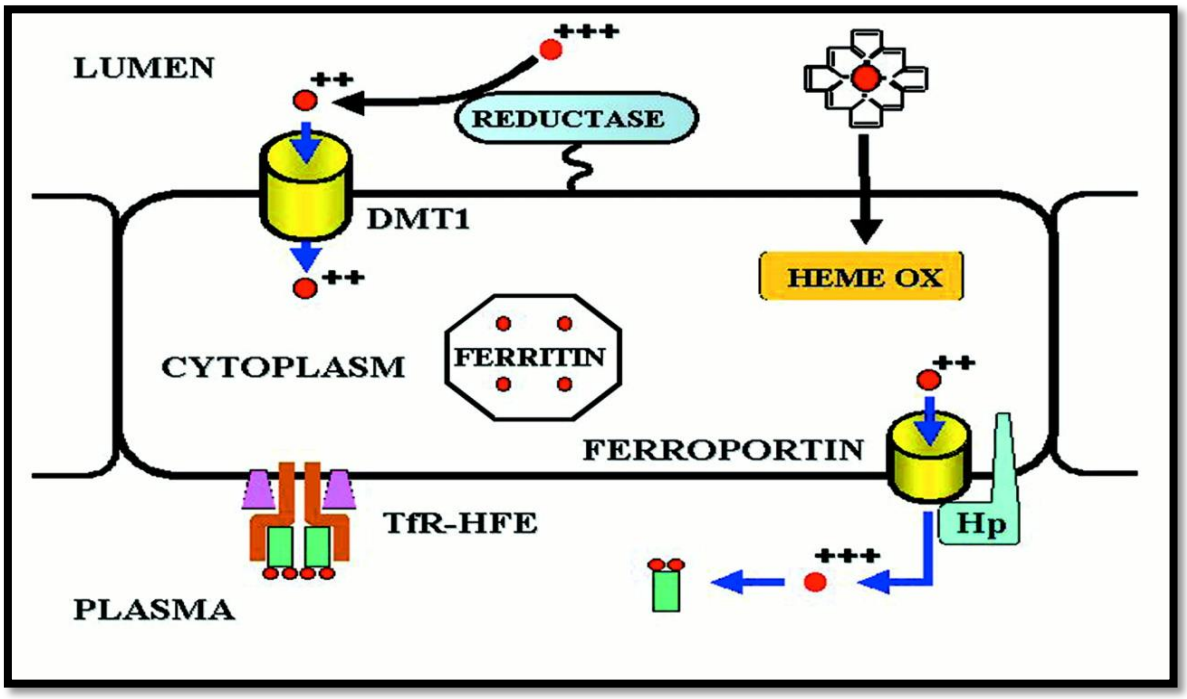


Iron is a trace mineral that plays essential roles in the human system. Two thirds of the iron inside the body is found within hemoglobin which is an iron-containing protein found in red blood cells that carries oxygen[48].The remaining iron is located in myoglobin, which assists in the storage and transport of oxygen within muscles[48]. The remaining iron, a significant portion is stored in the liver, both in the hepatocytes, and in the Kupffer cells (also known as Reticuloendothelial cells), a type of macrophage found in the liver. Kupffer cells play an important role in recycling body iron. They ingest aged red blood cells, liberating iron for reuse by breaking down hemoglobin[46].

There is some controversy even among health professionals regarding "normal" hemoglobin concentrations, but the generally accepted ranges for adults are 12-16 g/dl for women and 13.5 - 18 g/dl for men[49].Anemia is the condition associated with hemoglobin concentrations below the defined normal range. **Because :**All body cells need iron. It is crucial for oxygen transport, energy production, and cellular growth and proliferation. The human body contains an average of 3.5 g of iron (males 4 g, females 3 g). and only about 10% of dietary iron is absorbed (1–2 mg/day) Individuals absorb less than 10% of dietary iron, or 1–2 mg per day balancing the daily loss from desquamation of epithelia .Most absorbed iron is used in bone marrow for Erythropoiesis Iron homeostasis is closely regulated via intestinal absorption. So once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss (i.e., pregnancy, menstruation or other bleeding.).[47]

Hence, maintenance of systemic iron balance requires tight control of intestinal iron absorption since there is apparently no regulated mechanism for hepatic or renal excretion of iron in mammals. Gastrointestinal absorption of iron occurs in the duodenum and proximal jejunum as it shows in figure (15) where this essential nutrient is taken up in two forms: as heme iron from the digestive breakdown of hemoglobin and myoglobin contained in red meat, poultry and fish and as inorganic non-heme iron mainly released from vegetarian food [50]. Approximately 15–35% of dietary heme available in the intestinal lumen is absorbed via HCP1(Heme Carrier Protein 1) and heme is then degraded to ferrous iron, carbon monoxide and the bile pigment biliverdin by HO1 (Heme Oxygenase 1)[51]. Inorganic iron is absorbed by 2–20% of the amount initially ingested with food and occurs in two redox states, its ferric and ferrous forms.

Fig (15) Iron Absorption Mechanism



Where: DMT1 : Divalent metal transporter 1/ HEME OX : Heme oxygenase 1 enzyme /

TFR-HFE: Trans ferrin receptor

Iron is absorbed by villous enterocytes in the proximal duodenum. Efficient absorption requires an acidic environment, and antacids or other conditions that interfere with gastric acid secretion can interfere with iron absorption.

Ferric iron (Fe^{+3}) in the duodenal lumen is reduced to its ferrous form(Fe^{+2}) through the action of a brush border ferri reductase enzyme. Iron is co-transported with a proton into the enterocyte via the divalent metal transporter DMT-1. This transporter is not specific for iron, but also transports many divalent metal ions.

Once inside the enterocyte, iron follows one of two major pathways. Which path is taken depends on a complex programming of the cell based on both dietary and systemic iron loads:

• *Iron abundance states*: iron within the enterocyte is trapped by incorporation into ferritin and hence, not transported into blood. When the enterocyte dies and is shed, this iron is lost. A single ferritin molecule can store up to 4,000 iron atoms. When excess dietary iron is absorbed, the body responds by producing more ferritin to facilitate iron storage.

- *Iron limiting states*: iron is exported out of the enterocyte via a transporter (ferroportin) located in the basolateral membrane. It then binds to the iron-carrier transferrin for transport throughout the body.
- *Iron in the form of heme*, from ingestion of hemoglobin or myoglobin, is also readily absorbed. In this case, it appears that intact heme is taking up by the small intestinal enterocyte by endocytosis. Once inside the enterocyte, iron is liberated and essentially follows the same pathway for export as absorbed inorganic iron. Some heme may be transported intact into the circulation. [52, 53]

1.11.3 Anemia and Iron Deficiency Anemia:

1.11.3.1 Anemia:

Is a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiologic needs which vary by age, sex, smoking, and pregnancy status.

Iron deficiency is thought to be the most common cause of anemia globally, although other conditions, such as folate, vitamin B12 and vitamin A deficiencies, chronic inflammation, parasitic infections, and inherited disorders can all causes anemia. In its severe form, it is associated with fatigue, weakness, dizziness and drowsiness [54].

Iron deficiency anemia is a common type of anemia — a condition in which blood lacks adequate healthy red blood cells. Red blood cells carry oxygen to the body's tissues., Iron deficiency anemia is due to insufficient iron. Without enough iron, the body can't produce enough of a substance in red blood cells that enables them to carry oxygen (hemoglobin). As a result, iron deficiency anemia causes tiredness and short of breath[55].

1.11.3.2 Diagnosis of anemia.

The definition of anemia varies by sex and age. The most commonly used definitions of anemia come from the World Health Organization (WHO) as it shows in table (5)

Table (5) definition of anemia according to hemoglobin level : [56]

Minimum Hemoglobin levels used to define anemia	
Age or sex group	**Hemoglobin (g/dl)**
Children 6 months to 6 years	11
Children 5-11years	11.5
Children 12-13 years	12
Non-pregnant women	12
Pregnant women	11
Men	13
From WHO/UNICEF	

Iron deficiency results when iron demand by the body is not met by iron absorption from the diet.,[57]

1.11.3.3 Causes of Iron Deficiency:

The daily iron requirement for adolescent girls and premenopausal women is approximately 20 mg elemental iron. However, this amount often is not attained because absorption from dietary sources is limited by the absorptive capacity of the intestine [58].

Major causes are:

1-) Pregnancy or Blood Loss Due to Menstruation:

In women of child-bearing age, the most common causes of iron-deficiency anemia are heavy menstrual bleeding or blood loss during childbirth. The CDC found that about nine percent of women ages 12 to 49 years are deficient in iron .[59]

2-) Internal Bleeding:

Including ulcer in the stomach, polyps (tissue growths) in the colon or intestines, or colon cancer. Regular use of pain relievers, such as aspirin, can also cause bleeding in the stomach[60]

3-) Inability to Absorb Iron:

Certain disorders or surgeries that affect the intestines can also interfere with how the body absorbs iron. Celiac disease or an intestinal surgery such as gastric bypass may limit the amount of iron your body can absorb.[60].

1.11.3.4 people at Risk for Iron-Deficiency Anemia[61]

1) Young children who drink a lot of cow's milk may be at risk for iron-deficiency anemia. Milk is low in iron, and too much milk may take the place of iron-rich foods in the diet. Too much milk also may prevent children's bodies from absorbing iron from other food as the calcium is also absorbed by the same receptor.

2) Teens are at risk for iron-deficiency anemia if they're underweight or have chronic (ongoing) illnesses..

3) Women of childbearing age are at higher risk for iron-deficiency anemia because of blood loss during their monthly periods. About 1 in 5 women of childbearing age has iron-deficiency anemia. [61]

Pregnant women also are at higher risk for the condition because they need twice as much iron as usual. The extra iron is needed for increased blood volume and for the fetus' growth.

About half of all pregnant women develop iron-deficiency anemia. [61]

4) Adults who have internal bleeding, such as intestinal bleeding, can develop iron-deficiency anemia due to blood loss. Certain conditions, such as colon cancer and bleeding ulcers, can cause blood loss. Some medicines, such as aspirin, also can cause internal bleeding.

5) People who get kidney dialysis treatment may develop iron-deficiency anemia. This is because blood is lost during dialysis.

6) People who have gastric bypass surgery also may develop iron-deficiency anemia. This type of surgery can prevent the body from absorbing enough iron.

1.11.3.5 Signs and Symptoms of Anemia

The most common symptom of all types of anemia is fatigue (tiredness). Fatigue occurs because the body doesn't have enough red blood cells to carry oxygen to its parts. Anemia also can cause shortness of breath, dizziness, headache, coldness in your hands and feet, pale skin, chest pain, weakness, and fatigue (tiredness).Low limits of hemoglobin-carrying red blood cells, can lead to irregular heartbeat called arrhythmias, a heart murmur, an enlarged heart, or even heart failure. In infants and young children, signs of anemia include poor appetite, slowed growth and development, and behavioral problems.[61]

1.11.3.6 Signs and Symptoms of Iron Deficiency.

Signs and symptoms of iron deficiency may include brittle nails, swelling or soreness of the tongue, cracks in the sides of the mouth, an enlarged spleen, and frequent infections.

People who have iron-deficiency anemia may have an unusual craving for nonfood items, such as ice, dirt, paint, or starch. This craving is called pica (PI-ka or PE-ka).

Some people who have iron-deficiency anemia develop restless legs syndrome (RLS). RLS is a disorder that causes a strong urge to move the legs. This urge to move often occurs with strange and unpleasant feelings in the legs. People who have RLS often have a hard time sleeping.

Iron-deficiency anemia can put children at greater risk for infections. Some signs and symptoms of iron-deficiency anemia are related to the condition's causes. For example, a sign of intestinal bleeding is bright red blood in the stools or black, tarry-looking stools. Very heavy menstrual bleeding, long periods, or other vaginal bleeding may suggest that a woman is at risk for iron-deficiency anemia[61]

Table (6) summarizing the signs and symptoms of iron deficiency anemia :[62]

Common symptoms	Rare symptoms
Fatigue	Pica
Headache	Glossitis
Exertional dyspnea	Koilonychias (spoon nail)
Difficulty concentrating	Dysphagia (difficulty swallowing)

1.11.3.7 Tests that used to Diagnose Iron Deficiency Anemia:

- A complete blood count (CBC), to look at the shape, color, number, and size of your blood cells.
- Iron tests, which measure the amount of iron in your blood.
- A reticulocyte count, to see how well treatment is working. Reticulocytes are immature red blood cells produced by the bone marrow and released into the bloodstream. When reticulocyte counts increase, it usually means that iron replacement treatment is effective.
- A ferritin level test, which reflects how much iron may be stored in the body.[63]

1.11.3.8 Treatment of Iron Deficiency Anemia :

Medical care starts with establishing the diagnosis and reason for the iron deficiency. In most patients, the iron deficiency should be treated with oral iron therapy, and the underlying etiology should be corrected so the deficiency does not recur[64]If the anemia is caused by a disease or condition such as bleeding in the stomach, so one must take steps to treat the problem. If not having enough iron in the diet or not being able to absorb iron, one must develop a plan to increase iron level up take .[63]

So Treatments may include dietary changes and supplements, medicines, and surgery. Severe iron-deficiency anemia may require a blood transfusion, iron injections, or intravenous (IV) iron therapy[63].

Most people will start to feel better within a few days of beginning the treatment. Even though they will need to keep taking the pills for several months to build up the iron stores. Sometimes it takes up to 6 months of treatment with iron supplements before iron levels return to normal.[63].

For the treatment of iron deficiency anemia, current guidelines recommend the dose of 60 to 120mg of elemental iron of ferrous sulphate per day for a minimum duration of 3 months in adolescents and adults.[65, 66]

1.11.3.9 Types of iron salts that used in iron supplement:

There are two main iron salts forms (ferric and ferrous irons) and numerous formulation(amino-acid chelates, carbonyl iron, polysaccharide-iron complex, combination products, extended-release products, sulfate, gluconate , etc) All dietary iron have to be reduced to the ferrous form to enter the mucosal cells; therefore ferrous iron is absorbed three times more readily than the ferric form[67]

Several iron salts are available in tablet or liquid form for oral ingestion, as listed in Table (7)... Ferrous sulfate, which supplies 65 mg of elemental iron per 200 mg tablet, is the most widely used oral iron preparation.[68]

Table (7) available oral and parenteral iron preparations: **[68]**

Oral preparations	**Intravenous preparations**	**Intramuscular preparations**
Ferrous sulfate $FeSO_4$	Iron dextran(FeH_2O_4S)	Iron sorbitol citrate
Ferrous fumarate ($C_4H_2FeO_4$)	Iron dextrin	
Ferrous gluconate($C_{12}H_{22}FeO_{14}$)	Iron hydroxyl saccharate	
Ferrous succinate (C4H4FeO4)	Iron sodium gluconate	
Iron polymaltose		
Polysaccharide iron complex		
*this list is not exhaustive: other oral and parenteral iron preparations may be available.		

Most of these preparations vary in the bioavailability, efficacy, side-effects, and cost. The iron-containing preparations available on the market vary widely in dosage, salt, and chemical state of iron (ferrous or ferric form) contained in the preparation[65] as shown in table (8)

However, in clinical practice bivalent iron salts such as Ferrous Sulfate , ferrous gluconate, and ferrous fumarate are more widely used and are preferred over ferric iron preparations [69],

The bivalent iron salts preparations usually present good bioavailability (between 10 and 15%), while bioavailability of iron ferric preparations is(3 to 4 %)[70]. This is due to the extremely poor solubility of ferric iron in alkaline media and the fact that ferric iron needs to be transformed into ferrous iron before being absorbed into the enterocyte by the transporter DMT-1among ferrous preparations, Ferrous Sulfate, remains the established treatment of iron deficiency. (Santiago 2012)

Table (8) differences between bivalent and trivalent oral iron preparation. **(Santiago 2012)**

Iron supplement	Comments
Bivalent Ferrous fumarate (Fe2+) ferrousgluconate (Fe 2+) Ferrous sulphate (Fe2+) Ferrous glycine sulphate(Fe2+)	More adverse effects if not in a prolonged-release formulation.
Trivalent Iron protein succinylate (Fe3+) Iron polymaltose complex (Fe3+)	Poorer absorption. More expensive. A greater number of intake

The Side Effects of Iron Therapy: Is a common problem in the treatment of patients with iron deficiency. Gastrointestinal disturbances such as nausea, heartburn, pain, constipation, and diarrhea are the most commonly reported side effects, irrespective of the type of iron preparation. This occasional intolerance is usually viewed as a limiting factor for oral iron therapy, as it may impact patient compliance. The incidence of the gastrointestinal side effects seems to be generally associated with the use of unnecessary high doses of iron as reported [71, 72] .

Incidence of gastrointestinal side effects has been shown to be lower with controlled-release iron formulations compared to conventional ferrous salt preparations in three large controlled randomized studies[73-75]

Table (9) A Chart Summarizing the Iron Supplement Product Marketed in Palestine.

Brand name	Company	Active ingredients
Jefrol –R (tab)	Jerusalem	Ferrous sulphate +Folic acid
Jefrol –V (tab)	Jerusalem	Ferrous gluconate+ Folic acid+BcomlexVit +Nicotinamide+Ca-Pantothenate
Ferriton -3 (syrup+drops)	Jerusalem	Iron(III)hydroxide polymaltose complex
Ferriple -3 (syrup+drops)	C T S company	Iron(III)hydroxide polymaltose complex
Fergole (tab)	Bier zaiet company	Ferrous fumarate +folic acid
Ferric pregnancy(tab)	Meditec	Ferrous iron +folic acid
Super Iron (tab)	Dana med	Iron Fumrate +Vit B12+ folic acid +Vit C
Ferro grad folic (tab)	Abbott	Ferrous Sulphate dried +folic acid
Ferro more (tab)	National company	Ferrus bisglycenate
IRON 35(tab)	Jamieson	Ferrous gluconate
Ferro med plus (tab)	Catlant	Iron sulphate +folic acid +Iodine +Zn + Vit B6+Fish oil
Ferro green (tab)	Hadas	Iron bisglycinate +Vit B12+ folic acid

1.12 Iron deficiency anemia in Palestine:

According to the Palestinian Ministry of Health in its annual health report 2014 there is significant percent of pregnant and postnatal Palestinian women who attained to the ministry of health clinics in the west bank suffering mild and sever iron deficiency anemia according to this table (10)and postnatal table(11)

Table(10) Distribution of Anemia Percentage between Pregnant Beneficiaries in MCH Centers by Type and District, West Bank, Palestine**,** 2014[76]

Less 7gm/ dl	%Severe Anemia	7-9gm./ dl	% Moderate Anemia	11-9gm./ dl	% Mild Anemia	Number of Anemia	%of Anemia	NumberMore11 gm/dl	Total
2	0.0%	237	0.9%	6386	24.7%	6625	25.6%	19869	25894

Table (11) Distribution of Anemia Percentage of Postnatal Beneficiaries of MCH Centers by Type and District, West Bank, Palestine, 2014[76]

Less 7gm/ dl	%Severe Anemia	7-9gm./ dl	% Moderate Anemia	11-9gm./ dl	%Mild Anemia	Number of Anemia	%of Anemia	Number More11gm/dl	Total
29	0.1%	569	1.4%	8395	21.1%	8993	22.6%	30714	39707

So as we conclude from the two table that significant persent of pregnant and post partnatal women(which are amjor groub at risk suffering iron defcincy anemia) , about 26% of pregnant women attanding to MOH cliniecs are suffring mild anemai and about 23% of post natal women attanding to the MOH cilinecs also suffers mild anemai

1.13 Back ground on ferrous gluconate:

Chemical Names: Ferrous Gluconate; Iron(II) gluconate dihydrate; Iron(II) D-gluconate dihydrate; Ferrous gluconate **[**USP];[77]

Molecular Formula:$C_{12}H_{26}FeO_{16}$

CAS NO **299-29-6**

Formula weight 482.17

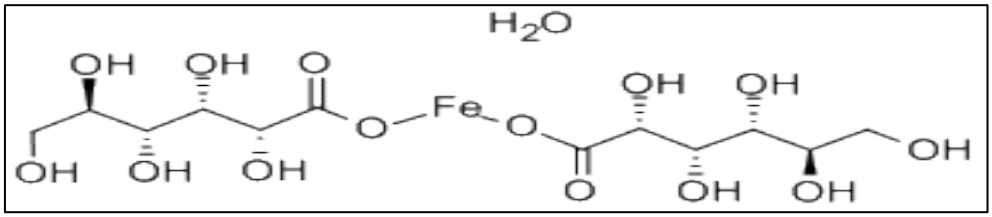
Assay 97-102% Not less than 95% on the dried basis

PH 7.0-8.5 (10% sol)

Description: Fine yellowish-grey or pale greenish-yellow powder or granules having a slight odour resembling that of burnt sugar

Functional uses : Colour, stabilizer, nutrient supplement.

[78]



1.13.1 Chemical and Physical Properties:[77]

Melting Point:188°C

Boiling Point:673.6 oC at 760 mmHg

Vapour:4.95E-21mmHg at 25°C

Flash Point:673.6 oC at 760 mmHg

Solubilities: Soluble with slight heating in water; practically insoluble in ethanol[78]Soluble in glycerin[79]

Solubility increase by adding Citric acidorCitrate Ions[80]1 gram dissolves in about 10 ml of water with slight heating and in 1.3 ml of water at 100 deg C. It forms supersaturated solutions which are stable for a period of time[81]

Color/Form: The color of /ferrous gluconate/ solution depends on pH; they are light yellow at pH 2, brown at pH 4.5, and green at pH 7. The iron rapidly oxidizes at higher pH.[81]

Stability:

Aqueous solutions are stabilized by the addition of glucose[82].

Approximetely neutral solutions undergo rapid oxidationOxidation retarded and stability improved by buffering to pH of 3.5 to 4.5 with citrate buffer[80]

Decomposition: When heated to decomposition it emits acrid smoke and irritating fumes[83]

Pharmacological Classification:

Hematinics: Agents which improve the quality of the blood, increasing the hemoglobin level and the number of erythrocytes. They are used in the treatment of anemia's [77]

Absorption:

Gastrointestinal absorption of iron is adequate and essentially equal from ferrous, sulfate, fumarate, gluconate, succinate, glutamate, and lactate.[84] iron bioavailability is about 18%

Methods of Manufacturing:

Prepared from barium gluconate and iron sulfate[82] and also by metathesis between hot solution of calcium gluconate and ferrous sulfate... . It may also be produced by heating ... ferrous carbonate with proper quantity of gluconic acid in aqeous solution/Dihydrate.[80]

Formulations/Preparations:

Capsules 435 mg (equivalent to 50 mg of elemental iron); Elixir 300 mg (equivalent to 37.5 mg of elemental iron)/5 mL; Tablets 320 mg (equivalent to 40 mg of elemental iron).[85]

Part 2

Problem statement

Literature review

Objectives

2.1 Problem Statements:

According to the World Health Organization(WHO), iron deficiency is the most common form of malnutrition in the world, affecting around 2 billion people worldwide, which corresponds to 25% of the population globally.[86].

According to annual Palestinian health report 2014(MOH) the percent of pregnant women attending to the ministry of health clinics in the west bank suffering mild iron deficiency anemia is 24.7% . and postnatal women attending ministry of health clinics in the west bank suffering mild iron deficiency anemia is 22.6% [76].

In the Palestinian market, the iron supplements are available in different pharmaceutical dosage forms such as tablet, syrup, injection.atc these dosage forms are developed by using different salts of iron (sulphate, fumerat, polysaccharides complex sugar, gluconateets.). , iron deficiency anemia is still the main malnutrition in the developing and developed country. This raises and important research question to investigate the reason of these phenomena.

Oral iron preparations may cause nausea, vomiting, dyspepsia, constipation, diarrhea or dark stools. All these side effects are a result of excess release of ferrous from the tablet and the inability of receptor to uptake all released iron from the stomach and upper part of the intestine, hence when ferrous iron reach the high PH intestine the iron change from Fe^{+2} to Fe^{+3} which poorly absorbed by intestine causing the side effect as stool discoloration and constipation and other side effects ,accordingly: Ineffectiveness of the present formulation of ferrous salts supplements (poor absorption equals poor bioavailability).and the discontinuation of treatment because of major GI disturbance. Are two major causes for not eradicate iron deficiency anemia problem .

To overcome this problem there are many techniques to use and formulate iron tablets with good iron absorption and bioavailability, i.e.

1- A change to another iron salt may also be beneficial; ferrous gluconate and ferrous fumarate are less irritating than ferrous sulfate.

Therapeutically there is no difference between ferrous sulfate and ferrous gluconate as both salts of irons are prescribed for the treatment of anima. There is slight difference between these two as ferrous sulfate is inorganic supplement and ferrous gluconate is organic

supplement. The rate of absorption of organic supplements is more in comparison to the inorganic supplements so large amount of ferrous sulfate is required to get desired effects. In addition Some patients better tolerate ferrous gluconate than ferrous sulfate[87],

2- Controlling the gastric emptying time of the iron tablet from the stomach that is the absorption window for the iron. By increasing the duration of drug retention in the stomach, increase the chance of drug absorbance and its bioavailability through providing more contact time and absorption area [88] This property can be made by mean of Gastroretentive drug delivery system.

In this study we use effervescent floating drug delivery system. Where carbon dioxide is released when exposed to acidic stomach contents and trapped within the swollen hydro-colloid polymer causing it to float and consequently increasing gastric retention time [89].

3- formulate a sustained release iron tablet by using special Swelling agent/Gel forming polymer as Hydroxy propyl methyl cellulose (HPMC) that is frequantlly used in the controlled release solid dosage formulations, HPMC also forms a gelatinous layer upon hydration in gastric fluid[15] that controls the release of iron from the tablet whish help in gradual release of the iron in a manner helping the synchronies to its absorption by divalent metal receptors located in the wall of the stomach and upper part of the intestine, in this way the saturation of receptor and the loss of the excess iron in the stool are prevented .

In our formulation we gathered all these techniques in one ferrous gluconate effervescent floating Gastroretentive sustained drug delivery system.

2.2Literature review:

Seth and Tossounian were the first to propose a simple and effective hydrodynamically balanced system (HBS) in 1975 ,[90]they used a large quantities of HPMC and fatty materials to regulate flotation and drug release ,and have a bulk density lower than gastric fluid . The inventors claimed that these floating systems remain in buoyant state upon the stomach content for a prolonged period of time and they recommended in using these system when aiming to enhance the gastrointestinal transit time or to obtain a sustained local action in specific site of absorption in the stomach and intestine [91]

This dosage form has been marketed by Hoffman La-Roche for sustained release form of Diazepam as (Valerlease) and for sustain release of combination of L-dopa and Benserazide (Modapar) .[92]

As a result of these novel HBS systems many research field and various other floating drug delivery system and formulation was proposed for achieving the same result. Researchers specialized in formulation aspect e.g. Banker, et al,1975/Watanabe .et al,1976/ Seth & Tossounian,et al,1978,1979/Balton& Desai et al, 1986 and many others and Researchers specialized in the in vivo investigation on human volunteers e.g. Bechgaard&Ladeforged et al,1978/Seth &Tossounian et al ,1984/ Davis et al 1986/Timmermans et al 1989 and many other researchers [91].

All these studies and investigation helped to get a better idea about the GRDDS:

1- The best drug candidate to be used in these systems.
2- Types of GRDDS.
3- Best physiological condition of the stomach for these system
4- Dosage form characteristic.
5- The bulk density of the tablet and floating duration time are the main parameter to describe the effectiveness of the GRDDS.

From these findings, we can conclude that iron is a good candidate as floating drug delivery system and knowing that the drug(iron) which is soluble in acidic media and absorbed in specific window of absorption in the stomach and upper part of the intestine which means it requires to increase gastric retention time allowing the maximum absorption of the drug(iron) and controlling the rate of the release .

Bothwell TH, Charlton RW, Cook J:(1979) in their book demonstrated various pharmaceutical preparations(sustained release formulation) that are designed to minimize the peak concentration of iron in the gastrointestinal lumen by slowing its dissolution rate . And Side-effects consequently will be reduced significantly , but this may be due to a reduction in the amount of absorbed iron. Indeed the efficacy of these preparations cannot be evaluated reliably unless absorption and side effects are examined together. The use of delayed-release preparations has been criticized because of its reduced extent of absorption and increased cost.[93]

James at.al.(1990) had formulated an iron gastric delivery system (GDS) containing hydroxypropyl methylcellulose(HPMC), hydrogenated vegetable oil, crospovidone, microcrystalline cellulose, xanthan gum, talcum powder, magnesium stearate, and colloidal silicone dioxide(P. R. Sheth, J. Tossounian, US patent 4126 672) [94] to which ferrous sulphate is added .When the capsule containing the above ingredients is placed in aqueous solution, the gelatin coating dissolves but the matrix remains intact. Buoyancy is made by the hydrocolloids which form a hydrated boundary layer that impedes the entry of water into the core of (GDS) it retained in the stomach for 5-12 h.

They conducted a study on 9 volunteers given a GDS containing 50 mg elementary iron once daily versus other group was given ferrous sulphate elixir with 50 mg elementary iron 3 times a day .They found a three to four-fold higher absorption from GDS iron compared with ferrous sulphate elixir.

In a double blinded study on 200 women (18-48 year) giving one group GDS tablet (50 mg elementary iron) once a day vs. placebo and a group given 3 time conventional iron sulphate (50 mg elementary iron) vs. placebo to study the gastric side effect. It was found that the conventional preparation was associated with a significantly higher frequency of nausea and anorexia, whereas there were no significant differences in reported side-effects between subjects receiving GDS or placebo. A single GDS capsule daily provides the same amount of absorbed iron as conventional ferrous sulphate given three times daily, and does not produce gastrointestinal side-effects.[95]

Simmon et.al:(1993) studied the efficacy of oral iron supplementation during pregnancy by using a gastric delivery system (GDS) 376 pregnant women (16-35year) suffering mild

anemia was selected in the study and divided into 3 groups the first group was given a placebo the second group was given 2 tablets of ferrous sulphate conventional tablet (100 mg elementary iron) The third group was given 1 tablet of the GDS of ferrous sulphate(50mg elementary iron).There was a significant and comparable improvement in hematologic and iron-status measurements in the two groups of women given iron whereas iron deficiency evolved in women given no iron supplement. They conclude that by eliminating gastrointestinal side effects and reducing the administration frequency of an iron supplement to once daily, a GDS offers significant advantages for iron supplementation of pregnant women. [96].

BahriNajafi et al : (2012) formulated Effervescent gastro retentive tablets of ferrous sulfate plus ascorbic acid. Tablets containing HPMC K4M and Carbopol as retarding polymers showed desirable in-vitro properties. The optimized formulation released the drug in a Higuchi-order fashion and demonstrated a short buoyancy lag time, total floating time of at least 18 h and could maintain drug release for 12 h. Based on pharmacokinetic parameters, once-daily administration of this new formulation can be a suitable alternative formulation compared to common forms of iron available in the market.[97].

Conviron ®: manufactured by Ranbaxy Laboratories Ltd/ INDIA is a Colloidal gel forming FDDS containing Ferrous Sulphate. And marketed in two formulations :

Conviron-TR ® contains :

Dried ferrous sulphate (TR) 60 mg
Folic acid 1.5 mg,
Ascorbic acid 75 mg,
Pyridoxine hydrochloride 1.5 mg,
Cyanocobalamin 15 mcg.

Conviron –Fort®: contains the same active pharmaceutical ingredients as Conviron-TR ® in addition to Folic Acid 15 mg and Zinc 15 mg.

This product is Prescribed For the treatment of anemia, but not recommended for pregnant or lactating women [98]

As a Conclusion: few studies were conducted using the formulation of sustained or Gastroretentive dosage forms of iron. All studies used ferrous sulphate as the active ingredient . Moreover, all studies focused on decreasing its side effects formulating it as a sustained release tablets without presenting a clear enhancement in the absorption of iron

2.3 Main Objective of the Study:

The main objective for this study is to formulate an effervescent floating sustained release tablets containing 150 mg ferrous gluconate and 10 mg of ascorbic acid (vitamin C) as absorption aid , the tablets were presumed to remain floating in the stomach for sufficient period of time to facilitate better absorption of iron in the stomach and upper part of the intestine .

2.4 The Specific Objectives of the Study are:

1-To formulate 150mg ferrous gluconateas floating gastro retentive delivery tablets which provide a sustained release of iron by choosing appropriate prototypes and amounts of polymers and by following either wet granulation or direct compression manufacturing methods.

2- To study the floating behavior, floating lag time and floating time.

3- To develop a suitable assay, suitable method of analysis for the ferrous gluconate tablet.

4- To Conduct an in vitro release study for the tablet and study the kinetics of the release.

6- To conduct quality control tests for the powder (pre formulation QT) and for the tablet (post formulation QT).

7- To study the accelerating stability studies of ferrous gluconate tablets for one and three month.

2.5 Advantage of Floating Gastric Retentive Drug System:[18]

The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior

Floating drug delivery systems have many advantages as listed below::

1) The principle of HBS can be used for any particular medicament or class of medicament

2) The HBS formulations are not restricted to medications which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medications which are absorbed from the intestine e.g. Chlorpheniramine maleate.

3) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

4) The efficacy of the medications which administered using the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments

5) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug will be available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine

6) When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

7) Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

8) Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate

Methods for preparing floating dosage form;

The Following approaches can be used for preparing floating dosage form:

1) Using gel forming hydrocolloids such as hydrophilic gums, gelatin, alginates, cellulose derivatives, etc.

(2) Using low density enteric materials such as methacrylic polymer, cellulose acetate phthalate.

(3) By reducing particle size and filling it in a capsule.

(4) By forming carbon dioxide gas and subsequent entrapment of it in the gel network

(5) By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.

(6) By incorporation of inflatable chamber which contained in a liquid e.g. solvent that gasifies at body temperature to cause the chambers to inflate in the stomach .

The factors which govern the effectiveness of active medicaments in HBS are :

1) Amounts of active ingredient to produce therapeutic effect.

2) Bulk density.

3) Hydrophilic and hydrophobic properties.

4) Stability in gastric fluids.

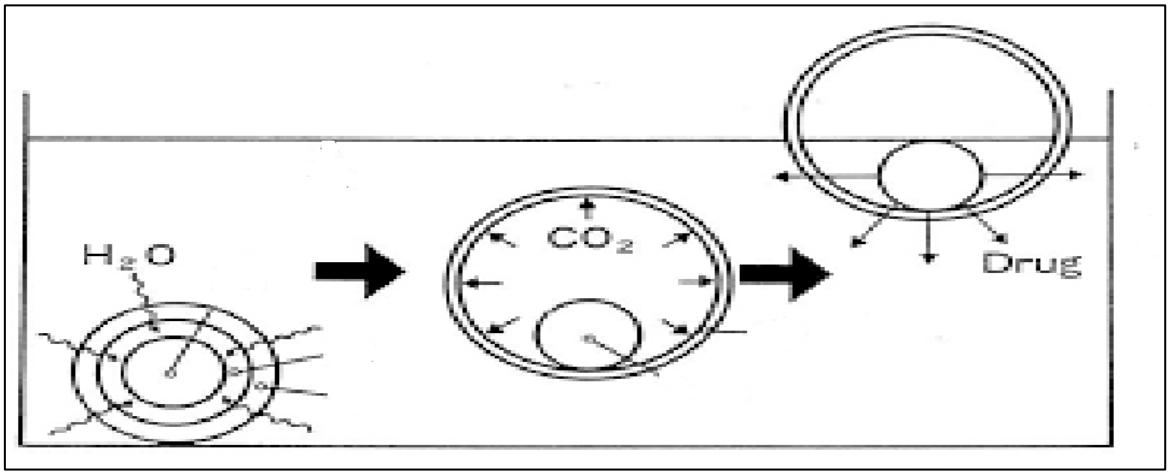
Stages of floating mechanism as it shows in figure (16):(Shaha, Patel et al. 2009)

(A) Penetration of water;

(B) Generation of CO2 and floating;

(C) Dissolution of drug. As it shows in the Figure (16)

Fig (16) stages of floating mechanism in FDDS



2.6 Why ferrous gluconate used in our study?

The standard preparation used in the oral management of iron deficiency anemia is ferrous sulfate. Other salts, such as ferrous gluconate and ferrous fumarate, are as effective as ferrous sulfate when administered in equivalent amounts of elemental iron[99].

Calculation of dosage for iron preparations should always be based on the amount of elemental iron to be administered. Ferrous sulfate salt contains 20% of elemental iron, ferrous gluconate contains ~12% and ferrous fumarate contains 33%. ,[99]

Oral iron preparations may cause nausea, vomiting, dyspepsia, constipation, diarrhea or dark stools, Pill-induced esophageal injury (Ferrous sulfate may injure the esophageal mucosa because it produces an acidic solution once it is dissolved (pH <3). These effects are generally dose-related and, with the exception of dark stools, usually subside with continued therapy.[99].

To minimize the intolerance,

Lower doses may be administered initially: not very effective..The medication may be given with or after meals. But this will reduce the bioavailability of iron absorption as the

PH will raise and reduce the formation of Fe^{+3}into Fe^{+2} that is the required form of iron to be absorbed by the transporter. A change to another iron salt may also be beneficial; ferrous gluconate and ferrous fumarate are less irritating than ferrous sulfate

Therapeutically there is slight difference between ferrous sulfate and ferrous gluconate as both forms of irons are prescribed for the treatment of anima.

The slight difference between these two is as ferrous sulfate is inorganic supplement and ferrous gluconate is organic supplement.

The rate of absorption of organic supplements is more in comparison with inorganic supplements so large amount of ferrous sulfate is required to get desired effects. Some patients can better tolerate ferrous gluconate than ferrous sulfate[87].

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Part 3

Materials and Methods

Materials and Methods:

3.1 Materials and Reagents:

All materials used in the formulations of ferrous gluconate FDDS are of pharmacopeia grade , the materials and reagents used are the ferrous gluconate powder and the reagent 1,10-O-phenanthroline were donated by Jerusalem pharmaceuticals Company.

HPMC K4M, HPMCK15M, HPMCK 100 M , sodium carbonate ,microcrystalline cellulose, starch, ethylcellulose , Mg stearate, Vit C (ascorbic acid), Polyvinylpyrrolidone K30, Iso Propyl Alcohol Stearic acid were donated from Bir Zeit Medical Company .

3.2 Tools and Equipment:

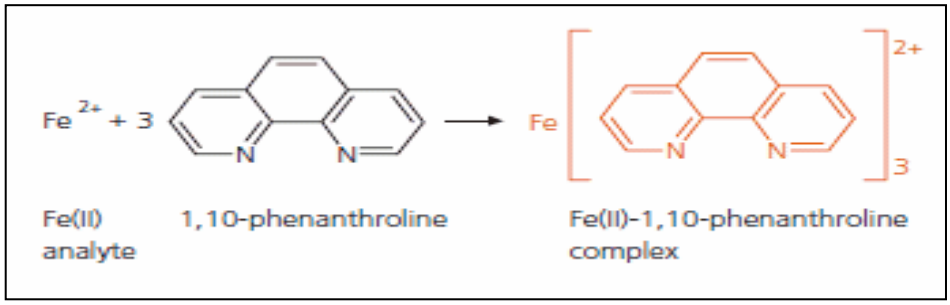
Table (12) list of the tools and equipments used in the study:

Equipment/Apparatus	Source/Model	Pharmaceuticals supplied by
Dissolution apparatus	Electrolab– India	Jerusalem Company
Rotary tablet Press	Pharmachine– China	Jerusalem Company
HMLHT-2 Tablet Hardness apparatus.	**Pharmachine– China**	Jerusalem Company
Copley fribilator Friability apparatus	Copley scientific – UK	Jerusalem Company
Mixer machine	Erweka AR402Heusenstamm lab	Alquds University
Tray Oven	Heraeus Oven /Kendro lab product	Alquds University
Walk In Humidity Chamber Incubator 30/65	Parameter Generation & Control (PGC) –US	Jerusalem Company
Firlabo Incubator 40/75	Firlabo– France	Jerusalem Company
pH meter	Metrohm	Jerusalem Company
UV-Visible spectro- photometer	Merch Hitadi U290, UV.visible spectrophotometer	Jerusalem Company

3.3 Spectrophotometric Determination of Iron:

The **Ferroin Reaction** which involves the formation of a red complex of ferrous iron with certain heterocyclic nitrogen compounds has been extensively used for the colorimetric determination of small quantities of iron.[100]

Iron in its ferrous state reacts with the complexing agent 1,10- Phenanthroline as shown below:



Ferrous ions (Fe^{2+}) can readily be air-oxidized to the ferric state , Fe^{3+} . To determine the total iron in the sample ,a mild reducing agent is added before the color is developed . Hydroxyl amine hydrochloride salt is used for this purpose .[101]

The possibly oxidized Fe^{3+} ions are reduced to ferrous ions according to the reaction.

$$2Fe^{3+} + 2NH_2OH.HCl + 2\ OH^- \leftrightarrow 2\ Fe^{2+} + N_2 + 4\ H_2O + H^+ + Cl^-$$

A red–orange complex ion is formed which is an indication that ferrous 1-10-phenanthroline complex is formed which is then measured by the UV visible Spectrophotometer at 510 wave length.

Taking benefits from this complexing reaction we conducted a Drug Release Study for ferrous gluconate. For this purpose a standard calibration curve was created.

To create the calibration curve stock solution of 0.1 N was prepared by dissolving ferrous gluconate in 25 ml 0.1 N sulfuric acid then dilute with distilled water a series of solutions with different concentrations were made as illustrated in table (13) .

Table (13) standard solutions preparation for calibration curve

Test-tube #	**Volume taken from the stock solution**	**Final volumes (ml)**
1	.05 ml	Up to 10 ml
2	0.1 ml	Up to 10 ml
3	0.5 ml	Up to 10 ml
4	1.0 ml	Up to 10 ml
5	2.0 ml	Up to 10 ml

Then take 5 ml from each test tube in table (13) add to it 5 ml from 1,10-phenanthroline and 1 ml hydroxyl amine (HA) and dilute it with distilled water up to 25 ml in a volumetric flask then measure the absorbance by the UV-Spectrophotometer at 510 nm .

3.4 Preparation of effervescent floating tablets:

Wet granulation and direct compression were used to prepare the tablets.

3.4.1 Wet Granulation Method:

The compositions of the tablets are listed in table (14).All powders except Mg stearate were mixed in(Ereweka mixer) at 100 rpm for 5 minutes. All the powder were passed through sieve no. 40, then the mix was put in a mortar and the wetting agent that was prepared earlier was added gradually to the mix .The granules were prepared manually by adding a solution of calculated quantity of PVP K30 in sufficient solvent (Isopropyl Alcohol (10 % PVP K30)). The wet mass is then passed through a mesh#20. Then dried by using oven (Heraeus Oven) for 30mins at 50 C° .the dried granules were passed through sieve with mesh # 20 ,then mix for 5 min finally the lubrication Mg stearate was add and mixed for 3 minutes then the mixed granules were compressed by a(Rotary tablet press) by Scored Circular Falt- 12 mm diameter punch ..

The compressed tablets were kept in airtight container for further study.

The amount of the ingredients in these various formulations was selected on the basis of formulation by trial . Gradual increase or decrease was conducted on one ingredient at a time to obtain the best results in floating behavior.

Table (14) summary of formula used in wet granulation method

Formula B.N(quantities in mg/tablet)							
Component	**Function**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Fe gluconate	Active ingredient	150	150	150	150	150	150
HPMC100	Swelling agent Gel forming agent	264	240	*****	****	****	*****
HPMCK4	Swelling agent Gel forming agent	****	*****	*****	240	240	240
HPMC K15	Swelling agent Gel forming agent	*****	*****	240	*****	****	****
Citric acid	Acidulent	10	10	10	10	10	10
Na HCO_3	Gas forming agent	40	40	40	40	50	34
Ethyl cellulose	Floating enhancer	*****	24	24	24	14	30
PVPK30	Binder	10	10	10	10	10	10
Vit C	Anti-oxidant and absorption enhancer	14	14	14	14	14	14
Mg.stearate	Lubricant	5	5	5	5	5	5
tablet weight		483mg	483mg	483mg	483mg	483mg	483mg
the total weight of the tablets doesn't include the Mg stearate weight							

3.4.2 Direct Compression Method:

The ingredient that were used are shown in table (15) , The tablets were prepared by first passing the powder through mesh #40 then mixing all except Mg stearate in(Ereweka mixer) for 5 min at 100 rpm then add the Mg stearate (lubricant) was added and mix for 5

min . The powder blend was compressed by using a (Rotary tablet press))by Scored Circular Falt- 12 mm diameter bunch, .All compressed tablets were kept in airtight container for further study.

Table (15) summary of formulas used in direct compression method

Component	Function	Formula B.N (quantities in mg/tablets)						
		H1	H2	H3	H4	H5	H6	H7
Fe gluconate	Active ingredient	150	150	150	150	150	150	150
HPMC100	Swelling agent Gel forming polymer	****	****	****	240	240	240	240
HPMCK4	Swelling agent Gel forming polymer	****	240	*****	****	****	*****	****
HPMC K15	Swelling agent Gel forming polymer	*****	*****	240	*****	****	****	*****
Citric acid	Acidulent	10	10	10	****	****	*****	10
Na HCO3	Gas forming agent	40	40	40	40	40	50	40
Ethyl cellulose	Floating enhancer	244	24	24	24	34	24	24
Vit C	Anti-oxidant and absorption enhancer	14	14	14	14	14	14	14
Mg.stearate	Lubricant	5	5	5	5	5	5	5
Starch	disintegrator	****	****	****	10	****	*****	****
MCC	Disintegrator	20	****	****	****	****	****	****
tablet weight		483mg	483mg	483mg	483mg	483mg	483mg	483

3.5 Quality Control Tests of tablets:

In vitro evaluation of floating tablets was performed to assess the physicochemical properties and release characteristics of the developed formulations

3.5.1 Pre-compression parameter:

a) Angle of Repose:[102]

The angle of repose of a powder bed is the maximum angle that allows a heap of powder to remain stable without failing. It is measured by putting 20 gm. of the powder as a single heap on a flat surface (a glass surface 30 cmX 30 cm), then raising the surface to the point at which the powder heap starts to fall apart (powder starts to flow). At this point the angle made between the flat surface and ground surface is measured as the angle of repose

Table (16) the relationship between Angle of repose and powder flow is as follows in

Angle of repose	**Powder flow**
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b) Compressibility Index: **[103]**

The compressibility index has become the simple and fast method of predicting powder flow characteristics .

The compressibility index is determined by measuring both bulk volume (unsettled apparant volume $V_\circ$) and the tapped volume (the final tapped volume V_f).

Compressibility index = $V_\circ$- V_f/ $V_\circ$ *100%

Table (17) Scale of flowability

Compressibility Index (%)	Flow charcters
≤ 10	Excellent
11-15	Good
16-20	Fair
21-25	Passible
26-31	Poor
32-37	Very poor
>38	Very very poor

3.5.2 Post-compression parameters:

3.5.2.1 **Shape of Tablets:** Compressed tablets were visually examined fortheir shapes. [104].

3.5.2.2 Tablet Dimensions:Thickness and diameter: measured using a calibrated varniear caliper.Tablets of each formulation is picked randomly and thickness measured individually[104]

3.5.2.3Hardness :[30]: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling it was measued by using HMLHT-2 Tablet hardness tester.

3.5.2.4 Friability test:[104] The friability of tablets was expressed in percentage (%). The tablets were initially weighed (W initial) and transferred into a friabilator(Copley friabilator tester). The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. 6,5 weight of tablet should be measured first and placed in the apparatus then the tablets were reweighed again (W_{final}).

The % friability was then calculated by :

$$\%F = (w_1-w_2)/w_1*100\%$$

The acceptance % Friability value of tablets is not more than (1%) original weight.

3.5.2.5 Weight Variation Test :[104] : Ten tablets should be selected randomly from the batch and weighed individually to check for weight variation. Variation allowed is indicated by U.S. Pharmacopoeia..

Table (18) the USP acceptable limits for the weight variation

USP-Official limits

Tablet weight	Limit
130 mg or less	± 10%
130-324 mg	± 7.5%
>324 mg	± 5.0%

3.5.2.6Buoyancy/ Floating Test:[15] The time between introduction of dosage form and its buoyancy in the1.2 N HCl puffer and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

3.5.2.7 Swelling Study:[15] The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. Tablets were intended in the dissolution apparatus 900 ml of 1.2 HCl at 37 C^0,and at different time points (,5 , 1,2.3,5,7 hour) 3 tablets were removed from the three dissolution basckets then lightly dried by a pieace of tissue paper to drain the loose water and weighted .

The swelling index is given by the equation:

$$WU = (W_1 – W_0)/ W_0 \times 100\ \%$$

Wt = Weight of dosage form at time t

W0 = Initial weight of dosage form

3.5.2.8In vitro drug release for the formulation : the tablets that passed the floating test were tested for drug release [105, 106] The invitro drug release was studied by conducting dissolution test for tablets. Dissolution was carried out using USP XIII dissolution apparatus type II (paddle type). 900 milliliters of 1.2 N HCl, which was maintained at 37°C, was used as the dissolution medium. The speed of paddle was maintained at 50 rpm for 10 hours .Five milliliters samples were withdrawn at the time intervals periodically up to 10 h and replaced with equal volume of fresh dissolution medium maintained at the same temperature. The samples were filtered and suitably dilutedthen assayed for iron content.Allexperementswere carried out in triplicates.

3.5.2.9Drug content uniformity study: 6 tablet were randomly chosen and each tablet was weighted and put in mortar and pestle and crushed

1) A standard solution was prepared by dissolving 150mg of Fe Gluconate in 50 ml 0.1 N Sulphuric Acid then dilute to 200 ml by Distilled Water . A 10 ml of the standard solution was withdrawn then dilute with Distilled Water to volume 100 ml . withdraw 3 ml from it +5 ml complexing agent+ 1 ml HA and measure the absorbance at UV 510 wave length

2) and measure at the absorbance ƛ 510 nm wavelength .

3) Sample preparation: transfer 1 tablet(grind it first) into 200 ml volumetric flask.Dissolve by adding 50 ml 0.1 N sulphuric acid (may use magnetic stirrer to help in dissolving it)dilute with Distilled Water to volume then take 10 ml from the sample and dilute up 100 ml distilled water .then withdraw 3 ml from it +5 ml complexing agent + 1ml HA and measure the absorbance at UV 510 wave length, this was in triplicate .

3.5.3 Stability test for tablet : [107]

Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product developmentThese studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO and-or other agencies. Importance of various methods followed for stability testing of pharmaceutical products, andgeneral recommendations on the storage conditions have been given by ICH and WHO. [108].

The packing container which was used HDPE 60 ml jars, with2*1 g silica gel caps+ sealing and 30 tabs for Jar

Two storage conditions were applied for the stabilitye test .

1) the intermediate storage condition=30±2°C/65±5% RH (WHO) usingWalk In Humidity Incubator[108]

2) accelarated storage test = 40±2°C/75±5% RH (WHO)using Firlabo Incubator (Cha, Gilmor et al. 2001)

After the specified storage peroids which are 1 month and three months the following tablets performance tests were carried out :

1- Invitro dissolution drug release test.

2- Content uniformity (assay).

3- Harrdness.

3.6 Kinetics of drug release:

To investigate the mechanism of drug release from the selected formulation, the drug release results were evaluated by all models for kinetic studies through appalling in DD Solver program

3.7 Mathematical modeling of dissolution rate profile:

In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for the assessment of Bio-equivalence. Several theories /kinetics models describe drug dissolution from immediate and modified release dosage forms.

There are several models to represent the drug dissolution profiles where f_t is a function of t(time) related to the amount of drug dissolved from the pharmaceutical dosage system. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms[109].

Mathematical models have been used extensively for the parametric representation of drug release kinetics from GRDDS formulations. Models that have been used include, the zero order, first order, Higuchi, Korsmeyer-Peppas and Weibull models. [109]

The major objectives of mathematical modeling are as listed below:

1. Designing the new drug delivery system based on general release expression.

2. Prediction of the exact behavior of drug or drug release rates from and drug diffusion behavior through polymers, thus avoid excessive experimentation.

3. Optimization of the release kinetics.

4. Elucidation of the physical mechanism of drug transport by simply comparing the release data to mathematical models.

3.7.1 Zero order models

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:[109]

$$\mathbf{Q_t = Q_0 + K_0\, t}$$

Where Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution and K is the zero order release constant.

3.7.2 First order model

The pharmaceutical dosage forms containing water-soluble drugs in porous matrices follow first order release kinetics, and can be expressed by the equation:

$$\mathbf{Q_t = Q_0 e^{-kt}}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the solution and k is the 1st order release constant. The above equation in decimal logarithm will take the form,

$$\mathbf{\ln Q_t = \ln Q_0 + kt}$$

This equation implies that a graphic of the decimal logarithm of the amount of drug versus time will be linear. The dosage forms that follow this dissolution profile release the drug in a way that is proportional to the amount remaining in the interior of the dosage form, in such a way that the amount of drug released by unit of time diminishes. Thus any system obeying this model releases the drug in such a way that the remaining amount in the system governs the rate of release of drugs [109]

3.7.3 Higuchi Model

In 1961 Higuchi introduced the most famous and often used mathematical equation to describe the release rate of drugs from matrix system initially; it was valid only for planar systems. It was later modified and extended to consider different Geometries and matrix characteristics including porous structure. Higuchi developed an equation for the release of a drug from an ointment base and later applied it to diffusion of solid drugs dispersed in homogeneous and granular matrix dosage system. In this model, it is assumed that solid drug dissolves from the surface layer of the device first; when this layer becomes exhausted of drug, the next layer begins to be depleted by dissolution through the matrix to the external solution. In this way the interface between the regions containing dissolved drug and that containing dispersed drug moves into the interior as a front [109].

In a general way it is possible to resume the Higuchi model to the following expression (generally known as the simplified Higuchi model):

$$\mathbf{Q_t = K_H t^{0.5}}$$

Where, K_H is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based on the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs. This modified Higuchi relationship has been used to describe drug release from various types of modified release pharmaceutical dosage forms [109].

3.7.4 Korsmeyer- Peppas Model:

Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Qt/Q\alpha = K_k t^{n}$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism as shown in Table(16).

Table(19): Various drug transport mechanisms

Release exponent (n)	**Drug transport mechanism**
0.5	Fickian diffusion
0.5<n<1.0	Anomalous transport Non fickian diffusion
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.[12]

3.7.5 Hixsonñ Crowell model:

Hixson and Crowell (1931) recognized that the particlesí regular area is proportional to the cube root of its volume. They derived the equation

$$W_0^{1/3} - Wt^{1/3} = \kappa t$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surfaceñvolume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets[110]

3.7.6 Selection of Best Model:

The selection of the appropriate model in the drug release studies is critical to ensure the effectiveness of the study. There are various criteria for the selection of the mathematical models which are based on the statistical treatments. The most widely used method employs the coefficient of determination, R^2, to assess the fit of the model equation. This method can be used when the parameters of the model equations are similar. But when the

parameters of the comparing equations increased; a modification is incorporated in this technique where an adjusted coefficient of determination (R^2 adjusted) given by:

$$R^2_{adjusted} = 1 - \frac{n-1}{n-p}(1-R^2)$$

Where n is the number of dissolution data points and p is the number of parameters in the model. Hence, the best model is the one with the highest adjusted coefficient of determination. A value for R^2 adjusted > 0.950 is considered acceptable for the purposes of comparison of modeling dissolution profiles generated.

Part 4

Results and discussion

Result and Discussion:

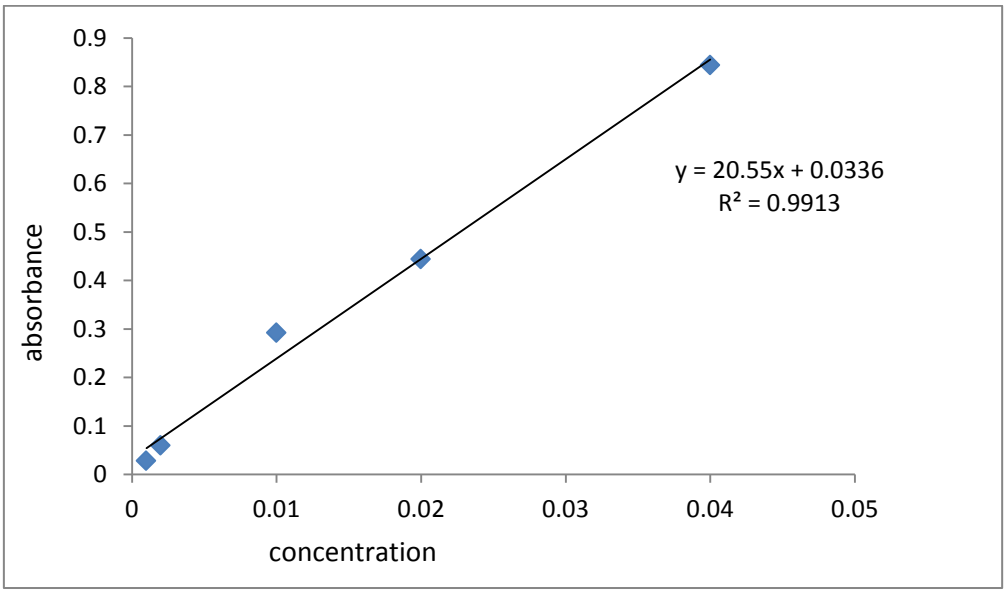
4.1 Spectrophotometric determination of iron :

From the calibration curve we got a linear relationship (R^2 = 0.991) which means a highly precision and accuracy.

table (13)Absorbance of ferrous phenanthroline complex versus concentrations of ferrous gluconate at ƛ 510 nm

Test tube #	Concentration (mg/ml)	absorbance
A	0.001	0.028
B	0.002	0.06
C	0.01	0.292
D	0.02	0.444
E	0.04	0.844

Fig (17) Calibration curve of ferrous gluconate



The aim of this study was to creat a gastroretentive floating system of ferrous gluconate , that release iron in a sustained release manner.

Ferrous salts are good candidates to be formulated as floating system as its absorption window is in the stomach and the upper part of the intestine . but iron absorption as GRFDD faces two proplems:i.e.

1- It is a heavy metal with a high molecular weight .

2 –It is highly soluble in water.

The tablets should allow enough water to water entrance so as to form CO_2 to initiate floating but at the same time allowing slow release of the iron . .

So we must formulate a floating system that help us in maintain the integrty of the tablet by slowing down the disentigration of the tablet.The challenge was to choose the appropiate polymer compisition to achive these aims .

The requierments was to formulate a floating system that has a short floating lag time(not more than 2 minutes) to make sure that our tablets will rapidlly float as they enter the stomach to escape gastric emptying in the case a house keeper wave and to obtian a floating time for minimum 12 hours to facilitate iron release for prolonge period time in sustained manner to allow a once dailly use of the tablet.

During our study we prepared 13 diffrenet formulas with different excipient as shown in tables (14,15) .Seven formulas were prepared by the so called Direct Compression method and the other six by wet granulation .

The tablets prepared for each formula were tested interms of buoyancy lag floating time (LFT) and total floating time (TFT) ,the acceptence criteria for buoyancy tests are included in table (20)

The results of the FLT and TFT of all formulations are shown in table (20). Our work was based on formulating a formulations by trail method to get best floating results befor persuing to dissolution testing .

Table (20) the floating lage time (FLT) and the total floating time (TFT) for all fromulas we studied in both wet garanulation and direct compression methods.

Formula of wet garnulation	FLT	TFT	Formula of direct compression	FLT	TFT
F1	Fail to float	Fail	H1	Fail to float	Fail
F2	Took > 5min	Up to 12 h	H2	12 sec	Disentegrated within 1 h
F3	Took >2 min	Dissapeared after 10 min	H3	Rapid disentegration	Disentegrated
F4	58 sec	Dissapeared after 15 min	H4	8 sec	Disentegrate within 1 h
F5	disentegrated	disentegrated	H5	4:45 min	Up to 12 h
F6	Fail to float	Fail	H6	15 sec	Disentegrate within30 min
			H7	40sec (avarage FLT for 6 tablets	Up to 24 h

*FLT:floating lag time

*TFT: toltal floating time .

*min: minute

*sec: seconde *h: hour

4.2 preparation of effervescent floating tablets :

4.2.1 Wet granulation method's formulas :

Formula F1 : it didn't float with little formation of gas bubbles .

Here we will discuss the results of each fromula and the logic of the changes done .

By studying the excpients uesd in this formula , HPMCK 100,000 polymer was used wich has a high viscous polymer to help in entrapping water and the generated gas to form floating and also slow down iron release HPMC100,00 is used here as a gel forming agent,and in contact with water it helps in entrapping the produced carbon dioxide to create a bulk desity for the tablet lesser than the density of gastric content so the tablet will float .This is the same with HPMCk15, HPMCk 4.which varry in the molucular weight and viscocity charastristics .[15]

citric acid:is used as acidulant, because this floating gastro retentive system should be taken after meals which will raise the PH of the stomach that will affect the gas formation, to solve this problem we added the citric acid to make sure that the inner part of the tablet is acidic to help in rapide formation of gas and rapid floating behavior .[15].

$NaHCO_3$:Is an Effervescent compound .(Sodium bicarbonate, with citric acid). When these compounds come in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swelled hydrocolloids, which provide buoyancy to the dosage forms .[15]as it shows in the follwing reaction :

$$NaHCO_3 + HCl \rightarrow CO_2 + H_2O$$

PolyVinylPyrrolidone, K 30 (**Povidone)**:povidone solutions are used as binders in wet-granulation processes [111].

Vitamine C: used here as Antioxidant.[112]

Mg stearate : used as hydrophobic lubricant,

Tablet from formula 1 failed to float .This can be explained by .in contact with water the tablet matrix is thought to form a very viscous gel layer, that prohibits the entrance of water into the tablet core subsequently and slow down the gas formation processes.So the

total density of the tablet remains higher than the gastric contents density so fail to float(it was heavy to float) .

Formula F2:.it needed to float with in >5 min and stayed floating up to 12 hours .

Addition of Ethyl Cellulose to formula F1.improved the floating behavior ,hence ethyl cellulose has bulk density less than one, thus it is used for enhancing the buoyancy of the formulation. [113].the compination of Ethyl cellulose and HPMCK100,000 enhanced the floating time .The tablet floated with in 5 minutes and stayed floating for 12 hours, which is considered good but not with in the acceptance criteria that we determined in this study.The effect of Ethyl cellulose is thought to be due to weakening of the viscous gel that HPMC K100,000 makes, so helping in the formation of gas by decreasing the total density of the tablets .The combination of ethyl cellulose and a hydrophilic component such as HPMC offers a flexible system to control the drug release by changing the viscosity, substitution type and concentration of HPMC [114]

Formula F3: This formula F3 took more than 2 minutes to floate and 10 minutes to disintegrate.

It is seen that using K15 instead of K 100,000 reduced the floating lag time becouse of reduced visicosity of the K15 polymer . But with time, more water enters the tablet , more gas will form and entraped by the gel .But this HPMCK15 dose not have the desired polymer entanglement to hold this pressure, and coused a rapid distintegration of the tablet after (10 min).It formed an effervisCent tablet that did not provide a sustained release .This formula had a lag time of more than 2 min which also not complying with the floating requirments (less than 2 min). So we tried a polymer having less vescosity in the following formulation.

Formula F4: it took 58 seconds to float and 15 minute to disentgrate .

In this formula F4 we used a lower viscosity HPMC polymer which is HPMC K 4 to study if this will decrease the floating lag time of the tablet .

As we observed, the tablet took only 58 seconds to float wich is very good. This because the low viscosity grade polymer allows rapid entrance of the water to the tablet so rapid gel forming layer of the polymer and rapid gas fromation and entrapment in the gel layer causing the the tablet to float,.But with time as more water enters and more gas forming the

low viscosity polymer couldn't handle the pressure from the gas that is formed causing the tablet to disentegrate arapidlly with in 15 minutes So, in the following formulation we tried to change the ratio of ethyl cellulose and $NaHCO_3$ to see if this will improve the floating characteristics.

Formula F5: Failed to float and rapid disintegrated .

Increasing the percentage of sodium bicarbonate with decreasing the percentage of ethyl cellulose resulted a tablet that rapidly disintegrated and failed to float

.

Formula F6 : alsofailed to float,and very little of gas bubbles was noticed .

The increase of the ethyl cellulose which is a more hydrophopic polymer.Lead to a decrease inthe entrance of water and low formation of the required amount of gas to be entraped and help floating of the tablet .

Formula F2 proved to have the closest properties to our requirments . The main proplem in this formula was the long floating lag time , that may be due to the use of the PVP K30 as binding agent .

.

4.2.2 Direct Compression Method:

The results for the tablet floating are sumarrized in table (22) .

Formula H1: failed to float.

In order to check our conclusions from the previous studies ,we tried the same polymers in Direct compression method.

In this formula ethylcellulose was used without gel forming polymer .Ethyl cellulose prevented the entrance of water into the tablet core, and supsequently no gas was evolved , as a result no gas genration occurred and the tablet did not float..

In this formulation ,we introduced the Microcrystaline cellulose as a hydrophillic polymer to counteract the hydrophobicity of the ethylcellulose . as a result no gas genration occurred and the tablet did not float .

Formula H2: it has good floating time ,12 secondes, but a rapid disintegration of the tablet was observed within 1 houre .

This may be due to the introduction of HPMCK 4 .in the formulation satisfactory intiation of floating was obtained , but the tablet disintegrated in 1 hour .This is probably due to the fact that the polymer dosent have the required integrity and entanglement to hold the trapped gas .

Formula H3 : failed to float, and was a rapidly disintgrated .

It is abvious that even HPMC K 15 (intermediate viscosity polymer), dosent have the required integriety and entanglement to hold the trapped gas and attain the required total floating time .

Formula H4 : In this formula there was also a rapid floating within 8 seconds but disintegration within 1 hour .

Here we added HPMC100,000 as gel forming polymer , and according to the previous result in using this polymer in wet granulation method we add starch .In attempt to increase the entrance of water initially to decrease floating lag time .The result was that the tablet floated rapidly (within 8 seconds) . However effervesces effect was so strong and a rapid disintegration occurred. So we thought to retard the water entrance by increasing the amount of the ethyl cellulose.

Formula H5:In this formula there was a delay in the floating up to 4:45 minutes, succeeded in floating for 12 hours.

Here we removed the starch, increased the ethyl cellulose amount to study the effect of increasing the ethyl cellulose amount on the floating behavior of the tablet. We observed that a delay in the floating lag time took place (more than 4 minute).This formula stayed floating for 12 hours. At this step we concluded that a fine tuning of the amount of ethyl cellulose and $NaHCO_3$ must be done.

Formula H6:in this formula there was a rapid disintegration within 30 minutes and rapid floating lag time 15 sec .

Here to overcome the long lag floating time of the tablet in H5, by decreasing the ethyl cellulose amount and increasing the amount of $NaHCO_3$ .This increase the gas forming

agent caused a rapid and large amount of gas formation causing rapid floating and rapid disintegration of the tablet.

At this point, we concluded that there should be a factor that increases the formation of gas but keeps that tablet integrity.

So we decided to keep the amounts in formula H4 but introduce the citric acid.

Formula H7: .In this formula there was a rapid floating lag time 40 seconds and total floating time up to 24 hour.

Here the amount of the ethyl cellulose and $NaHCO_3$ remain unchanged but we added the citric acid as enhancer for gas formation with the $NaHCO_3$.

This approach is appeared to be the right combination. Citric acid used helped in internal gas formation, and ethyl cellulose helped in preventing the tablet from disintegration.
The result was a good effervescent gastro retentive floating tablet that had a short floating lag time and long floating time and maintained its integrity. This complies with our objectives. So formula was a successful formula and the one to conduct all the quality control and stability tests
So formula(H7) was chosen to conduct quality control test that is required.

4.3 The pre-compression physical properties for the powder for H7:

The powder blend was evaluated for flow properties. The angle of repose value was 20 ^{o} degrees (table (16)) the flowability of powder blend is excellent.

Compressibility index = $V_\circ - V_f / V_\circ$ *100%

The compressibility index of the powder was =100%*(22,5-19.12)/22.5= 15

This means the powder blend has good flow properties (table 17)

4.4 The post- compression physical properties for the tablets (for formula H7):

4.4.1 Shape of Tablets:it is a flat faced bisect tablet

4.4.2 Dimensions of the tablets:the tablets have 12 mm radius and 4.4 mm thickness.

4.4.3 Friability test : by using the equation of friability :

$\%F = 100*(W_1-W_2)/W_1$

$\% F= 100*(6.5g-6.435g)/6.5g = 1$

A maximume mean wight loss from the tablets of not more than1% is cosidered accepteple for most of the productus .

4.4.4 Hardness of the tablet (H7):

Sample of 6 tablets was taken from formulation (H7): the tablets average weight was:478.5 mg,and the hardness results are shown in table (20) as shown in table (20)

Hardness(kgf)	6.3
	7.3
	8.8
	7.2
	5.5
	8.1
Average	**7.2**

These results agree with USP requirements. Oral tablets have a hardness of 4 to10 kg [115]; it means that our tablets are in the acceptable range.

4.4.5 Weight variation: randomly sample was taken from formulation (H7)and their weight were measured . the results are shown in table (21)

Table (21) Results of Weight Variation Quality Control Test

Weight variation for 10 tablets		
Table number	**Tablet weight (g)**	**%weight deviation from average**
#1	0.483	0.104
#2	0.483	0.104
#3	0.483	0.104
#4	0.485	0.518
#5	0.480	0.518
#6	0.481	0.311
#7	0.482	0.104
#8	0.485	0.518
#9	0.484	0.311
#10	0.479	0.725
average tablets weight (g)	0.4825	

All tablets weight are within acceptance limit, none of the tablets deviated from the allowed limit according to the USP limits (if tablet weight >324 mg the allowed limit is ± 5%)

4.4.6 Content Uniformity Test:

Table (22) shows the results of the content uniformity for 6 tablets

Content Uniformity		
Tablet No.	**Abs ()**	**% Content**
1	0.4999	95.09226
2	0.5252	99.90489
3	0.4981	94.74986
4	0.5093	96.88035
5	0.5003	95.16835
6	0.4983	94.7879
abs of STD	**0.5272**	
Average		**96.09727**

To ensure the consistency of dosage units, each unit in abatch should have a drug substance content within narrow range around the label claim.So according to the USP criteria the compressed tablets coated or non coated for 6 dosage form unites should be 85-115% of lable claim (USP 2011). So as shown in table (22) the result are within the accepetd range

4.4.7 Buoyancy / Floating Test: here we studied the floating lag time (FLT), and Toltal floating time (TFT). for all the formula in both method the direct compression and the conventional wet garanulation .as the result is summrized in table (23)-

For the LFT test we bicked 6 tablets from the batch (H7) with avarage wighet 0.4825 g .in 1.2 PH buffer in dissolution

Table (23) Floating time measured for 6 tablet

Average Tablets Weight	Tablet number	Floating Time(Sec)
478.5 mg	1	52
	2	50
	3	45
	4	20
	5	55
	6	20
Average FLT for(H7)		40.333

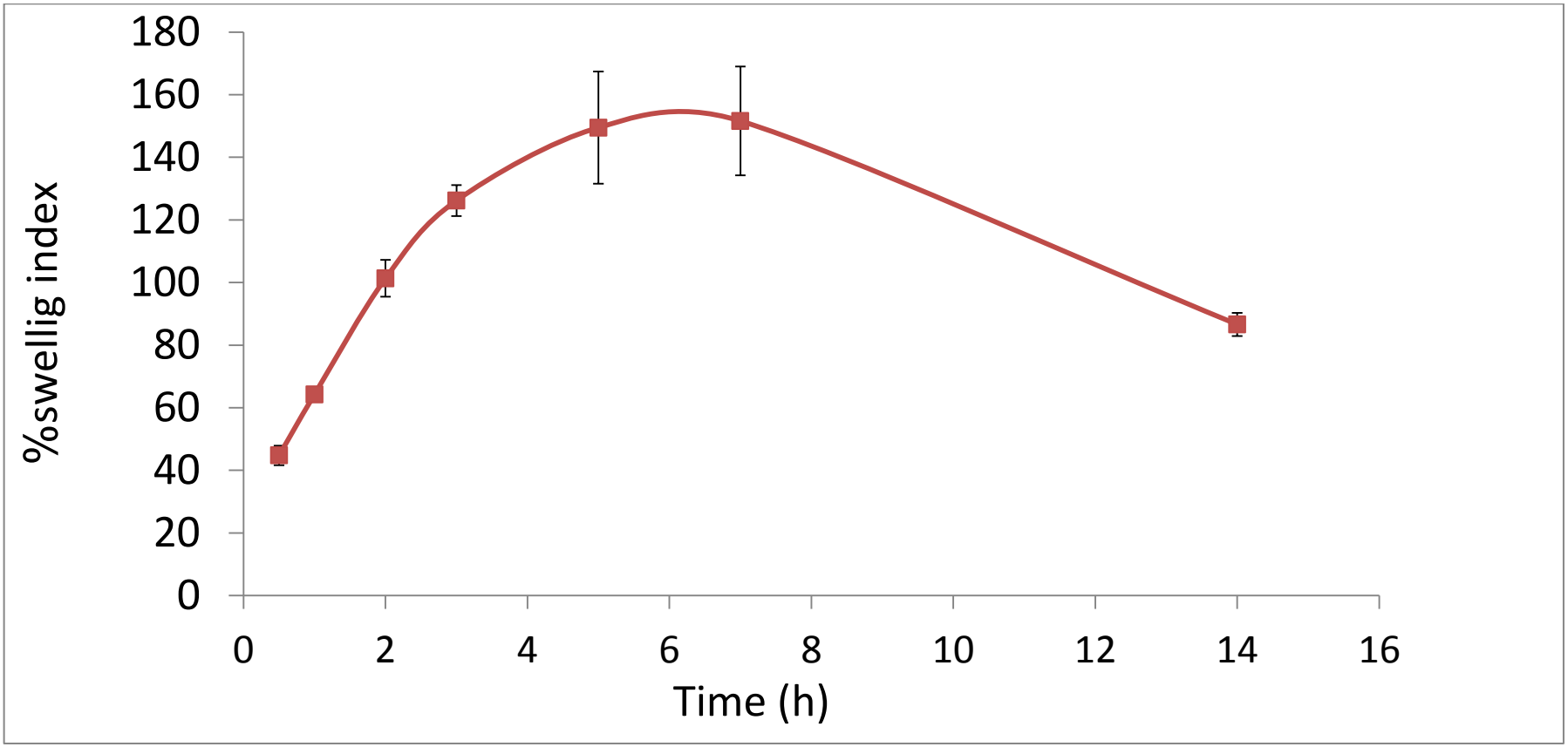
So H7 shows that it has a very good byouncy behvioer as its avarage FLT is 40 sec which is very good and it keep byount for at least 24 hours which all result helped us in choosing this formula H7 for further study .

4.4.8 Swelling Study:the swelling properties of formula(H 7) were determaine , and table (24) summrises the results .

The table (24) showes the results for the swelling index for formula H7

	weight of tablets (gm)			**% water uptake for each tablet**				
time (h)	basket1	basket2	basket3	%water uptake tab1	%water uptake tab2	%water uptake tab3	Average swelling index	standard deviation for the swilling
0.5	0.7137	0.6835	0.7003	47.76	41.51	44.98	44.75	3.13
1	0.7849	0.791	0.8044	62.50	63.76	66.54	64.27	2.06
2	1.005	0.952	0.9603	108.07	97.10	98.81	101.33	5.90
3	1.1011	1.0656	1.111	127.97	120.62	130.02	126.20	4.94
5	1.303	1.172	1.140	169.77	142.65	136.02	149.48	17.88
7	1.186	1.15	1.310	145.54	138.09	171.221	151.62	17.37
14	0.8887	0.9141	1.30	83.99	89.25	87.98	86.62	3.71

Fig (18) Swelling Index with time:



It is shown in table (24) and graph (17) that in the initial 5 hours there was an increase in the weight due to swelling of the polymer. After the 5th hour the weight was stable then it decreased after wards indicating that erosion of the polymer beginning to tack place

4.4.9 The in vitro release study for Ferrous gluconate :(H7)

The results of the dissolution pattern of ferrous gluconate for the formula H7 is shown in table (25) and fig (18)

The study was done on 6 tablets for 10 hours.

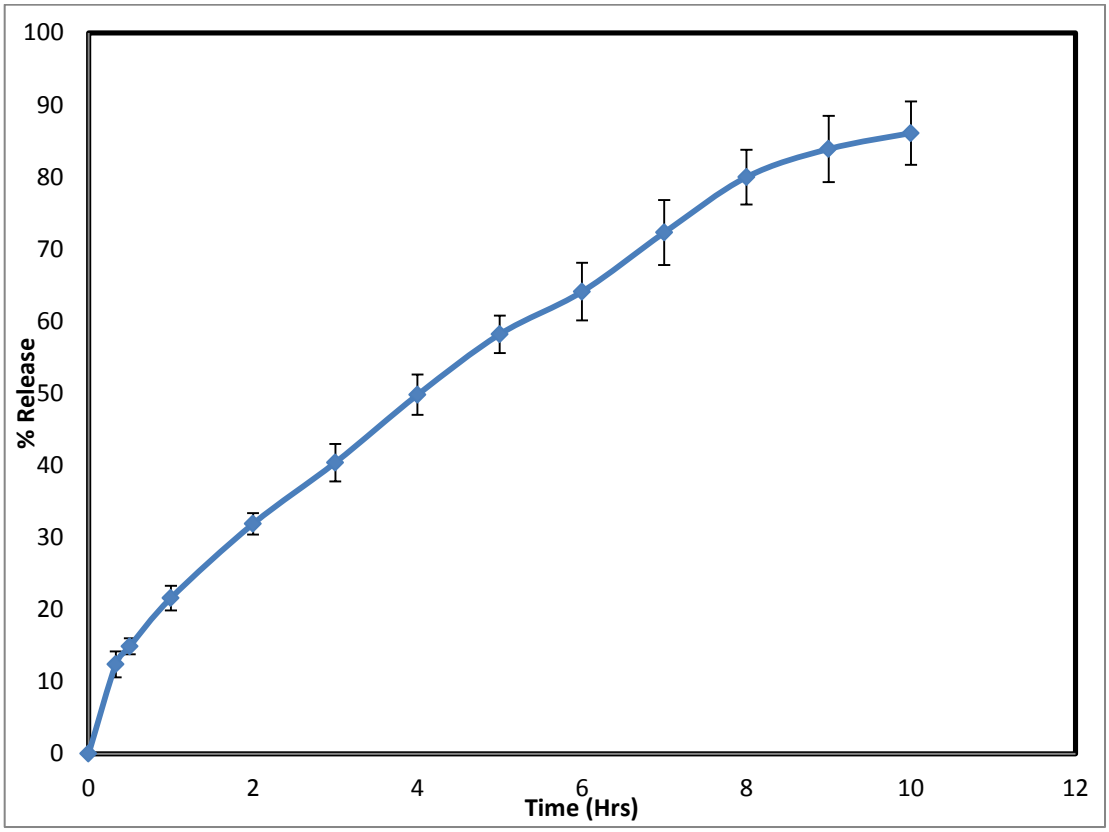
Table (25) shows the result of the % release of the ferrous from the tablet of formula H7 for 10 hours

Time	20 min		30min		1hr		2hr		3hr		4hr	
Tablet#	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release
1	0.0484	10.88	0.0669	15.04	0.0869	19.53	0.1367	30.73	0.1677	37.70	0.2083	46.83
2	0.0508	11.42	0.0751	16.88	0.0957	21.51	0.1384	31.11	0.1718	38.62	0.2115	47.54
3	0.0569	12.79	0.063	14.16	0.0995	22.36	0.1475	33.16	0.1938	43.57	0.2292	51.52
4	0.0506	11.37	0.0669	15.04	0.0912	20.50	0.1355	30.46	0.1703	38.28	0.2359	53.03
5	0.0705	15.84	0.0632	14.20	0.1083	24.34	0.1524	34.26	0.1916	43.07	0.2112	47.48
6	0.0528	11.87	0.0616	13.84	0.0944	21.22	0.1416	31.83	0.1841	41.38	0.2328	52.33
%Average Release		12.36		14.86		21.58		31.92		40.44		49.79
SD		1.824		1.103		1.658		1.497		2.571		2.798

Continue: the result of the % release of the ferrous from the tablet of formula H7 for 10 hours

5hr		6hr		7hr		8hr		9hr		10hr	
Absorbance	%Release	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release	Absorbance	%Release
0.2405	54.06	0.2669	60.00	0.3041	68.36	0.3316	74.55	0.3545	79.69	0.3705	82.70
0.2582	58.04	0.2662	59.84	0.3004	67.53	0.3656	82.19	0.3482	78.28	0.3594	80.22
0.2583	58.07	0.287	64.52	0.3202	71.98	0.3504	78.77	0.3769	84.73	0.3862	86.20
0.2536	57.01	0.278	62.50	0.314	70.59	0.3433	77.18	0.367	82.50	0.382	85.26
0.27	60.70	0.3068	68.97	0.3458	77.74	0.3713	83.47	0.3937	88.51	0.4028	89.91
0.272	61.15	0.3052	68.61	0.3455	77.67	0.3728	83.81	0.3984	89.56	0.4127	92.12
%Average Releases	58.17		64.07		72.31		79.99		83.88		86.07
SD	2.587		4.043		4.465		3.757		4.587		4.417

Fig (19) Dissolution Release Profile of Ferrous Gluconate for Formula (H7).



A gradual sustained release of ferrous gluconate obtained with staisfactory properties between the 6 tablets tested . Up to this point we succedded in obtaining the required tablets features that exhibited both floating charactristics and sustained release of iron on a period of time more than 10 hours .This indicated possible use of this dosage form once daily.

4.4.10 In vitro release kinetics data analysis for optimized formula H7 :

In the in vitro release data of the formulation (H 7) was examined with varoius release equation and kinetic models .The most familiar kinetics modle in sustained release tablets are shown in table (25).

Table (26) Mathematical Models used to describe Drug Release Kinetics from various Matrices[116]

Kinetic Model	Systems that follow the Model
First Order	Water soluble drugs in porous matrix
Zero Order	Osmotic systems, transdermal systems drug release independent of drug (concentration
Higuchi's square root of time equation	Diffusion matrix formulations
Weibull	Erodible matrix formulations
Hixon-crowell's cube-root equation	Erodible matrix formulations
Korsmeyers-Peppa's power law equation	Swellable polymeric devices

Our release data was intermeded to the DD Solver programe to fit the different kintecs release modle. The resulting R^2 and the fitting curves are shown in table (27) ang fig (19) respectivlly .

The R^2 are shown in table(27) for the 5 kintecs modle we studied :

Model	R^2	
Zero order R^2	0.9057	
First order R^2	0.9861	
Higuchi's R^2	0.9832	
Korsmeyer's R^2	0.9974	n value: 0.616
Hixon 's R^2	0.9815	

According to these results of R^2 values we conclud that the korsmeyer pappas model is the best model that describes the release in our formula hightest .This modelexplain the drug

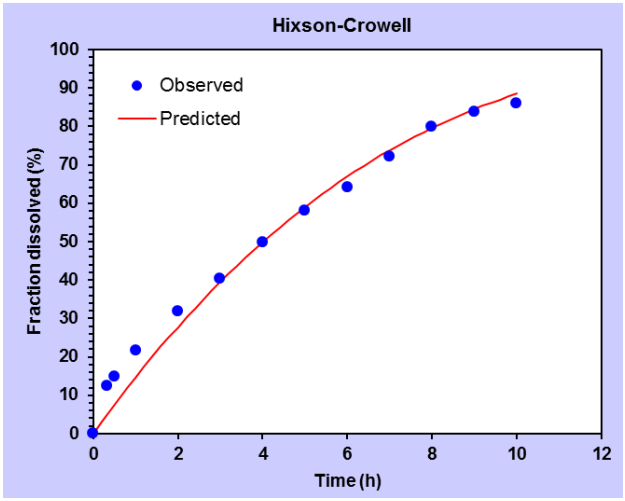
relaesr from a swallable polymer device which is the exactform that we have.In this model, the value of n characterizes the release mechanism of drugs as it showes in this table (28).

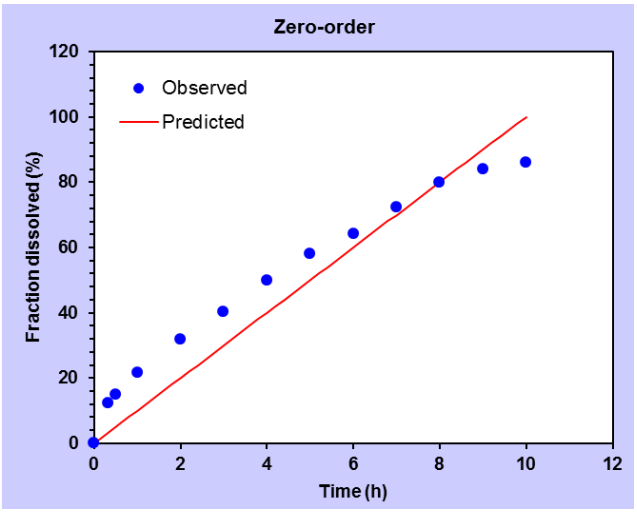
Table(28): The interperation of diffusion exponent (n) value for release from polymeric film

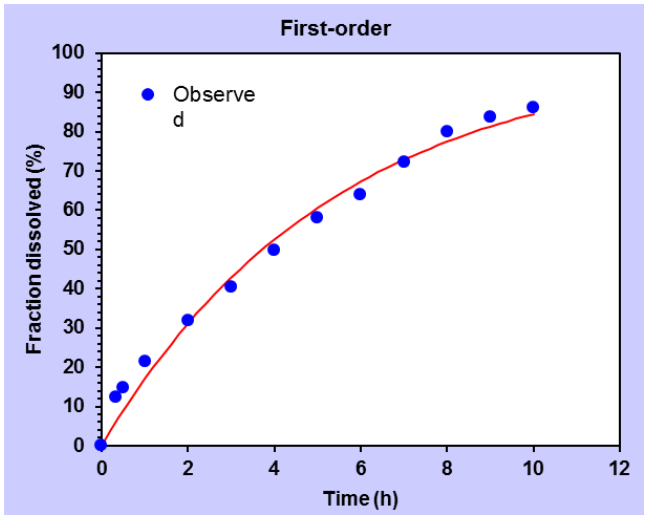
Release exponent n	**Drug transport mechanism**	**Rate as a function of time**
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1	Non -Fickian transport	t^{n-1}
n =1	Case II transport	Zero order release
>1	Super case II transport	t^{n-1}

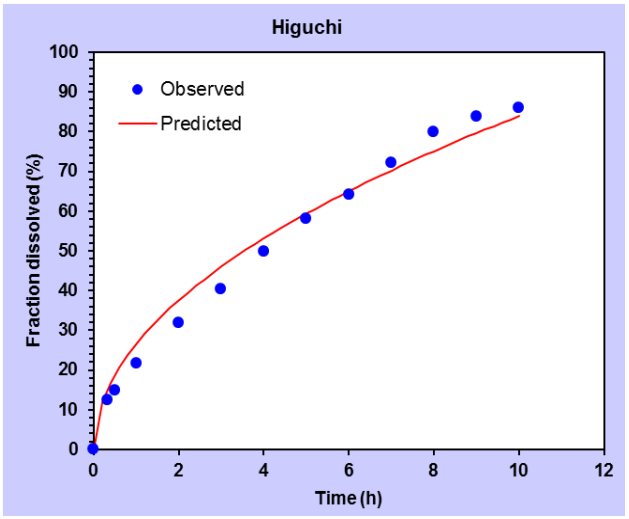
So as it showes in the table(28) that from the n value that our releasr follow the non-fickian (anamolous) diffusion which acombination of both diffusion and erosion controlling the release of the drug.This result is also reflected by the result of the swelling index that up to 7 houres, there is an increase in the swelling index of the tablet then after that there is a decrease in the swilling index wich indicates that there is an erosion process taking place in a later step after the beginnig of the diffusion

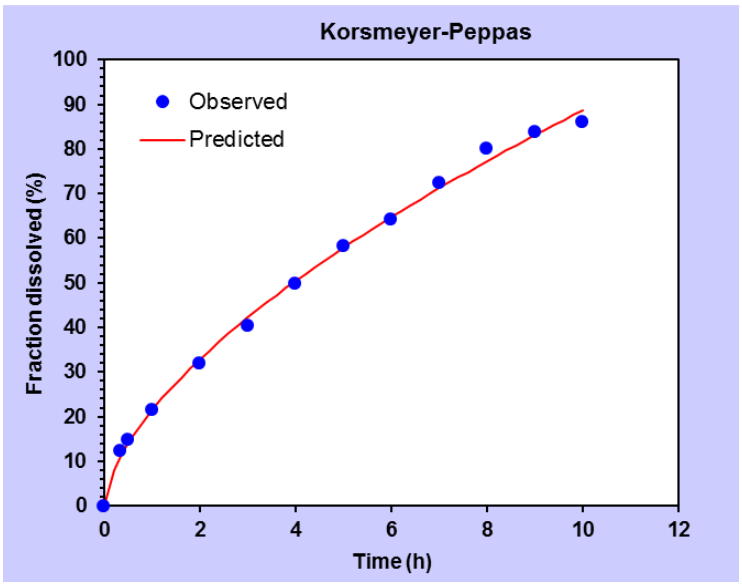
As it is seen in Figure (20) the best model in which the predicted curve fits the data is koresmeyerpeppas model.











4.4.11 Stability studies :

4.4.11.1 For One Month:

1- Disolution study for30 C/65 %RH: for one month :

Table (29) % release of iron from (6) tablets after one month stability at 30 C/65 %RH

Time	Absorbance 1hr	%release 1 hr	Absorbance 5hr	%release 5 hr	Absorbance 10hr	%release 10 hr
Tablet 1	0.0858	19.42	0.2388	54.05	0.3874	87.68
Tablet2	0.0986	22.31	0.2679	60.63	0.422	95.51
Tablet3	0.0877	19.85	0.2659	60.18	0.406	91.89
Tablet4	0.0833	18.85	0.2498	56.54	0.4266	96.55
Tablet5	0.0983	22.24	0.25	56.58	0.4102	92.84
Tablet6	0.0875	19.80	0.267	60.43	0.42	95.06
average		20.41		58.07		93.26

Disolution test for 40 C/75 %RH for one month :

Table(30) % release of Fe from (6) tablet after one month stability at 40 C/75 %RH

Time	1hr	%release 1 h	Absorbance 5hr	%release 5 hr	Absorbance 10hr	%release 10 hr
1	0.0927	20.98	0.2428	54.95	0.375	84.88
2	0.1008	22.81	0.272	61.56	0.432	97.78
3	0.089	20.14	0.2769	62.67	0.4266	96.55
4	0.097	21.95	0.2788	63.10	0.389	88.04
5	0.0892	20.19	0.271	61.33	0.451	102.08
6	0.0977	22.11	0.278	62.92	0.431	97.55
average		21.36		61.09		94.48

In compression to the result we got befor dissolution test we founde no diferrence which give us a good idea that our tablets are stable after 1 month .

2. Assay :

Table (31) showes the result of assay for(10) tablets after one month stability test at both 30C/65 RH and 40C/ 75RH

Assay :	
30/65	100.70%
40/75	100.10%

A 100 % consrvation of the ferrouse gluconate in the tablets after one month in both stability conditions was obtained.

3- Hardness :

Table (32) the hardness results for (6) tablets after one month at 30C/65 RH

Incubator 30/65	**Hardness**	**7.1**
		7
		7.1
		8.4
		7.2
		6.5
	Average	**7.2Kgf**

Tablel (33) the Hardness results for (6) tablets after one month stability test at 40 C/75 RH

Incubator40/75	**Hardness**	5.8
		8
		8.4
		8.1
		7.3
		9.2
	Average	**7.8Kgf**

Hardness of the formulation (H7) as it shown in table (32,33) was presrved under the specified storage conditions up to 1 month . the hardness acceptence criteria for Oral tablets in range of 4 to10 kg [115];

4.4.11.2 Stability studies for three months :

1- Disolution study for30 C/65 %RH: for three months :

30 C/65 %RH

Table(34) shows the %release of iron from (6) tablets up to 10 hours after 3 month stability test at30 C/65 %RH.

Time	Absorbance 1hr	%release 1hr	Absorbance 5hr	%release 5 hr	Absorbance 10hr	%release 10 hr
1	0.0857	19.84	0.2426	56.17	0.3874	87.68
2	0.0779	18.03	0.2415	55.91	0.421	95.29
3	0.092	21.30	0.2414	55.89	0.406	91.89
4	0.0826	19.12	0.229	53.02	0.411	93.02
5	0.0832	19.26	0.23	53.25	0.403	91.21
6	0.081	18.75	0.2355	54.52	0.3718	84.15
average		19.38		54.79		90.54

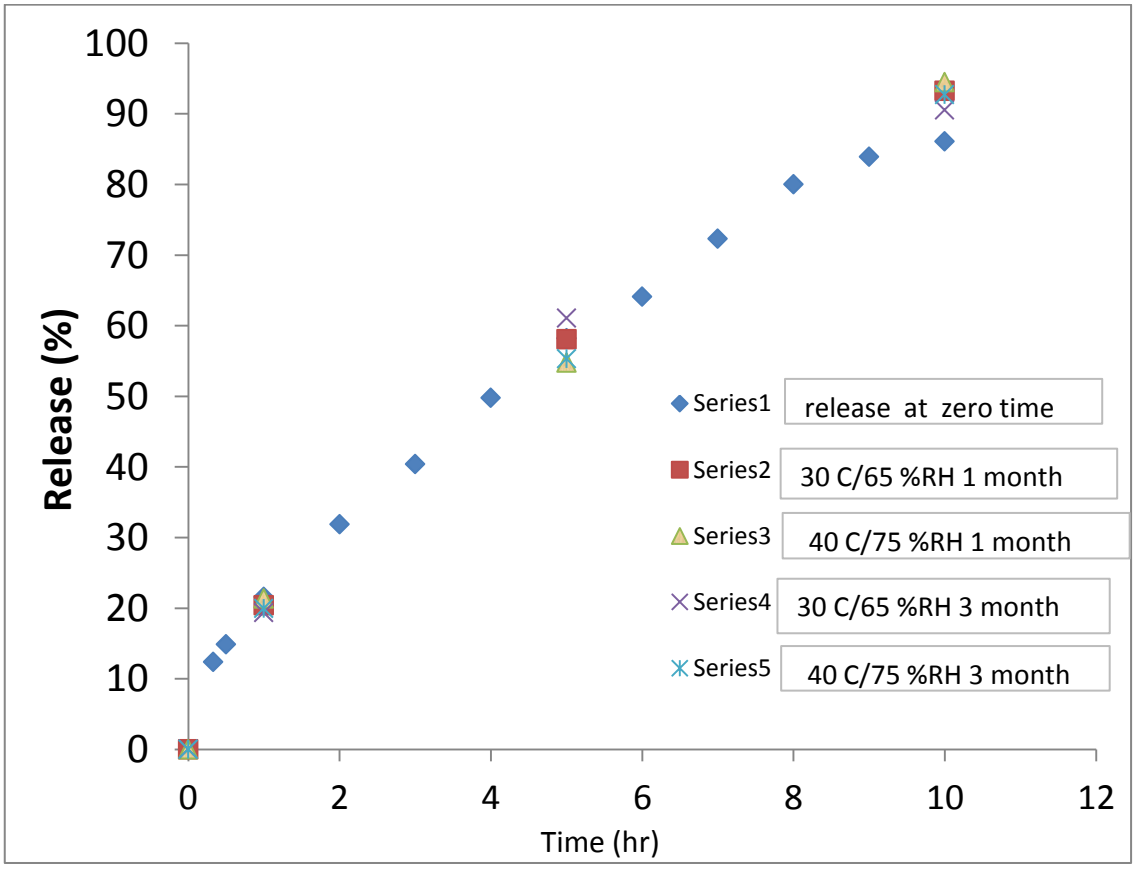
Disolution study for 40C/75 RH for three monthes :

40 C/75 %RH

Table (35) shows the % release of iron from (6) tablets up to 10 hours after 3 month stability test at 40 C/75 %RH.

Time	Absorbance 1hr	%release 1 hr	Absorbance 5hr	%release 5 hr	Absorbance 10hr	%release 10 hr
1	0.0838	19.40	0.2405	55.68	0.3633	82.23
2	0.086	19.91	0.2311	53.50	0.422	95.51
3	0.0867	20.07	0.2447	56.65	0.401	90.76
4	0.0897	20.7	0.245	56.72	0.408	92.34
5	0.0855	19.79	0.242	56.03	0.4311	97.57
6	0.0855	19.79	0.2301	53.27	0.432	97.70
average		19.95		55.31		92.70

Fig (21) Release after different incubation conditions



In compression to the result we got befor in the dissolution test we founde no siginficant diferrence which give us a good idea that our tablets are stable after 3 month also.

2- Assay :

Table (36): the assay result of (6) tablets after three month at different incubation condition

Conditions	Assay
30/65RH	100.00%
40/75RH	97.90%

It is Shown the stability of the tablet was preserved for 3 months under the specific conditions .Ferrus gluconat still in the accpentance USP criteria that compressed tablets coated and uncoated for 6 dosage unites must be within 85-115% of lable claime .

3- Hardness Tast:

at 30 C/ 65 RH:

Table(37) hardness result of (6) tablets after 3 months at 30C/ 65 RH.

Hardness	7.5
	9.2
	7.9
	9.5
	9.5
	8.4
Average	**8.6** Kgf

At 40C/ 75RH:

Table (38) hardness result of (6) tablets after 3 months after 40C/ 75 RH.

Hardness	8.9
	8.1
	8.2
	7.5
	7.7
	7.4
Average	**7.9**

Hardness of the formulation (H7) as it is shown in table (37,38) was presrved under the specified storage conditions up to 3 months The hardness acceptence criteria for Oral tablets in range of 4 to10 kg [115];

Part 5

5.1Conclusion:

This study showed the formulation of a gastroretentive floating tablet of ferrous glucont. A successful formulation was obtained using HPMC k100,000 and ethyl cellulose and specific amount of $NaHCO_3$and citric acid .Direct compression method was more suitable in producing the required results of floating and sustained releasee. HPMC K4 and HPMCK15 was not sutabile to attain good floating characteristics.The obtained tablet (H7) showed a sustained release pattern that fitted the Korsmeyer Peppa's model, indicating a diffusion and erosion kintetics. The stability studies indicates that the tablets are stable up to 3 months when challanged with accelarated stability tests. This formulated gastroretentive tablet will hopefully increase the absorption of iron through providing sustained amounts at the absorption site; the duodenum. This will also decrease the side effects (as constipation) by decreasing the residual unabsorbed amount of iron in the GIT .Future recomndations further in vivo sudies on human voulnteers is recommended

. 

5.2 .Appendix:

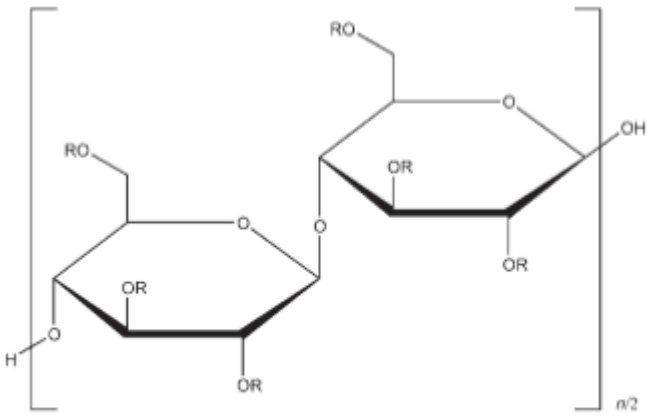
5.2.1Hypromellose: (HPMC K 100.000/HPMCK 4/ HPMC K15):

Chemical Name and CAS Registry Number: Cellulose hydroxypropyl methyl ether [9004-65-3] .

EmpiricalFormulaandMolecularWeight:

ThePhEur6.3describeshypromelloseasapartlyO-methylatedand O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, inmPas, of a 2% w/w aqueous solution at 208C. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis.Itcontainsmethoxyandhydroxypropoxygroupsconforming to the limits for the various types of hypromellose;. Molecular weight is approximately 10000–1500000.

Structural Formula:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category :

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming

agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extendedrelease tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.High-viscosity grades may beused to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lowerviscosity grades are used in aqueous film-coating solutions, whileH326 Hypromellose higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificialt ear solutions.It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. Inaddition ,hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses.It is also widely used in cosmetics and food products.

Description Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.[117]

ORISON CHEMICALS LIMITED
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■ Tel: +86-22-59886076
■ Fax: 86-22-59886075
■ E-mail:info@orison.com.cn
■ web site: www.orisonchem.com

CERTIFICATE OF ANALYSIS

Name: Hydroxypropyl Methyl Cellulose (HPMC)
Grade: E15 USP36 Conforming Microbiological Test
Quantity: 100 KGS
Date of Manufacture: 2013-09-20
Lot Number: 1309-235
Date of Expiry:2016-09-19
-Specification

Test Item	Specification	Test Result
Identification A to C	Conforms	Conforms
Methoxyl Content (wt%)	28.0-30.0	29.0
Hydrooxypropoxyl Content (wt%)	7.0-12.0	8.7
PH (25℃)	5.5-8.0	6.68
Loss on drying (wt%)	5.0 max	3.0
Heavy metal (ppm)	10 max	Less than 10
Arsenic (ppm)	2 max	Less than 2
Apparent Viscosity (cp)	12-18	14.5
Residue On Ignition (wt%)	1.5 max	1.04
Total Bacterium	1000/gram max	200
Mold	100/gram max	33
Appearance	White Powder	Conform

This material meets all requirement of USP36 for the monograph Hydroxypropyl Methyl cellulose 2910. The EP third edition and JP 13
This material passes USP identification test A, B and C.
This product has been manufactured in accordance with FDA's GMP

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CERTIFICATE OF ANALYSIS

Name: Hydroxypropyl Methyl Cellulose (HPMC)

Grade: E4 USP31 Conforming Microbiological Test

Quantity: 400 KGS Date of Manufacture: 2013-8-4

Lot Number: 1308-183 Date of Expiry: 2016-8-3

-Specification

Test Item	Specification	Test Result
Identification A to C	Conforms	Conforms
Methoxyl Content (wt%)	28.0-30.0	28.3
Hydrooxypropoxyl Content (wt%)	7.0-12.0	9.0
PH (25℃)	5.5-8.0	5.9
Loss on drying (wt%)	5.0 max	3.1
Heavy metal (ppm)	10 max	Less than 10
Arsenic (ppm)	3 max	Less than 2
Apparent Viscosity (cp)	3.0-6.0	4.6
Residue On Ignition (wt%)	1.5 max	0.74
Total Bacterium	1000/gram max	233
Mold	100/gram max	33
Appearance	White Powder	Conform

This materialm eets all requirement of USP31 for the monograph Hydroxypropyl Methyl cellulose 2910.T he EP third edition and JP 13

This material passes USP identification test A, B and C.

This product has been manufactured in accordance with FDA's GMP

ORISON CHEMICALS LIMITED

For and on behalf of
康佐森（天津）化工有限公司
ORISON CHEMICALS LIMITED

Authorized Signature

ShinEtsu

2015/06/02 (1/1)

Certificate of Analysis

Shin-Etsu Chemical
Naoetsu Plant [redacted] Division Department
28-1, Nishifukushima, Kubiki-ku,
Joetsu-shi, Niigata, Japan

Product Name	METOLOSE
	(Hypromellose, USP)
Grade	90SH-100000SR
Substitution Type	2208
Viscosity Type	100000 mPa·s
Lot Number	6058288
Quantity	40kg
Manufacture Date	2015/05/13
Recommended Re-Evaluation Date *	2018/05/12
Analysis Date	2015/05/15
Issue No.	0512015050314000002-1-01
Remark	P.O.1900690

This product complies with the specifications described in the current USP, EP and JP.
This product is manufactured in accordance with GMP.
* Shin-Etsu Chemical recommends that the customer's quality control unit may re-evaluate the quality of this material on its own responsibility prior to use after the Recommended Re-Evaluation date.
Storage Conditions: Store containers sealed and in a dry place. Keep away from heat or sunlight.

Test Item	Unit	Test Result	Specification	Method
Description		Conforms	Conforms	JP/USP
Characters		Conforms	Conforms	EP
Identification (1)/A		Conforms	Conforms	JP/USP/EP
Identification (2)/B		Conforms	Conforms	JP/USP/EP
Identification (3)/C		Conforms	Conforms	JP/USP/EP
Identification (4)/D		Conforms	Conforms	JP/USP/EP
Identification (5)/E		Conforms	Conforms	JP/USP/EP
Appearance of solution		Conforms	Conforms	EP
Viscosity	mPa·s	105000	75000 - 140000	JP/USP/EP
pH		6.7	6.0 - 8.0	JP/USP/EP
Heavy metals	ppm	Not more than 20	Not more than 20	JP/USP/EP
Loss on drying	%	1.0	Not more than 5.0	JP/USP/EP
Residue on ignition	%	0.08	Not more than 1.5	JP/USP/EP
Methoxy content	%	23.6	22.0 - 24.0	JP/USP
Hydroxypropoxy content	%	8.0	6.5 - 10.0	JP/USP
Particle size: 20% cumulation (D10)	μm	32.2	20 - 40	SEC
Particle size: Average (D50)	μm	64.4	50 - 80	SEC
Particle size: 80% cumulation (D90)	μm	127.0	100 - 150	SEC

E. Machida
Eiichi Machida
General Manager, Q.A. Dept.

Shin-Etsu No. : 65058988-01-01

Issue:
Shin-Etsu Chemical Co., Ltd.
Cellulose Department
6-1, Otemachi 2-chome, Chiyoda-ku, Tokyo, Japan
TEL 81-3-3246-5251 FAX 81-3-3246-5312

Judgment:
Shin-Etsu Chemical Co., Ltd.
Naoetsu Plant Quality Assurance Department
28-1, Nishifukushima, Kubiki-ku,
Joetsu-shi, Niigata, Japan

Recycled Paper

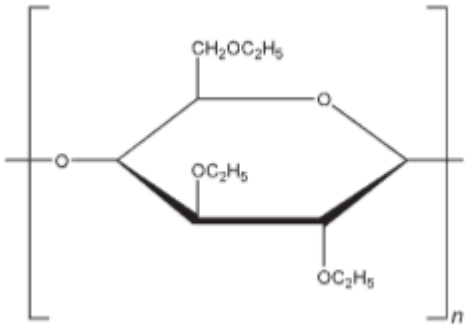
5.2.2 Ethyl Cellulose:

Chemical Name and CAS Registry Number: Cellulose ethyl ether [9004-57-3]

Empirical Formula and Molecular Weight :

Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is C12H23O6(C12H22O5)nC12H23O5 where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined together by acetal linkages.

Structural Formula:



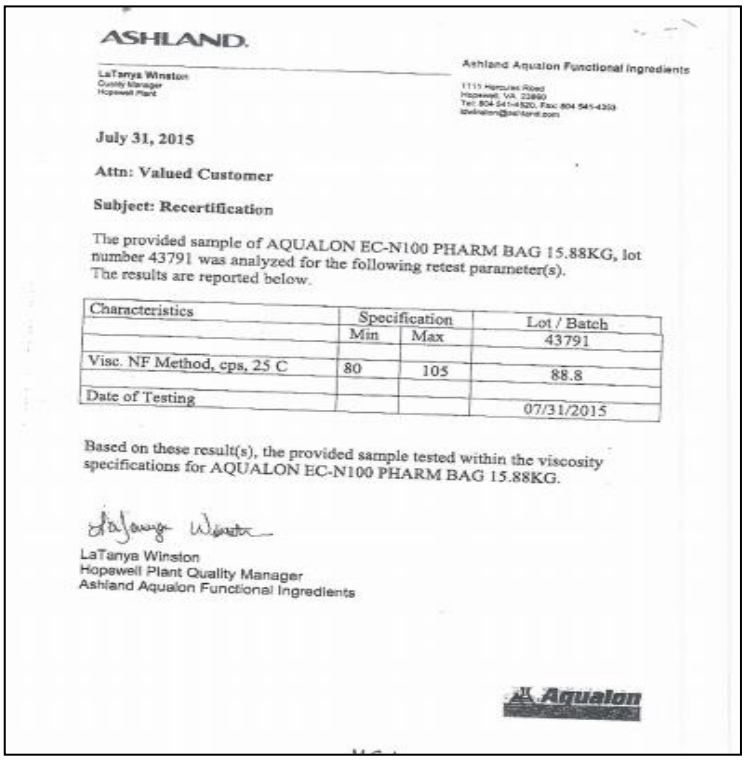
Functional Category: Coating agent; flavoring agent; tablet binder; tablet filler; viscosityincreasing agent.E262 Ethylcellulose

Applications in Pharmaceutical Formulation or Technology :

Ethylcellulose is widely used in oral and topical pharmaceutical formulations; The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask anunpleasant taste,or toimprovethestabilityofa formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer; see Section 18. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents. Drug

release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow processunlessalargesurfacearea(e.g.pelletsorgranulescompared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethylcellulose are used in drug microencapsulation. Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wetgranulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used.Ethylcellulose has been studied as a stabilizer for emulsions. Ethylcellulose is additionally used in cosmetics and food products.

Description; Ethylcellulose is a tasteless, free-flowing, white to light tan-colored powder.[117]



ASHLAND

LaTanya Winston
Quality Manager
Hopewell Plant

Ashland Aqualon Functional Ingredients

July 31, 2015

Attn: Valued Customer

Subject: Recertification

The provided sample of AQUALON EC-N100 PHARM BAG 15.88KG, lot number 43791 was analyzed for the following retest parameter(s). The results are reported below.

Characteristics	Specification		Lot / Batch
	Min	Max	43791
Visc. NF Method, cps, 25 C	80	105	88.8
Date of Testing			07/31/2015

Based on these result(s), the provided sample tested within the viscosity specifications for AQUALON EC-N100 PHARM BAG 15.88KG.

LaTanya Winston
Hopewell Plant Quality Manager
Ashland Aqualon Functional Ingredients

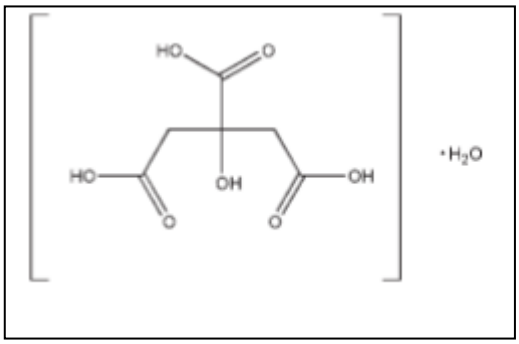
Aqualon

5.2.3 Citric acid :[117]

Chemical Name and CAS Registry Number:2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate [594929-1}

Empirical Formula and Molecular Weight: C6H8O7H2O 210.14

Structural Formula:



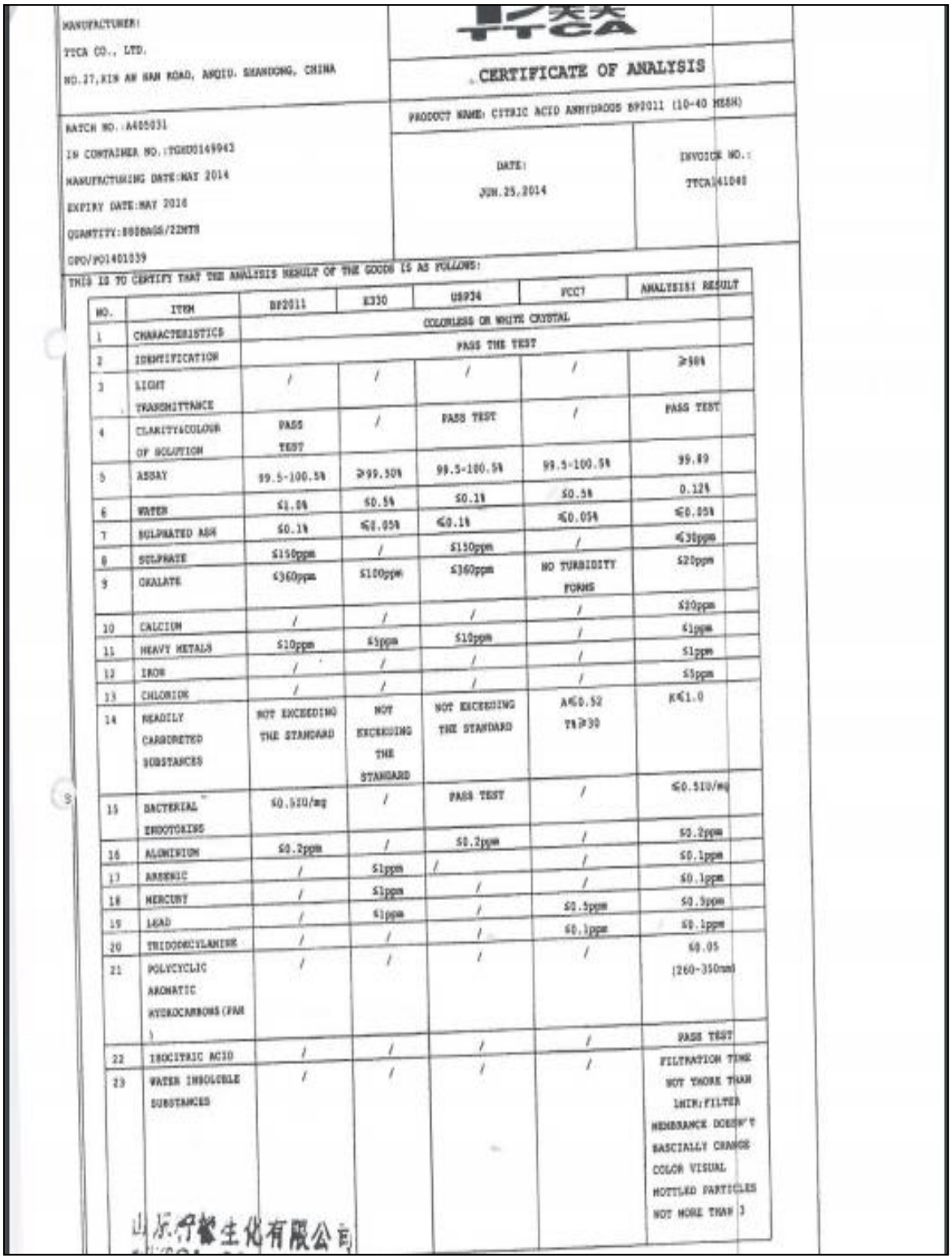
Functional Category: Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer; preservative.

Applications in Pharmaceutical Formulation or Technology:

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets. Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalation formulations. In food products, citric acid is used as a flavor enhancer for its tart, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist; It is also a component of anticoagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi

Description:

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder .It is odorless and has a strong acidic taste. The crystal structure is orthorhombic [117].



MANUFACTURER:
TYCA CO., LTD.
NO.27,RIN AN HAN ROAD, ANQIU. SHANDONG, CHINA

TYCA

CERTIFICATE OF ANALYSIS

BATCH NO.:A405031
IN CONTAINER NO.:TGHU0149943
MANUFACTURING DATE:MAY 2014
EXPIRY DATE:MAY 2016
QUANTITY:8000KGS/22MTS
DPO/PO1401039

PRODUCT NAME: CITRIC ACID ANHYDROUS BP2011 (10-40 MESH)

DATE:
JUN.25,2014

INVOICE NO.:
TYCA141040

THIS IS TO CERTIFY THAT THE ANALYSIS RESULT OF THE GOODS IS AS FOLLOWS:

NO.	ITEM	BP2011	E330	USP34	FCC7	ANALYSIS RESULT
1	CHARACTERISTICS	COLORLESS OR WHITE CRYSTAL				
2	IDENTIFICATION	PASS THE TEST				
3	LIGHT TRANSMITTANCE	/	/	/	/	≥98%
4	CLARITY&COLOUR OF SOLUTION	PASS TEST	/	PASS TEST	/	PASS TEST
5	ASSAY	99.5-100.5%	≥99.50%	99.5-100.5%	99.5-100.5%	99.89
6	WATER	≤1.0%	≤0.5%	≤0.1%	≤0.5%	0.12%
7	SULPHATED ASH	≤0.1%	≤0.05%	≤0.1%	≤0.05%	≤0.05%
8	SULPHATE	≤150ppm	/	≤150ppm	/	≤38ppm
9	OXALATE	≤360ppm	≤100ppm	≤360ppm	NO TURBIDITY FORMS	≤20ppm
10	CALCIUM	/	/	/	/	≤20ppm
11	HEAVY METALS	≤10ppm	≤5ppm	≤10ppm	/	≤1ppm
12	IRON	/	/	/	/	≤1ppm
13	CHLORIDE	/	/	/	/	≤5ppm
14	READILY CARBONIZED SUBSTANCES	NOT EXCEEDING THE STANDARD	NOT EXCEEDING THE STANDARD	NOT EXCEEDING THE STANDARD	A≤0.52 T%≥90	K≤1.0
15	BACTERIAL ENDOTOXINS	≤0.5IU/mg	/	PASS TEST	/	≤0.5IU/mg
16	ALUMINIUM	≤0.2ppm	/	≤0.2ppm	/	≤0.2ppm
17	ARSENIC	/	≤1ppm	/	/	≤0.1ppm
18	MERCURY	/	≤1ppm	/	/	≤0.1ppm
19	LEAD	/	≤1ppm	/	≤0.5ppm	≤0.5ppm
20	TRIDODECYLAMINE	/	/	/	≤0.1ppm	≤0.1ppm
21	POLYCYCLIC AROMATIC HYDROCARBONS (PAH)	/	/	/	/	≤0.05 (260-350nm)
22	ISOCITRIC ACID	/	/	/	/	PASS TEST
23	WATER INSOLUBLE SUBSTANCES	/	/	/	/	FILTRATION TIME NOT MORE THAN 1MIN; FILTER MEMBRANCE DOESN'T BASCIALLY CHANGE COLOR VISUAL MOTTLED PARTICLES NOT MORE THAN 3

山东[illegible]生化有限公司

5.2.4 Sodium bi carbonate:[117]

Chemical Name and CAS Registry Number:

Carbonic acid monosodium salt [144-55-8].

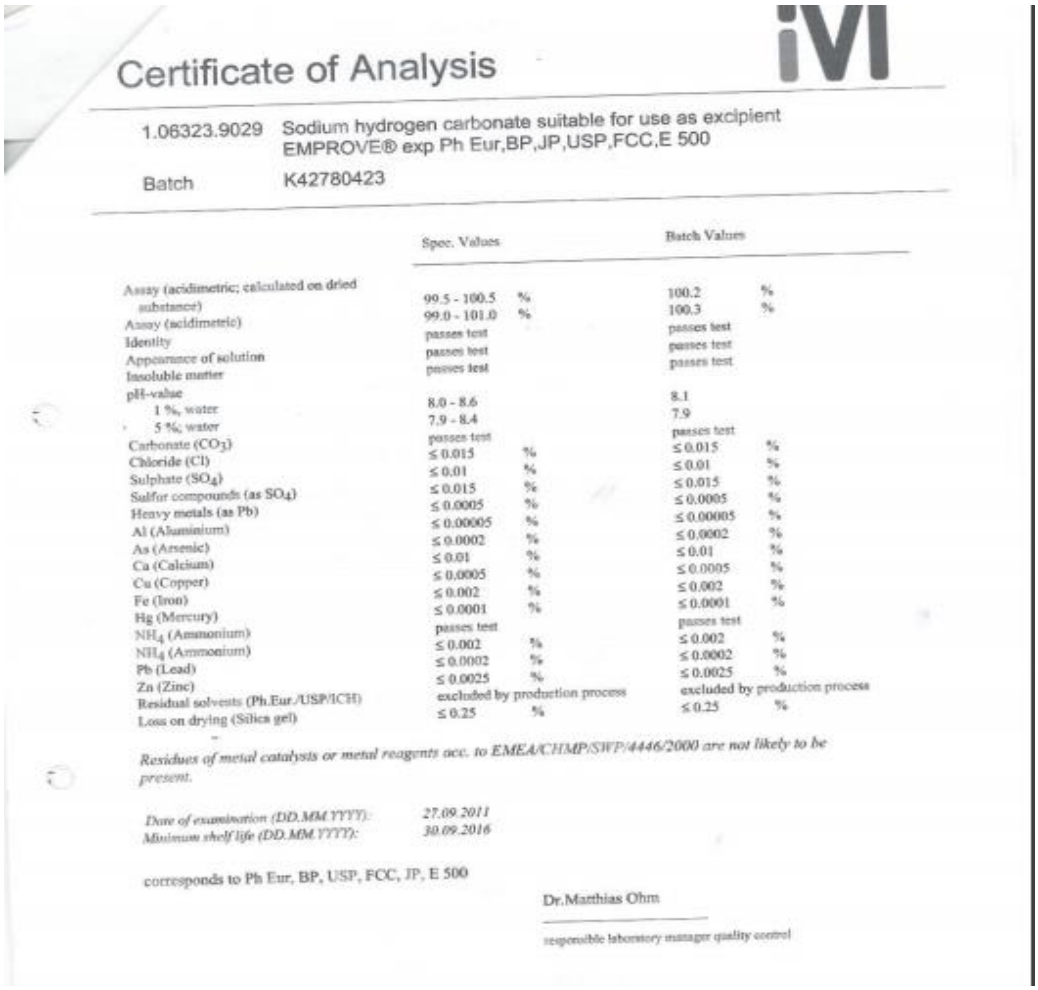
Empirical Formula and Molecular Weight: $NaHCO_3$ 84.01

Functional Category : Alkalizing agent; therapeutic agent.

Applications in Pharmaceutical Formulation or Technology: Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid; combinations of citric and tartaric acid are of tenpreferredin formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone, granules lose firmness. When the tablets or granules come into contact with water, a chemical reaction occurs, carbon dioxide is evolved, and the productdisintegrates. Melt granulation in a fluidized bed dryer has been suggested as a one-step method for the manufacture of effervescent granules composed of anhydrous citric acid and sodium bicarbonate, for subsequent compression into tablets. Tablets may also be prepared with sodium bicarbonate alone since the acid of gastric fluid is sufficient to cause effervescence and disintegration. Sodium bicarbonate is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. The effects of tablet binders, such as polyethylene glycols, microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, and povidone, on the physical and mechanical properties of sodium bicarbonate tablets have also been investigated.Additionally, sodium bicarbonate is used in solutions as a buffering agent for erythromycin, lidocaine, local anesthetic solutions, and total parenteral nutrition (TPN) solutions. In some parenteral formulations, e.g. niacin, sodium bicarbonate is used to produce a sodium salt of the active ingredient that has enhanced solubility. Sodium bicarbonate has also been used as a freeze-drying stabilizer and in toothpastes. Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for a range of drugs. Tablet formulations containing sodium bicarbonate have been shown to increase the

absorption of paracetamol, and improve the stability of levothyroxine. Sodium bicarbonate has also been included in formulations of vaginal bio adhesive tablet and in carbon dioxide releasing suppositories. Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysis fluids; it has also been suggested as a meansofpreventing radiocontrast-induced nephrotoxicity. Sodium bicarbonate is used in food products as an alkali or as a leavening agent, e.g. baking soda.

Description : Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules, are commercially available



Certificate of Analysis

1.06323.9029 Sodium hydrogen carbonate suitable for use as excipient EMPROVE® exp Ph Eur,BP,JP,USP,FCC,E 500

Batch K42780423

	Spec. Values	Batch Values
Assay (acidimetric; calculated on dried substance)	99.5 - 100.5 %	100.2 %
Assay (acidimetric)	99.0 - 101.0 %	100.3 %
Identity	passes test	passes test
Appearance of solution	passes test	passes test
Insoluble matter	passes test	passes test
pH-value		8.1
1 %; water	8.0 - 8.6	7.9
5 %; water	7.9 - 8.4	passes test
Carbonate (CO_3)	passes test	≤ 0.015 %
Chloride (Cl)	≤ 0.015 %	≤ 0.01 %
Sulphate (SO_4)	≤ 0.01 %	≤ 0.015 %
Sulfur compounds (as SO_4)	≤ 0.015 %	≤ 0.0005 %
Heavy metals (as Pb)	≤ 0.0005 %	≤ 0.00005 %
Al (Aluminium)	≤ 0.00005 %	≤ 0.0002 %
As (Arsenic)	≤ 0.0002 %	≤ 0.01 %
Ca (Calcium)	≤ 0.01 %	≤ 0.0005 %
Cu (Copper)	≤ 0.0005 %	≤ 0.002 %
Fe (Iron)	≤ 0.002 %	≤ 0.0001 %
Hg (Mercury)	≤ 0.0001 %	passes test
NH_4 (Ammonium)	passes test	≤ 0.002 %
NH_4 (Ammonium)	≤ 0.002 %	≤ 0.0002 %
Pb (Lead)	≤ 0.0002 %	≤ 0.0025 %
Zn (Zinc)	≤ 0.0025 %	excluded by production process
Residual solvents (Ph.Eur./USP/ICH)	excluded by production process	≤ 0.25 %
Loss on drying (Silica gel)	≤ 0.25 %	

Residues of metal catalysts or metal reagents acc. to EMEA/CHMP/SWP/4446/2000 are not likely to be present.

Date of examination (DD.MM.YYYY): 27.09.2011
Minimum shelf life (DD.MM.YYYY): 30.09.2016

corresponds to Ph Eur, BP, USP, FCC, JP, E 500

Dr.Matthias Ohm

responsible laboratory manager quality control

5.2.5 starch:[117]

Functional Category: as Binding agent; compression aid; disintegrant; tablet and capsule diluent; tablet and capsule filler.

Applications in Pharmaceutical Formulation or Technology : starch can be used in both capsules and tablets to improve flow ability, enhance disintegration and improve hardness.

Description: Corn occurs as a white free-flowing powder. It is a compressed mixture ..

Starch: Included in the FDA Inactive Ingredients Database (buccal tablets, oral capsules, powders, suspensions and tablets; topical preparations; and vaginal tablets). Included in no parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

5.2.6 Mg stearate :[117]

Chemical Name and CAS Registry Number:Octadecanoic acid magnesium salt [557-04-0}

Empirical Formula and Molecular Weight: C36H70MgO4 591.24

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

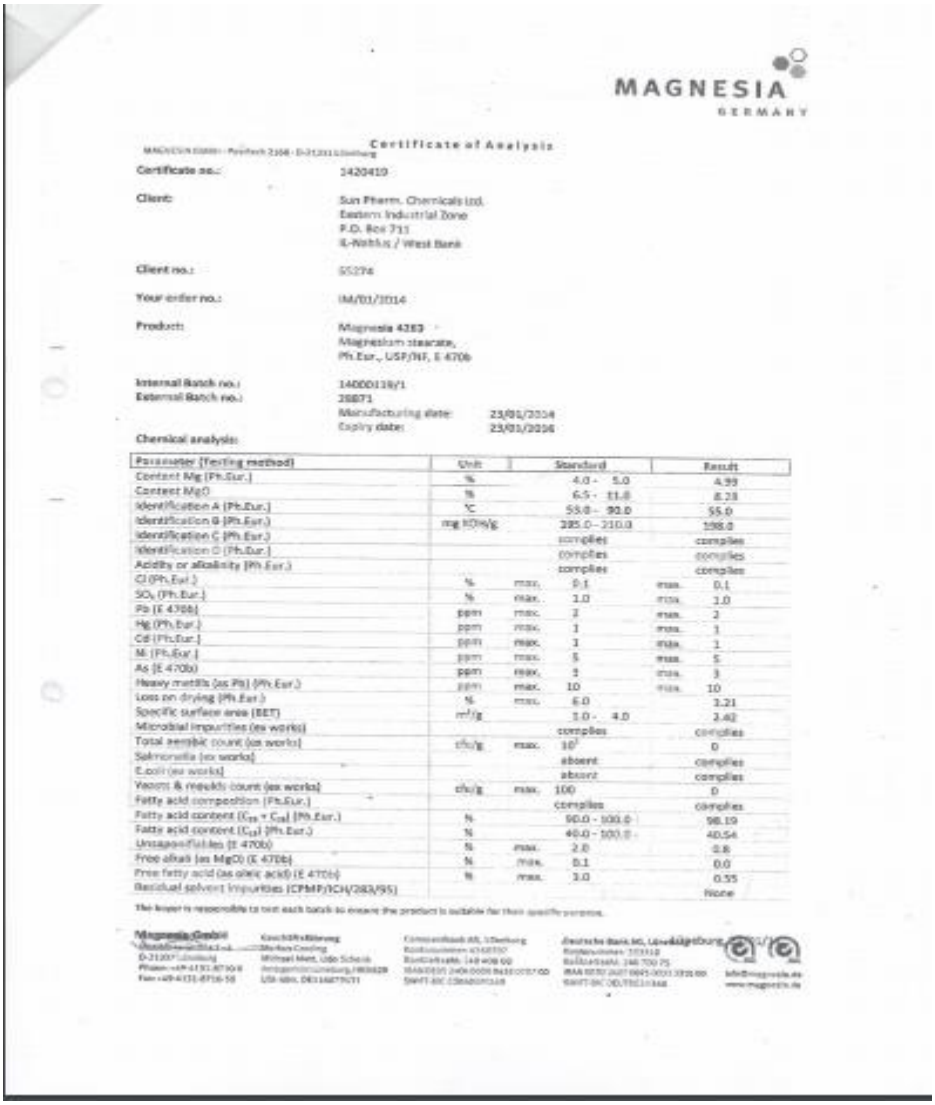
Structural Formula: [CH3(CH2)16COO]2Mg

.**Functional Category:** Tablet and capsule lubricant

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations .between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description : Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powderisgreasytothe touch and readily adheres to the skin.



MAGNESIA
GERMANY

Certificate of Analysis

Certificate no.: 1420410

Client: Sun Pharm. Chemicals Ltd.
Eastern Industrial Zone
P.O. Box 711
IL-Within / West Bank

Client no.: 55274

Your order no.: IM/01/2014

Product: Magnesia 4183
Magnesium stearate,
Ph.Eur., USP/NF, E 470b

Internal Batch no.: 14000118/1
External Batch no.: 28871
Manufacturing date: 23/01/2014
Expiry date: 23/01/2016

Chemical analysis:

Parameter (Testing method)	Unit		Standard		Result
Content Mg (Ph.Eur.)	%		4.0 - 5.0		4.99
Content MgO	%		6.5 - 11.8		8.28
Identification A (Ph.Eur.)	°C		55.0 - 90.0		55.0
Identification B (Ph.Eur.)	mg KOH/g		185.0 - 210.0		198.0
Identification C (Ph.Eur.)			complies		complies
Identification D (Ph.Eur.)			complies		complies
Acidity or alkalinity (Ph.Eur.)			complies		complies
Cl (Ph.Eur.)	%	max.	0.1	max.	0.1
SO_4 (Ph.Eur.)	%	max.	1.0	max.	1.0
Pb (E 470b)	ppm	max.	2	max.	2
Hg (Ph.Eur.)	ppm	max.	1	max.	1
Cd (Ph.Eur.)	ppm	max.	1	max.	1
Ni (Ph.Eur.)	ppm	max.	5	max.	5
As (E 470b)	ppm	max.	3	max.	3
Heavy metals (as Pb) (Ph.Eur.)	ppm	max.	10	max.	10
Loss on drying (Ph.Eur.)	%	max.	6.0		3.21
Specific surface area (BET)	m^2/g		1.0 - 4.0		2.42
Microbial impurities (ex works)			complies		complies
Total aerobic count (ex works)	cfu/g	max.	10^3		0
Salmonella (ex works)			absent		complies
E.coli (ex works)			absent		complies
Yeasts & moulds count (ex works)	cfu/g	max.	100		0
Fatty acid composition (Ph.Eur.)			complies		complies
Fatty acid content (C_{16} + C_{18}) (Ph.Eur.)	%		90.0 - 100.0		98.19
Fatty acid content (C_{18}) (Ph.Eur.)	%		40.0 - 50.0		40.54
Unsaponifiables (E 470b)	%	max.	2.0		0.8
Free alkali (as MgO) (E 470b)	%	max.	0.1		0.0
Free fatty acid (as oleic acid) (E 470b)	%	max.	3.0		0.55
Residual solvent impurities (CPMP/ICH/283/95)					None

The buyer is responsible to test each batch to ensure the product is suitable for their specific purpose.

Magnesia GmbH · Geschäftsführung: Michael Mett, Udo Schenk · Commerzbank AG, Lüneburg · Deutsche Bank AG, Lüneburg

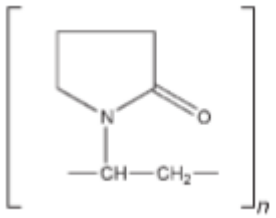
5.2.7 Povidine : (PVP K30):[117]

Chemical Name and CAS Registry Number:

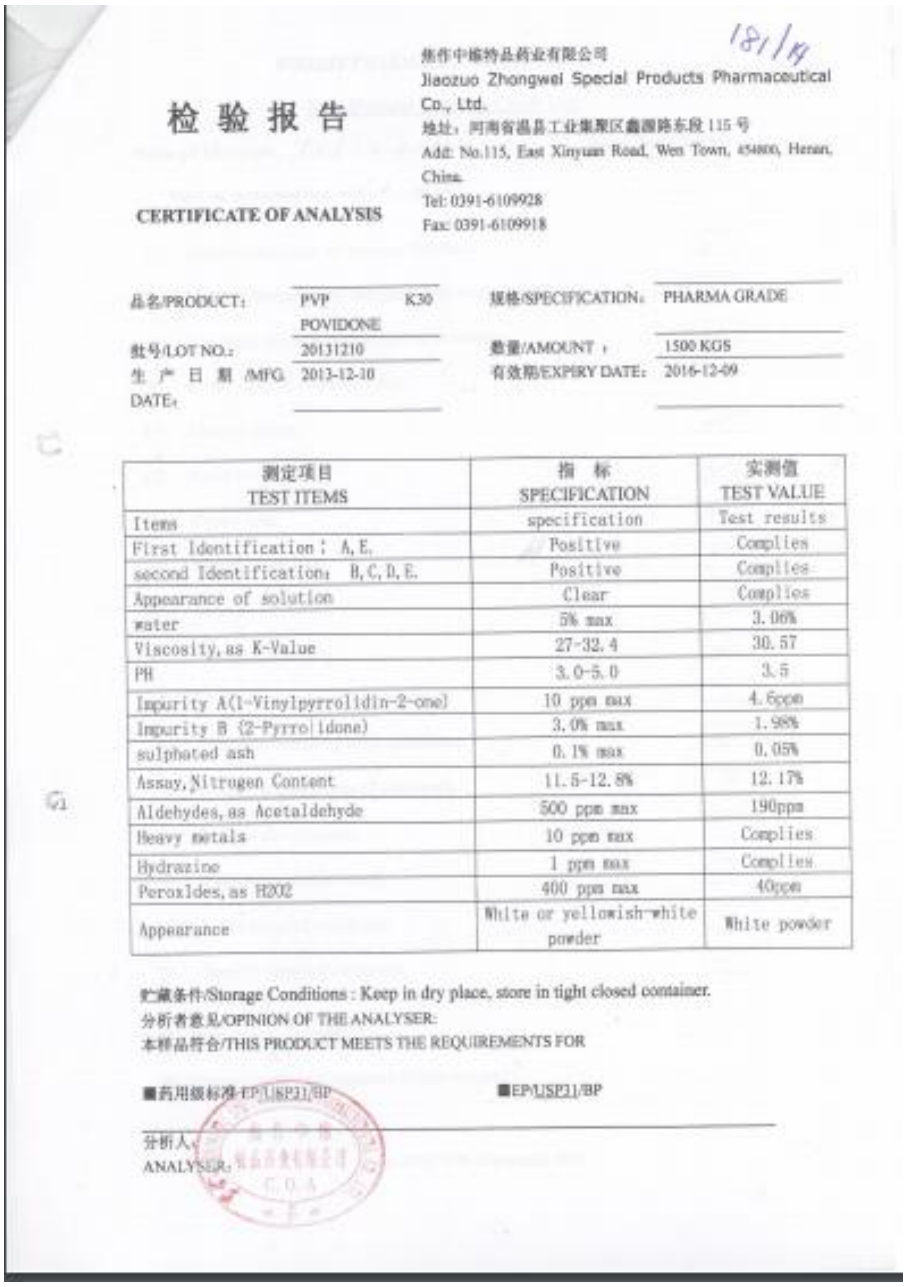
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8}

Empirical Formula and Molecular Weight: (C6H9NO)n 2500–3000000 TheUSP32describes Povidine as a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the differing degree of polymerization of which results in polymers of various molecular weights. It is characterized by its viscosity in aqueous solution

Structural Formula:



Functional Category: Disintegrant; dissolution enhancer; suspending agent; tablet binder.



焦作中维特品药业有限公司
Jiaozuo Zhongwei Special Products Pharmaceutical Co., Ltd.
地址：河南省温县工业集聚区鑫源路东段115号
Add: No.115, East Xinyuan Road, Wen Town, 454800, Henan, China.
Tel: 0391-6109928
Fax: 0391-6109918

检 验 报 告

CERTIFICATE OF ANALYSIS

品名/PRODUCT:	PVP K30 POVIDONE	规格/SPECIFICATION:	PHARMA GRADE
批号/LOT NO.:	20131210	数量/AMOUNT :	1500 KGS
生 产 日 期 /MFG DATE:	2013-12-10	有效期/EXPIRY DATE:	2016-12-09

测定项目 TEST ITEMS	指 标 SPECIFICATION	实测值 TEST VALUE
Items	specification	Test results
First Identification: A, E.	Positive	Complies
second Identification: B, C, D, E.	Positive	Complies
Appearance of solution	Clear	Complies
water	5% max	3.06%
Viscosity, as K-Value	27-32.4	30.57
PH	3.0-5.0	3.5
Impurity A(1-Vinylpyrrolidin-2-one)	10 ppm max	4.6ppm
Impurity B (2-Pyrrolidone)	3.0% max	1.98%
sulphated ash	0.1% max	0.05%
Assay, Nitrogen Content	11.5-12.8%	12.17%
Aldehydes, as Acetaldehyde	500 ppm max	190ppm
Heavy metals	10 ppm max	Complies
Hydrazine	1 ppm max	Complies
Peroxides, as H2O2	400 ppm max	40ppm
Appearance	White or yellowish-white powder	White powder

贮藏条件/Storage Conditions : Keep in dry place, store in tight closed container.
分析者意见/OPINION OF THE ANALYSER:
本样品符合/THIS PRODUCT MEETS THE REQUIREMENTS FOR

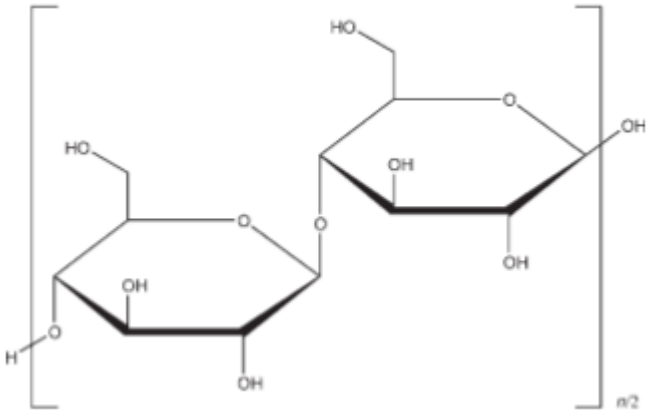
■药用级标准 EP/USP31/BP ■EP/USP31/BP

分析人/ANALYSER:

5.2.8 Microcrystalline cellulose:[117]

Chemical Name and CAS Registry Number: Cellulose [9004-34-6].

Structural Formula:



Empirical Formula and Molecular Weight :(C6H10O5)n 36000 where n 220.

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as abinder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

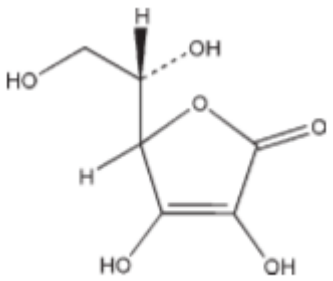
5.2.9 Ascorbic Acid : [117]

Chemical Name and CAS Registry Number: L-(þ)-Ascorbic acid [50-81-7].

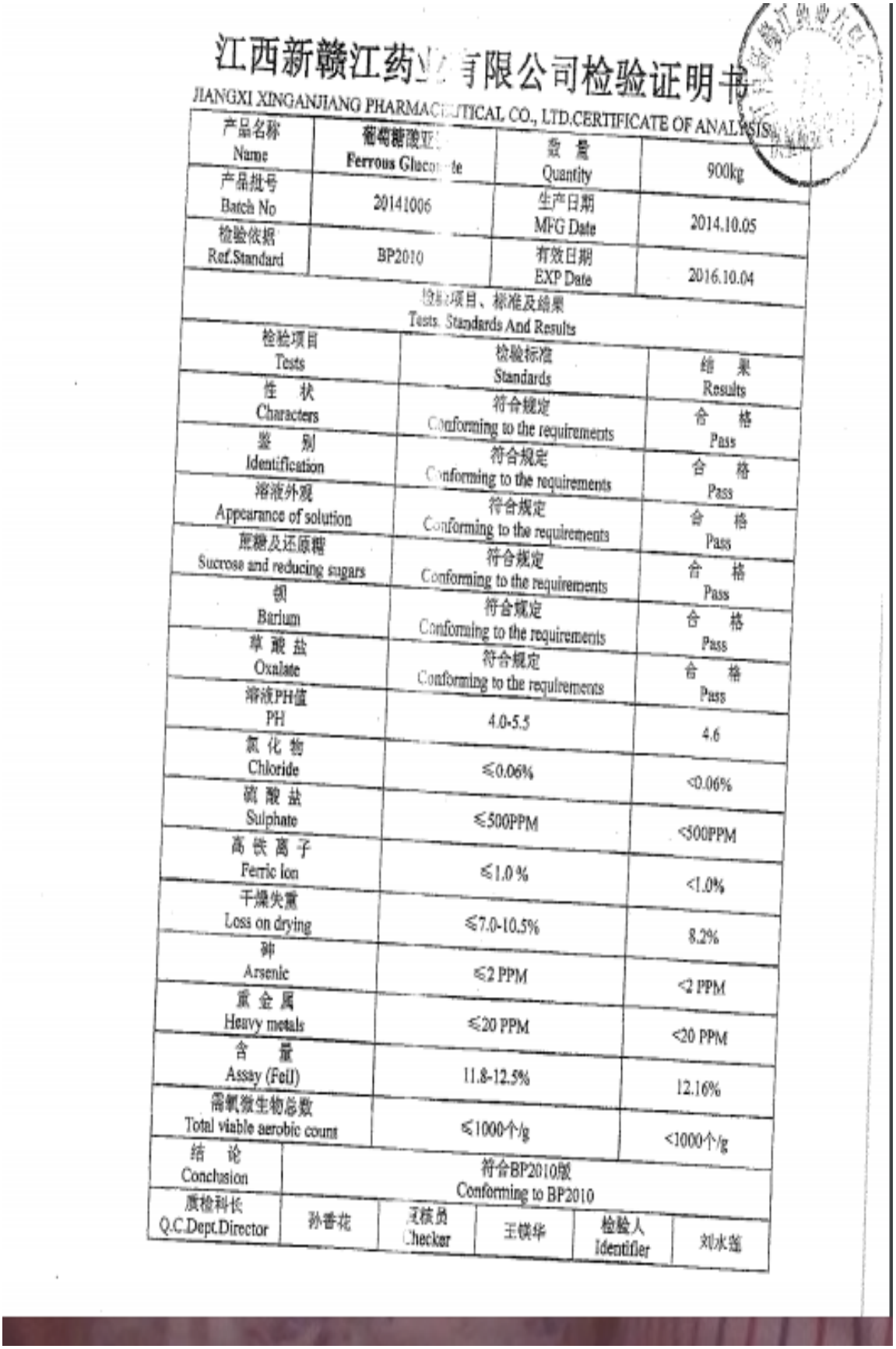
Empirical Formula and Molecular Weight : C6H8O6 176.13

Functional Category: Antioxidant; therapeutic agent.

Structural Formula:



5.2.10 ferrous gluconate :



江西新赣江药业有限公司检验证明书

JIANGXI XINGANJIANG PHARMACEUTICAL CO., LTD.CERTIFICATE OF ANALYSIS

产品名称 Name	葡萄糖酸亚铁 Ferrous Gluconate	数量 Quantity	900kg
产品批号 Batch No	20141006	生产日期 MFG Date	2014.10.05
检验依据 Ref.Standard	BP2010	有效日期 EXP Date	2016.10.04

检验项目、标准及结果
Tests, Standards And Results

检验项目 Tests	检验标准 Standards	结果 Results
性状 Characters	符合规定 Conforming to the requirements	合格 Pass
鉴别 Identification	符合规定 Conforming to the requirements	合格 Pass
溶液外观 Appearance of solution	符合规定 Conforming to the requirements	合格 Pass
蔗糖及还原糖 Sucrose and reducing sugars	符合规定 Conforming to the requirements	合格 Pass
钡 Barium	符合规定 Conforming to the requirements	合格 Pass
草酸盐 Oxalate	符合规定 Conforming to the requirements	合格 Pass
溶液PH值 PH	4.0-5.5	4.6
氯化物 Chloride	≤0.06%	<0.06%
硫酸盐 Sulphate	≤500PPM	<500PPM
高铁离子 Ferric Ion	≤1.0 %	<1.0%
干燥失重 Loss on drying	≤7.0-10.5%	8.2%
砷 Arsenic	≤2 PPM	<2 PPM
重金属 Heavy metals	≤20 PPM	<20 PPM
含量 Assay (FeII)	11.8-12.5%	12.16%
需氧微生物总数 Total viable aerobic count	≤1000个/g	<1000个/g
结论 Conclusion	符合BP2010版 Conforming to BP2010	

质检科长 Q.C.Dept.Director	孙香花	复核员 Checker	王模华	检验人 Identifier	刘水莲

5.3 References:

1. Bhoyar, P., J. Baheti, and V.V. Burde, *An overview of a gastro-retentive floating drug delivery system.* World journal of pharmaceutical research, 2012. **1**(2): p. 22-40.
2. Gupta, G. and A. Singh, *A Short Review on Stomach Specific Drug Delivery System.* International Journal of Pharmaceutical Technology and Research, 2012. **4**(4): p. 1527-1545.
3. Hirtz, J., *The gastrointestinal absorption of drugs in man: a review of current concepts and methods of investigation.* British journal of clinical pharmacology, 1985. **19**(S2): p. 77S-83S.
4. Sharma, M., *A Review of Floating Drug Delivery Systems.* Asian Journal of Biomedical and Pharmaceutical Sciences, 2013. **3**(24): p. Page Numbers: 1-6 Review.
5. Nayak, A.K., J. Malakar, and K.K. Sen, *Gastroretentive drug delivery technologies: Current approaches and future potential.* J Pharm Educ Res, 2010. **1**(2): p. 1-10.
6. Garg, S. and S. Sharma, *Gastroretentive drug delivery systems.* 2003.
7. Dehghan, M. and F. Kha, *Gastroretentive drug delivery systems: A patent perspective.* International Journal of Health Research, 2009. **2**(1).
8. Klausner, E.A., et al., *Expandable gastroretentive dosage forms.* Journal of controlled release, 2003. **90**(2): p. 143-162.
9. Nagesh, H., et al., *Advances in Gastroretentive Drug Delivery System: An Review.* 2014.
10. Ummadi, S., et al., *Overview on controlled release dosage form.* System, 2013. **7**: p. 8.
11. Ware, M., et al., *New insights into gastro-retentive floating drug delivery systems.* World journal of pharmacy and pharmaceutical sciences, 2013. **3**(1): p. 252-270.
12. Bhowmik, D., et al., *Trends in scope and opportunities of control release oral drug delivery systems.* Critical review in pharmaceutical sciences, 2012. **1**: p. 20-33.
13. Mandapati, L., et al., *Gastroretentive drug delivery system.* Indo American Journal of Pharmaceutical Research, 2013. **3**(9): p. 7207-7215.
14. Bardonnet, P., et al., *Gastroretentive dosage forms: Overview and special case of Helicobacter pylori.* Journal of controlled release, 2006. **111**(1): p. 1-18.
15. Sharma, N., et al., *A comprehensive review on floating drug delivery system.* International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011. **2**(2): p. 428-432.
16. Arunachalam, A., et al., *Floating drug delivery systems: A review.* Int. J. Res. Pharm. Sci, 2011. **2**(1): p. 76-83.
17. Manish, J. and P. Hardik, *Gastro retentive floating drug delivery system: a review.* IJPRBs, 2013. **2**(2): p. 358-77.
18. Bhowmik, D., et al., *Floating drug delivery system-A review.* Der Pharmacia Lettre, 2009. **1**(2): p. 199-218.
19. Singh, B.N. and K.H. Kim, *Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention.* Journal of Controlled release, 2000. **63**(3): p. 235-259.
20. Narang, N., *An updated review on: floating drug delivery system (FDDS).* International journal of applied pharmaceutics, 2011. **3**(1): p. 1-7.
21. Patel, H.K., A. Nagle, and R. Murthy, *Characterization of calcium alginate beads of 5-fluorouracil for colon delivery.* Asian Journal of Pharmaceutics, 2008. **2**(4): p. 241.
22. Nasa, P., S. Mahant, and D. Sharma, *Floating systems: a novel approach towards gastroretentive drug delivery systems.* International Journal of Pharmacy and Pharmaceutical Sciences, 2010. **2**(3): p. 2-7.
23. Moes, A., *Gastroretentive dosage forms.* Critical reviews in therapeutic drug carrier systems, 1992. **10**(2): p. 143-195.
24. Faivre, V., *Aspects théoriques de la bioadhésion.* Nonvelles formes medicamenteuses, Editions Medicales Internationales, Editions TEC and DOC, Cachan, 2004: p. 1-24.

25. Huang, Y., et al., *Molecular aspects of muco-and bioadhesion:: Tethered structures and site-specific surfaces.* Journal of controlled release, 2000. **65**(1): p. 63-71.
26. Chen, J., et al., *Gastric retention properties of superporous hydrogel composites.* Journal of Controlled Release, 2000. **64**(1): p. 39-51.
27. Prajapati, V.D., et al., *Raft forming system—An upcoming approach of gastroretentive drug delivery system.* Journal of controlled release, 2013. **168**(2): p. 151-165.
28. Jha, P., et al., *PHARMACEUTICAL ASPECTS OF VARIOUS FLOATING DRUG DELIVERY SYSTEM.* 2015.
29. Jayanthi, G., S. Jayaswal, and A. Srivastava, *Formulation and evaluation of terfenadine microballoons for oral controlled release.* Die Pharmazie, 1995. **50**(11): p. 769.
30. Timmermans, J. and A.J. Moës, *Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy.* Journal of pharmaceutical sciences, 1994. **83**(1): p. 18-24.
31. Vyas, S. and R.K. Khar, *Gastroretentive systems.* Controlled drug Delivery. Vallabh Prakashan, Delhi, India, 2006: p. 197-217.
32. Rathod, H., V. Patel, and M. Modasia, *Floating drug delivery system: innovative approach of gastroretention.* International Journal of Pharmaceutical Sciences Review and Research, 2010. **4**(3): p. 183-192.
33. Moes, A., *Gastric retention systems for oral drug delivery.* Business Briefing: Pharmatech, 2003: p. 157-59.
34. Van Gansbeke, B., et al., *Intragastric positioning of two concurrently ingested pharmaceutical matrix dosage forms.* International journal of radiation applications and instrumentation. Part B. Nuclear medicine and biology, 1991. **18**(7): p. 711-718.
35. Waugh, A. and A. Grant, *Ross & Wilson anatomy and physiology in health and illness*. 2014: Elsevier Health Sciences.
36. Pawar, V.K., et al., *Industrial perspective of gastroretentive drug delivery systems: physicochemical, biopharmaceutical, technological and regulatory consideration.* Expert opinion on drug delivery, 2012. **9**(5): p. 551-565.
37. Joseph, R. and C. Rhodes, *Modern pharmaceutics.* Marcel Dekker, Inc., New York, 1996. **72**(3): p. 58.
38. Hoffman, A., *Pharmacodynamic aspects of sustained release preparations.* Advanced drug delivery reviews, 1998. **33**(3): p. 185-199.
39. Vyas, S.P. and R.K. Khar, *Controlled drug delivery concepts and advances.* vallabh prakashan, 2002. **1**: p. 411-447.
40. Streubel, A., J. Siepmann, and R. Bodmeier, *Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release.* European journal of pharmaceutical sciences, 2003. **18**(1): p. 37-45.
41. Institute, I.D. *what is iron*. 2009; Available from: http://www.irondisorders.org/what-is-iron/.
42. Food and D. Administration, *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Report of the Panel on Micronutrients.* Report of the Panel on Micronutrients, 2001.
43. Weiss, G., *Iron and immunity: a double-edged sword.* European journal of clinical investigation, 2002. **32**(s1): p. 70-78.
44. Hentze, M.W., M.U. Muckenthaler, and N.C. Andrews, *Balancing acts: molecular control of mammalian iron metabolism.* cell, 2004. **117**(3): p. 285-297.
45. Papanikolaou, G., et al., *Hepcidin in iron overload disorders.* Blood, 2005. **105**(10): p. 4103-4105.
46. Burke, D.E., et al., *Effects of Lean Beef Supplementation on Iron Status, Body Composition and Performance of Collegiate Distance Runners.* Food and Nutrition Sciences, 2012. **3**(06): p. 810.

47. CDC.gov. *normal iron absorption and storage* 2013; Available from: http://www.cdc.gov/ncbddd/hemochromatosis/training/pathophysiology/iron_cycle_popup.htm.
48. National Institutes of Health. *iron absobtion* 2011; Available from: National Institutes of Health, 2011.
49. Mahan, L.K. and S. Escott-Stump, *Krause's food & nutrition therapy*. 2008: Saunders/Elsevier St. Louis, Mo.
50. Conrad, M.E. and J.N. Umbreit, *Pathways of iron absorption.* Blood Cells, Molecules, and Diseases, 2002. **29**(3): p. 336-355.
51. Poss, K.D. and S. Tonegawa, *Heme oxygenase 1 is required for mammalian iron reutilization.* Proceedings of the National Academy of Sciences, 1997. **94**(20): p. 10919-10924.
52. Miret, S., R.J. Simpson, and A.T. McKie, *Physiology and molecular biology of dietary iron absorption.* Annual review of nutrition, 2003. **23**(1): p. 283-301.
53. Wessling-Resnick, M., *Iron transport.* Annual review of nutrition, 2000. **20**(1): p. 129-151.
54. WHOreport. *aniemia defention who*. 2015; Available from: http://www.who.int/topics/anaemia/en/.
55. clinic, m. *mayo clinc iron* 2015; Available from: http://www.mayoclinic.org/diseases-conditions/iron-deficiency-anemia/basics/definition/con-20019327.
56. Stein, J. and A.U. Dignass, *Management of iron deficiency anemia in inflammatory bowel disease–a practical approach.* Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology, 2013. **26**(2): p. 104.
57. Killip, S., J.M. Bennett, and M.D. Chambers, *Iron deficiency anemia.* Am Fam Physician, 2007. **75**(5): p. 671-8.
58. Haddad, E.H., et al., *Dietary intake and biochemical, hematologic, and immune status of vegans compared with nonvegetarians.* The American journal of clinical nutrition, 1999. **70**(3): p. 586s-593s.
59. prevention, c.o.d.a., *aniemia.* 2012.
60. line, h. *iron defesincy* 2011; Available from: http://www.healthline.com/health/iron-deficiency-anemia#Causes2.
61. istutes, n.l.h.a.b. *anemia defecincy risk* 2014; Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/ida/atrisk.
62. Alleyne, M., M.K. Horne, and J.L. Miller, *Individualized treatment for iron-deficiency anemia in adults.* The American journal of medicine, 2008. **121**(11): p. 943-948.
63. © 1995-2015 Healthwise, I.H., Healthwise for every health decision, and the Healthwise logo are trademarks of Healthwise, Incorporated. *Iron Deficiency Anemia*. 2014; Available from: http://www.webmd.com/a-to-z-guides/iron-deficiency-anemia-treatment-overview.
64. James L Harper, M.A.P., Department of Pediatrics, Division of Hematology/Oncology and Bone Marrow Transplantation, Associate Chairman for Education, Department of Pediatrics, University of Nebraska Medical Center; Associate Clinical Professor, Department of Pediatrics, Creighton University School of Medicine; Director, Continuing Medical Education, Children's Memorial Hospital; Pediatric Director, Nebraska Regional Hemophilia Treatment Center. *anemia treatment*. 2015; Available from: http://emedicine.medscape.com/article/202333-treatment.
65. Santiago, P., *Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: a clinical overview.* The Scientific World Journal, 2012. **2012**.
66. Stolfus, R. and M. Deyfuss, *Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia*. 1998, International Nutritional Anemia Consultative Group. Washington, DC: International Life Sciences Institute Press.
67. Bhadra, S., H. Ahir, and A. Gupta, *Sustained Release Floating Tablet Of Ferrous Sulfate.*

68. Macdougall, I.C., *Strategies for iron supplementation: oral versus intravenous.* Kidney International, 1999. **55**: p. S61-S66.
69. Davidsson, L., et al., *Iron bioavailability in infants from an infant cereal fortified with ferric pyrophosphate or ferrous fumarate.* The American journal of clinical nutrition, 2000. **71**(6): p. 1597-1602.
70. Nagpal, J. and P. Choudhury, *Iron formulations in pediatric practice.* Indian pediatrics, 2004. **41**(8): p. 807-816.
71. Hayhoe, F., *Iron preparations for anaemia.* British medical journal, 1960. **1**(5180): p. 1195.
72. Gatenby, P. and E. Lillie, *Iron-deficiency anaemia in pregnancy.* The Lancet, 1955. **265**(6867): p. 740-743.
73. Rybo, G. and L. Sölvell, *Side-Effect Studies on a New Sustained Release Iron Preparation.* Scandinavian journal of haematology, 1971. **8**(4): p. 257-264.
74. Elwood, P. and G. Williams, *A comparative trial of slow-release and conventional iron preparations.* The Practitioner, 1970. **204**(224): p. 812.
75. Brock, C., et al., *Adverse effects of iron supplementation: a comparative trial of a wax-matrix iron preparation and conventional ferrous sulfate tablets.* Clinical therapeutics, 1984. **7**(5): p. 568-573.
76. MOH2014. *annual health report* 2014; Available from: www.moh.ps
77. pubchem. *ferrous gluconate* 2015; Available from: http://pubchem.ncbi.nlm.nih.gov/compound/71372#section=Top.
78. pharmacopia29, U. *ferrous gluconate monograph* 1999; Available from: http://www.pharmacopeia.cn/v29240/usp29nf24s0_m32940.html.
79. Sax, N.I. and R.D. Bruce, *Dangerous properties of industrial materials*. 1975: Van Nostrand Reinhold Co.
80. Remington, J.P., et al., *Remington's pharmaceutical sciences.* 1975.
81. Hoover, J.E. and A. Osol, *Remington's pharmaceutical sciences*. 1970.
82. O'Neil, M.J., et al., *The Merck Index-An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co*. 2001, Inc.
83. Lewis, R.J., *Sax's dangerous properties of industrial materials.* 1996.
84. Gilman, A., *The pharmacological basis of therapeutics*. 1975, New York: Macmillan.
85. Drugs, A.M.A.D.o., *AMA drug evaluations*. 1973: Publishing Sciences Group, Incorporated.
86. Organization, W.H., *Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia.* 2008.
87. HAYAT, K. *Which Salt is Better Ferrous Gluconate or Ferrous Sulfate?* 2012; Available from: http://medimoon.com/2012/08/which-salt-is-better-ferrous-gluconate-or-ferrous-sulfate/?aohc=&pm=%3D0qvh6L0k3v7%2FDe%2FqXfr&h=597c949c1462de515b73e42b71243a53bf3c7e36&k=561807fcdce912218337.2374999.3251078&ban=2218337.2374999&zp=http%3A%2F%2Fzg1.zeroredirect1.com%2Fzcvisitor%2Ff258dee1-6eb3-11e5-95f8-0a0b2cace8ed&time=1444415484.
88. Krögel, I. and R. Bodmeier, *Floating or pulsatile drug delivery systems based on coated effervescent cores.* International journal of Pharmaceutics, 1999. **187**(2): p. 175-184.
89. Hoener, B.-a. and L.Z. Benet, *Factors influencing drug absorption and drug availability.* Modern pharmaceutics, 2002. **2**.
90. Sheth, P. and J. Tossounian, *The hydrodynamically balanced system (HBS™): a novel drug delivery system for oral use.* Drug Development and Industrial Pharmacy, 1984. **10**(2): p. 313-339.
91. Timmermans, J. and A. Moes, *How well do floating dosage forms float?* International journal of pharmaceutics, 1990. **62**(2): p. 207-216.
92. Erni, W. and K. Held, *The hydrodynamically balanced system: a novel principle of controlled drug release.* European neurology, 1987. **27**(Suppl. 1): p. 21-27.
93. Bothwell, T.H., et al., *Iron metabolism in man.* Iron metabolism in man., 1979.

94. Sheth, P.R. and J.L. Tossounian, *Sustained release pharmaceutical capsules*. 1978, Google Patents.
95. Cook, J., et al., *Gastric delivery system for iron supplementation.* The Lancet, 1990. **335**(8698): p. 1136-1139.
96. Simmons, W.K., et al., *Evaluation of a gastric delivery system for iron supplementation in pregnancy.* The American journal of clinical nutrition, 1993. **58**(5): p. 622-626.
97. Najafi, R.B., L. Saghaei, and T. Babaeimehr, *Preparation and pharmaceutical evaluation of ferrous sulfate and ascorbic acid floating matrix tablet for prevention of anemia.* Journal of Reports in Pharmaceutical Sciences (J. Rep. Pharm. Sci.), 2013. **1**(2): p. 73-80.
98. b4drug. *conviron* 2015; Available from: http://b4drug.com/Ferrous-Sulphate-Conviron-Forte/.
99. Ibrahim, D. *Oral Iron Supplements: A Review Feb 14, 2003* 2003; Available from: http://medsask.usask.ca/documents/hot-topics/Oral_Iron_Supplements.pdf.
100. FrederickáSmith, G., *The colorimetric determination of iron in raw and treated municipal water supplies by use of 4: 7-diphenyl-1: 10-phenanthroline.* Analyst, 1952. **77**(917): p. 418-422.
101. Adhikamsetty, R., N. Gollapalli, and S. Jonnalagadda, *Complexation kinetics of Fe2+ with 1, 10-phenanthroline forming ferroin in acidic solutions.* International Journal of Chemical Kinetics, 2008. **40**(8): p. 515-523.
102. Pascale, C.R., *Comparison of Methods for the Measurement of the Angle of Repose of Granular Materials.* 2013.
103. Pharmacopia, v.N. *evaluating flow properities of solids* 1996; Available from: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1174.html.
104. Caldwell, L.J., C.R. Gardner, and R.C. Cargill, *Drug delivery device which can be retained in the stomach for a controlled period of time*. 1988, Google Patents.
105. Pharmacopoeia, I., *Government of India, Ministry of Health and Family Welfare, vol. II.* Delhi: The Controller of Publication, 1996: p. 634.
106. Bodea, A. and S.E. Leucuta, *Optimization of propranolol hydrochloride sustained release pellets using a factorial design.* International journal of pharmaceutics, 1997. **154**(1): p. 49-57.
107. Bajaj, S., D. Singla, and N. Sakhuja, *Stability Testing of Pharmaceutical Products.* 2012.
108. Cha, J., et al., *Stability studies in Handbook of modern pharmaceutical analysis.* Separation Science and Technology. Elsevier, 2001: p. 459-505.
109. Costa, P. and J.M.S. Lobo, *Modeling and comparison of dissolution profiles.* European journal of pharmaceutical sciences, 2001. **13**(2): p. 123-133.
110. AW, H., *Crowell JH. Dependence of reaction velocity upon surface and agitation.* Ind Eng Chem, 1931. **23**: p. 923-931.
111. Becker, D., T. Rigassi, and A. Bauer-Brandl, *Effectiveness of binders in wet granulation: A comparison using model formulations of different tabletability.* Drug development and industrial pharmacy, 1997. **23**(8): p. 791-808.
112. Hammad, M. and B. Müller, *Solubility and stability of tetrazepam in mixed micelles.* European journal of pharmaceutical sciences, 1998. **7**(1): p. 49-55.
113. Gopalakrishnan, S. and A. Chenthilnathan, *Floating drug delivery systems: A Review.* Journal of Pharmaceutical Science and Technology, 2011. **3**(2): p. 548-554.
114. Verhoeven, E., C. Vervaet, and J.P. Remon, *Xanthan gum to tailor drug release of sustained-release ethylcellulose mini-matrices prepared via hot-melt extrusion: in vitro and in vivo evaluation.* European journal of pharmaceutics and biopharmaceutics, 2006. **63**(3): p. 320-330.
115. Deshpande, R.D., et al., *Bi-layer tablets-An emerging trend: a review.* International Journal of Pharmaceutical Sciences and Research, 2011. **2**(10): p. 2534-2544.
116. Brahmankar, D. and S.B. Jaiswal, *Biopharmaceutics and pharmacokinetics: A treatise*. 2005: Vallabh prakashan.

117. Raymond, C.R., J.S. Paul, and C.O. Sian, *Handbook of pharmaceutical excipients.* Americian Pharmaceutical Association, 2006: p. 262-267.

تطوير وتقييم مخبري لمستحضر صيدلاني جديد يحتوي على فِيرّس جلوكونيت في حبه طافية في المعدة لفترة زمنية طويلة

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الملخص:

بالرجوع إلى منظمه الصحة العالمية فان الأنيميا (مرض فقر الدم) الناتج عن فقر الحديد يعتبر أكثر شكل من أشكال سوء التغذية انتشارا حول العالم إن الأشكال الصيدلانية التي تحتوي على الحديد حاليا بالصيدليات لا تؤدي إلى امتصاص جيد للحديد بسبب إن الحديد له امتصاص عالي في الجزء الأول من الأمعاء الدقيقة وإن الشكل الذي يمتص بصوره اكبر هو الجزء غير المؤكسد. وبالتالي ومن اجل إن نحصل على امتصاص اكبر من الحديد يجب استخدام أشكال من الحديد لها امتصاص عالي، ويجب توجيه امتصاص الحديد للجزء العلوي من الأمعاء، وذلك للتغلب أيضا على الأعراض الجانبية للحديد مثل الإمساك الناشئ عن سوء الامتصاص.

كان الهدف من هذه الدراسة تشكيل شكل دوائي من الحديد(Ferrous Gluconate) والذي يظل متماسكا في المعدة لفترة طويلة، و يقوم بتحرير الحديد لفترة طويلة ,هذا الشكل الدوائي له صفه انه يطفو على السطح المعدة ولا ينزل إلى الأمعاء إلا بعد فتره طويلة و بالتالي يتم إمداد الأمعاء بكميات متتالية من الحديد ليتم امتصاصه تدريجيا.

قمنا بعمل أكثر من تركيبه تجريبية من الحبوب، والتي احتوت على كميات متنوعة من المبلمرات: Ethyl cellulose,HPMC وماده صوديوم بيكربونات والتي تنتج الغاز اللازم لكي تطفو الحبة. كانت النتيجة أن الحبات التي صنعت بوساطة الضغط المباشر و ليس التحبيب بالترطيب هي التي كانت لها الصفات المطلوبة من حيث الفترة التي تطفو فيها و كميه الحديد التي تحررها.

أفضل تركيبه كانت التي تحتوي على HPMCK 100,000 مع كميات محدده من الصوديوم بيكربونات و,Ethyl cellulose، حيث بقيت الحبة طافية لمده تزيد عن 24 ساعة وكان تحرر الحديد منها تدريجيا لمده 10 ساعات و كل صفات الحبة كانت مطابقة لما هو موجود في دساتير الادويه.
عند تحليل نتائج تحرر الحديد، وجدنا انتظام التحرر الحديد مطابق لنظام Korsmeyer–PeppasModel. والذي يصف تحرر الدواء من بين المبلمرات القابلة للانتفاخ، وأيضا من نتائج فحص كميات دخول الماء وجدنا أن الحبات تنتفخ و لكن تبدأ بالتفتت بمرحله لاحقه، كل هذا يدعم نظريه إن الحديد يخرج من الحبة بنظام الانتشار بداية ومن ثم بمساعده تفتت البوليمر في وقت لاحق.

بالمحصلة في هذه الدراسة استطعنا تشكيل حبوب من الحديد تبقى ثابتة في المعدة لفترة طويلة وتقوم بتحرير الحديد تدريجيا، هذا النوع من الحبات يمكن ان يكون له اثر كبير في زيادة امتصاص الحديد.
وفي الختام نوصي بإجراء دراسات سريريه على هذه الحبات لفحص مدى فعاليتها في زيادة امتصاص الحديد عند المرضى.