DEVELOPMENT AND *IN VITRO - IN VIVO* EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF NIZATIDINE USING NATURAL AND SEMI SYNTHETIC POLYMERS

A Dissertation Submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI-600032

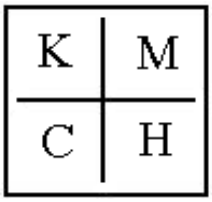
In partial fulfillment of the requirement for the award of the Degree of

MASTER OF PHARMACY

in

PHARMACEUTICS

OCTOBER-2018



DEPARTMENT OF PHARMACEUTICS,

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Submitted by

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CERTIFICATE

This is to certify that the dissertation work entitled "**DEVELOPMENT AND *IN VITRO - IN VIVO* EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF NIZATIDINE USING NATURAL AND SEMI SYNTHETIC POLYMERS"** was carried out by **(Reg. No. 261610901)**. The work mentioned in the dissertation was carried out at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, Tamilnadu, under the guidance of **Mr. K. Selvaraju, M.Pharm, for** the partial fulfillment for the degree of Master of Pharmacy during the academic year 2017-2018 and is forwarded to the Tamilnadu Dr. M.G.R. Medical University, Chennai.

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Place: Coimbatore **Prof. Dr. A. RAJASEKARAN, M.Pharm., Ph.D.**

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This research work either in part or full does not constitute any of any thesis/dissertation.

Date:

Place: Coimbatore **Mr. K. Selvaraju M. Pharm.**

DECLARATION

I do here by declare that to the best of my knowledge and belief ,the dissertation work entitled **"DEVELOPMENT AND *IN VITRO - IN VIVO* EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF NIZATIDINE USING NATURAL AND SEMI SYNTHETIC POLYMERS"** submitted to the Tamil Nadu Dr. M.G.R. Medical university, Chennai, in the partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** was carried out at Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the academic year 2017-2018.

Date:

Place: Coimbatore **(Reg. No.261610901)**

EVALUATION CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"DEVELOPMENT AND *IN VITRO -IN VIVO* EVALUATION OF GASTRORETENTIVE DRUG DELIVERY OF NIZATIDINE USING NATURAL AND SEMI SYNTHETIC POLYMERS"** submitted by **(Reg. No:261610901)** to the Tamil Nadu Dr. M.G.R. Medical university, Chennai, in the partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide research work carried out by the candidate during the academic year 2017-2018 at KMCH College of Pharmacy, Coimbatore, Tamilnadu and the same was evaluated by us.

Examination Center: K.M.C.H College of Pharmacy, Coimbatore

Date:

Internal Examiner **External Examiner**

Convener of Examination

Dedicated to Almighty,

My Beloved Parents ,

Sisters & Friends

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LIST OF ABBREVIATIONS

GIT	:	Gastro Intestinal Tract
CRDDS	:	Controlled Release Drug Delivery System
SGF	:	Simulated Gastric Fluid
GRT	:	Gastric Residence Time
GRDF	:	Gastro Retentive Dosage Form
GERD	:	Gastro Esophageal Reflux Disease
mg	:	Micro gram
gm	:	Gram
HCl	:	Hydrochloric acid
TFT	:	Total Floating Time
USP	:	United State Pharmacopeia
SI	:	Swelling Index
P-gp	:	Permeability glycoprotein
CR	:	Controlled Release
N	:	Normality (or) Molarity
FDDS	:	Floating Drug Delivery System
HPMC	:	Hydroxy Propyl Methyl Cellulose
MCC	:	Micro Crystalline Cellulose
HBS	:	Hydrodynamically Balanced System
PUD	:	Peptic Ulcer Disease
GERD	:	Gastro Esophageal Reflux Disease
FTIR	:	Fourier Transform Infra Red
DSC	:	Differential Scanning Calorimetry
b.i.d.	:	bis in die (twice daily)
RH	:	Relative Humidity
MCC	:	Micro Crystalline Cellulose

UV	:	Ultra-Violet
DSC	:	Differential Scanning Calorimetric
Fig	:	Figure

INTRODUCTION:

Oral administration is the most convenient and chosen means of any drug delivery to the systemic circulation. Oral controlled release drug delivery has been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.

Drug delivery refers to approaches, formulations technologies and system for transporting a pharmaceutical compound in the body as need to safety achieve its desired therapeutic effect.

TYPES OF DRUG DELIVERY SYSTEM:

1. CONVENTATIONAL DRUG DELIVERY SYSTEM:

- Oral Delivery
- Buccal / Sublingual delivery
- Rectal Delivery
- Intravenous Delivery
- Subcutaneous Delivery
- Intra muscular Delivery etc.,

2. NOVEL DRUG DELIVERY SYSTEM:

a) Targeted drug delivery

- Nanoparticles
- Niosomes
- Microspheres
- Monoclonal antibodies
- Liposome’s
- Magnetic microspheres
- Released erythrocytes

b) Controlled /Sustained Release drug delivery system

- Oral
- Parenteral
- Buccal/Sublingual
- Rectal
- Nasal
- Pulmonary
- Intrauterine / vaginal
- Transdermal

c) Gastro retentive drug delivery system:

- Floating Drug delivery system
- Bio / muco adhesive system

GASTRORETENTIVE DRUR DELIVERY SYSTEMS[1]

A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drug that;

i. Are local active in the stomach.

ii. Have an absorption window in the stomach or in the upper small intestine

iii. Are unstable in the intestinal or colonic environment or

iv. Exhibit low solubility at higher value.

NEED FOR GASTRO RETENTION IN GRDDS[2, 3]:

- Drugs that are absorbed from the proximal part of the GIT
- Drugs that are less soluble or that degrade by the alkaline pH the encounters at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Advantageous of local action by Prolonged gastric retention time (GRT) in stomach e.g. Treatment of peptic ulcer, etc.,

- Drugs with variable bioavailability.
- Drugs with short half-life.
- Drugs those degrade in colonic ulcers caused by H. Pylori infections[13]

PHYSIOLOGICALCONSIDERATIONS[1, 2]

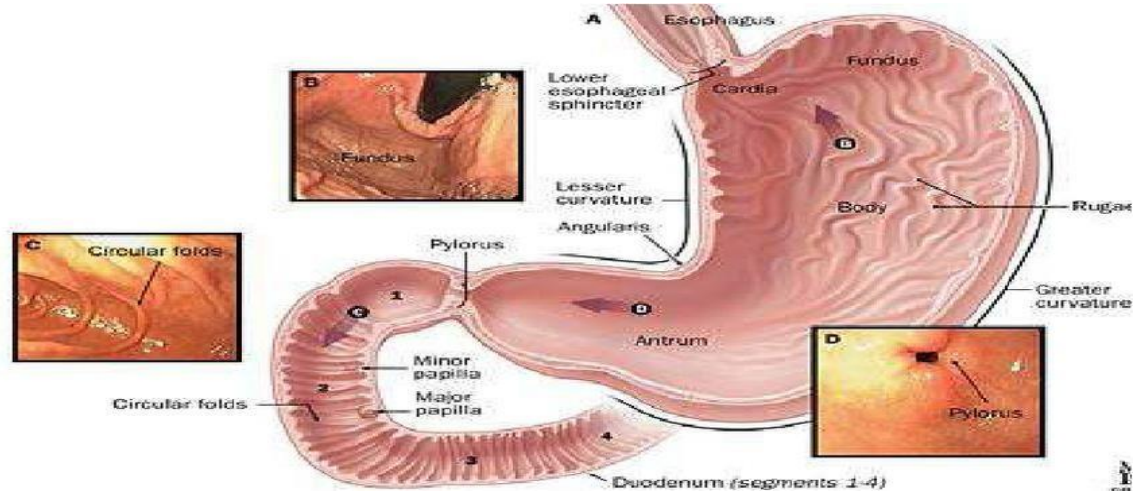


Fig. No. 1: Anatomy of stomach

Stomach Physiology[2, 3]:

The stomach is categorized into 3 anatomic regions: fundus, body, and antrum (pylorus). The part of fundus and body turns as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. The separation between stomach and duodenum is the pylorus. The pylorus, plays a major role in gastric residence time of GRDF due to its size.

The stomach provides for short term food reservation and quick consumption of relatively large meal. The primary substantial metabolism of enzymes is promoted in stomach of proteins. The peristalsis of stomach mix up and grind consumed food with secretions of the stomach, turning food in simplified liquid form. The liquefied bulk is transported to the small intestine for further digestion.

Different Features of Stomach:

Gastric pH	:	Fasted healthy subject 1.1 ± 0.15 Fed healthy subject 3.6 ± 0.4
Volume	:	Resting volume is about 25-50 ml
Intestinal pH	:	In the duodenum, the section closest to the pyloric sphincter of the stomach may be acidic (due to the HCl). However, the acidic chime from the stomach is quickly neutralized through the release of secretin which targets the pancreas to release an alkaline solution, bringing the pH back up to around
Gastric secretion	:	Acid, pepsin, gastrin, mucus and some enzymes about 60ml with approximately 4ml of hydrogen ions per hour.
Intestinal secretion	:	Pancreatic secretion: trypsin, chymotrypsin and carboxy Polypeptidase, pancreatic amylase, pancreatic lipase
Intestinal Enzymes	:	Peptidase, disaccharides, intestinal lipase, intestinal amylase.
Effect of food on Gastric secretion	:	About 3 liter of secretions are added to the food.

Both the fasting and fed states cause gastric emptying. However the two states are varied upon pattern of motility. The phenomenon, series of electric events takes place in cycles via stomach and intestine every 2 to 3hours. This is named as inter digestive mylo electric cycle or migrating mylo electric cycle (MMC), which is further divided into following four phases[1]:

- Phase I (basal phase)
    - The quiescent period lasts from 30 to 60 min with rare contractions.
    - Is Period of contraction.
- Phase II (Preburst phase)
    - Exhibits intermittent action potential for 20 to 40 min with increasing contractile motions. Bile enters the duodenum during this phase while the gastric discharge occurs during the latter part of phase II and throughout phase III.
    - Is Period of Intermittent Contractions.
- Phase III (Burst phase)
    - It has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine and lasts for 10 to 20 min. Consequently, a controlled- release gastrointestinal drug delivery system must capable of resisting the action of phase III. Studied release that in fed state, the gastric emptying rate is slowed and the onset of MMC is delayed. It concluded that feeding result in a lag time before onset of gastric emptying rate.
    - Period of regular contraction at the maximal frequency that migrate distally.
- Phase IV lasts for 0 to 5 min is a transition period between phase III and I of decreasing activity until the next cycle begins.

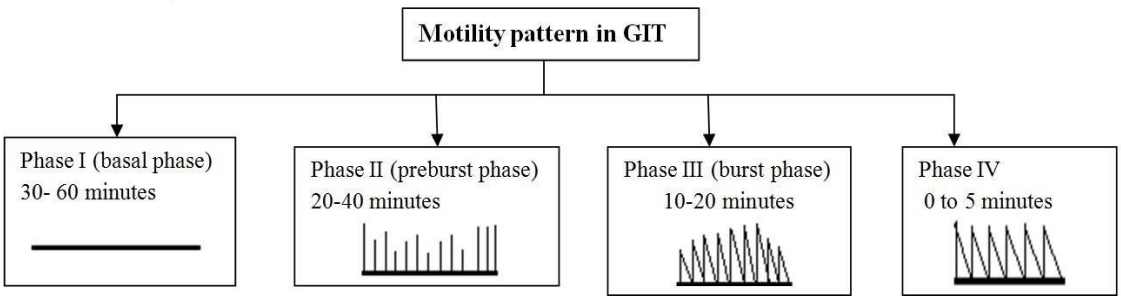


Table 1: Transit times of different dosage forms across the segments of GIT

Dosage form	Transit time (hours)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Solution	0.3±0.07	4.1±0.5	4.4

pH (Hydrogen Ion Concentration) :

The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach. The various pH of the gastro intestinal tract is shown below,

Table 2: The mean pH (+ S.D.) along the G.I. Tract in normal subjects

Region	Mean pH
Stomach	1.8 + 0.6
Proximal Small Intestine	6.6 + 0.5
Mid Small Intestine	7.4 + 0.4
Distal Small Intestine	7.5 + 0.5
Right Colon	6.3 + 0.6
Mid Colon	6.6 + 0.8
Left Colon	7.1 + 0.7

FACTORS CONTROLLING GRDDS[4]: Factors controlling GRDDS are shown in Figure 2 and some of the factors are enumerated below:

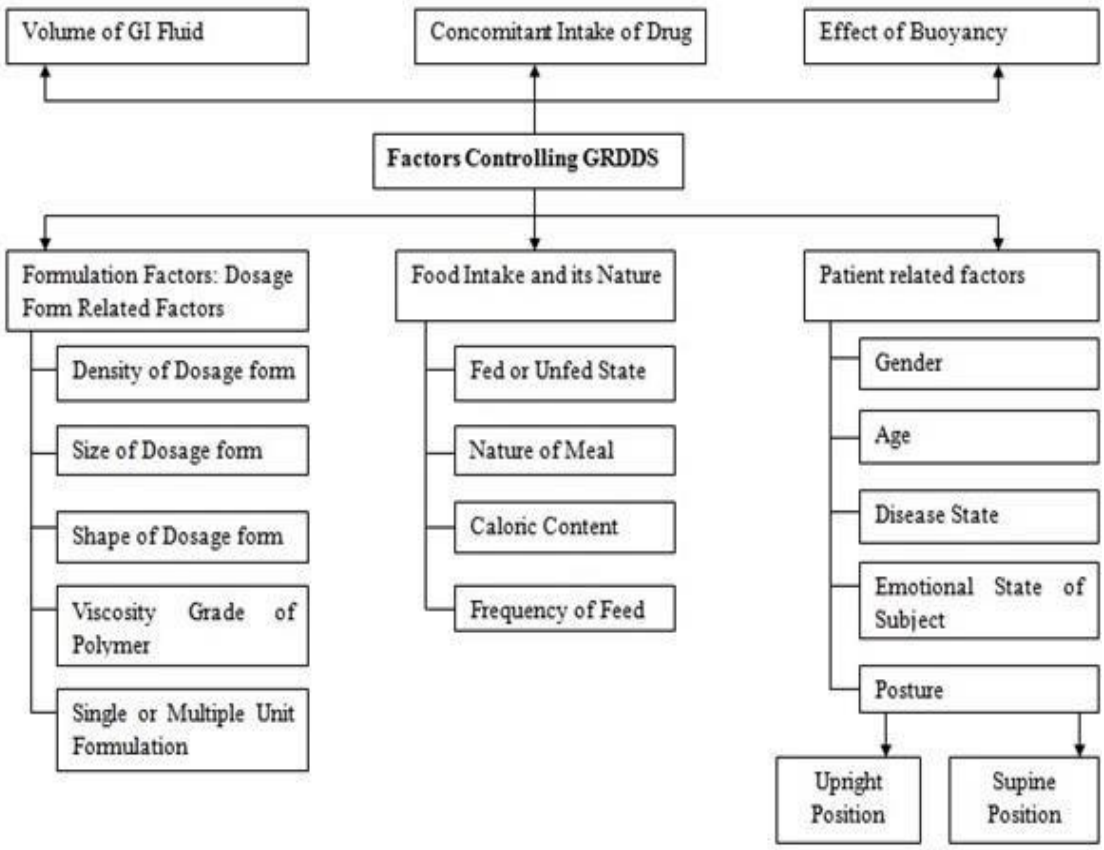


Fig. No. 2: Factors controlling GRDDS

1. **Density:**

   Dosage form with lower density in the gastric content can float to the surface while high density sink to the bottom of the stomach. Suitable density required for floating property is less than 1.0 gm/ cm^3

2. **Size:**

   Size should be more than 7.5 mm in diameter.

3. **Shape:**

   Either round or spherical shaped dosage form exhibit better property related to other shapes.

4. **Single or multiple unit formulation:**

   Multiple units are desirable due to foretell release profile.

5. **Fed or Unfed State:** Gastric retention time is less during fasting condition due to rise in gastric motility.

6. **Nature of Meal:**

   High amount of fatty acid and other indigestible polymers slow down the gastric retention time due to variation in gastric motility

7. **Frequency of Feed:**

   Low frequency of migrating myoelectric complex (MMC) contributes to GRT up to 400 times which in turn depends on the frequency of food intake

8. **Caloric Content:**

   A high protein and fat rich diet can increase GRT by 4 to 10h.

9. **Gender:**

   Males have greater GRT than females

10. **Age:**

    GRT is more in geriatric patients and less in neonates and children. Age above 70 (>70) exhibit longer GRT.

11. **Disease State:**

    Gastric disease such as diabetes, Chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc fluctuates the GRT

12. **Concomitant Intake of Drug:**

    Combination of some drugs along with gastric motility enhancers or depressants, affect GRT.

13. **Posture:**

    Floating can vary between supine and upright ambulatory states of the patient. Supine position offers no reliable protection against early and erratic emptying.

APPROACHES TO GASTRICRETENTION [5]

To enhance the gastro retention of the orally administered drugs by different approaches which including floating and non-floating systems [11].

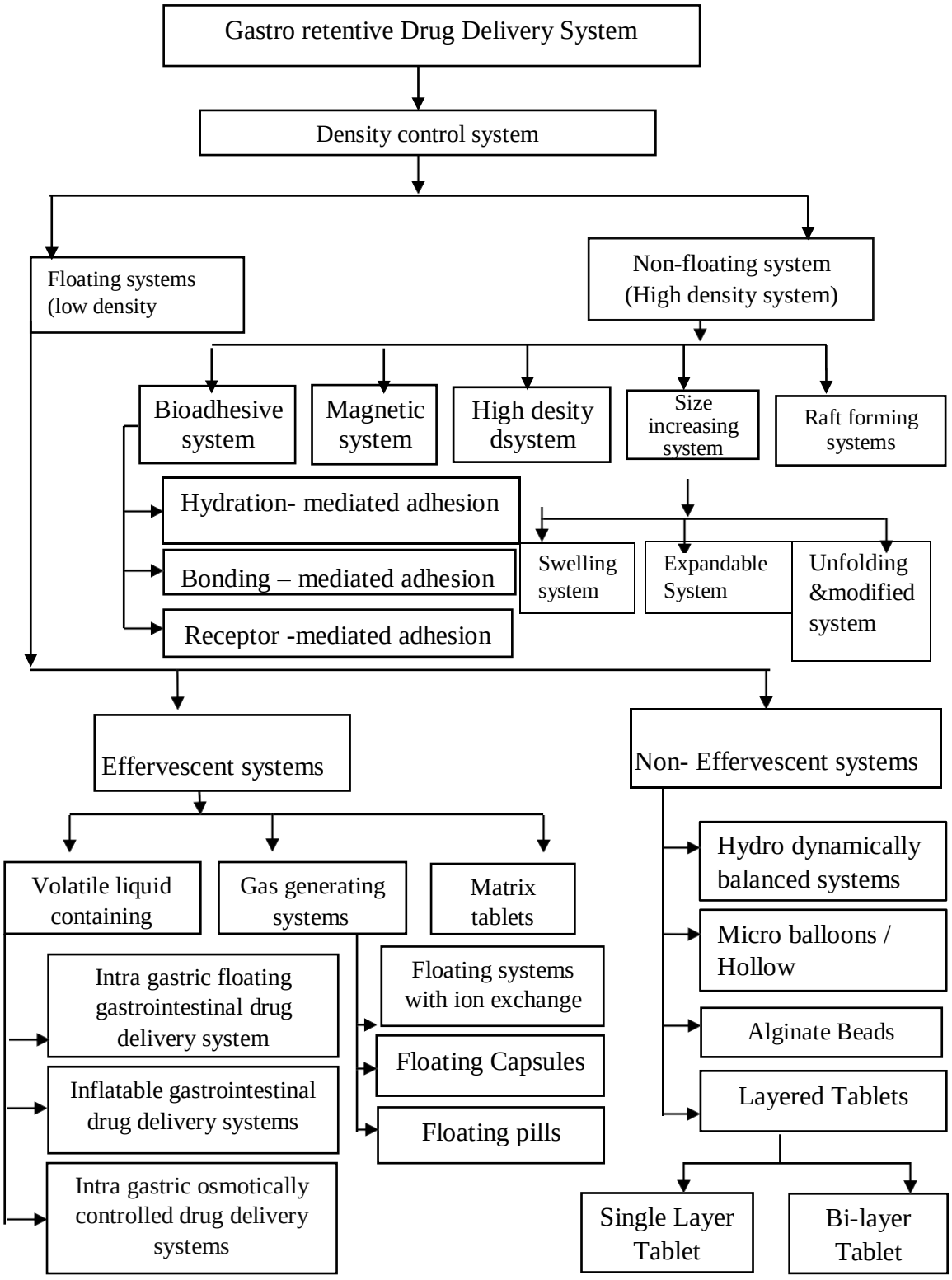
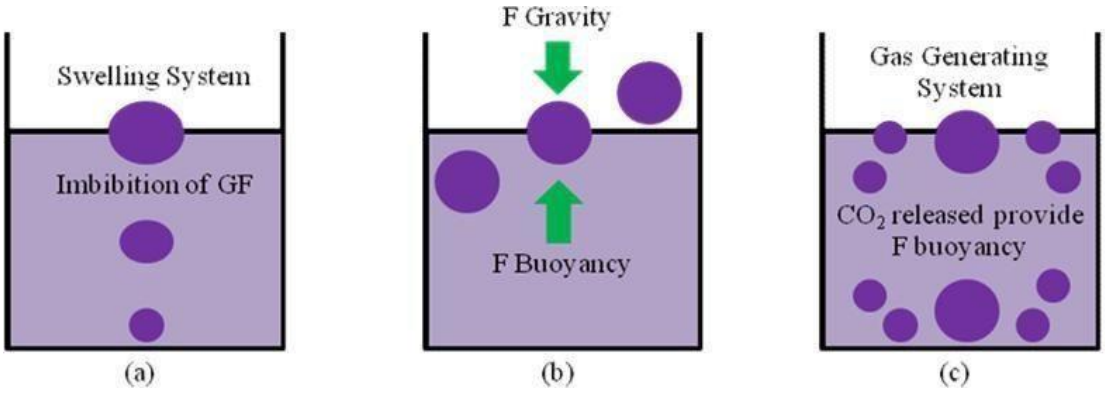


Fig.No. 3: Approaches to gastric retention drug delivery system

I. FLOATING DRUG DELIVERY SYSTEMS

The concept of FDDS was described in the literature as early as. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.



a=swelling system **b=force of gravity** **c=gas generating system**

Fig.No.4: Mechanism of floating system

Mechanism of action involves in floating drug delivery systems[6]

Floating system on the gastric, the drug are released slowly at the desired rate from the system. After release of drug, the residual system are emptied from the stomach besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form dependably buoyant on the surface of the meal[18].

$$F = F_{buoyancy} - F_{gravity}$$

$$F = (D_F - D_s)\, g$$

Where,

F=total vertical force,

D_F= fluid density,

D_s = object density,

v = volume and

g = acceleration due to gravity.

Diffusion:

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particles. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion:

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particles.

Osmosis:

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating[18].

TYPES OF FLOATING DRUG DELIVERY SYSTEMS

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

I. Effervescent Floating Drug Delivery System

II. Non- Effervescent Floating Drug Delivery System

I.1. EFFERVESCENT FLOATINGDRUG DELIVERY SYSTEM[1, 7]:

Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid and, release the drug slowly for a longer period of time.

I.1.1. Volatile liquid / vacuum containing systems:

i. Intra-gastric floating gastrointestinal drug delivery system:

These systems can be made to float in the stomach because of floatation chamber, which may have a vacuum or filled with air or an harmless gas, while drug reservoir is encapsulated inside a micro-porous compartment.

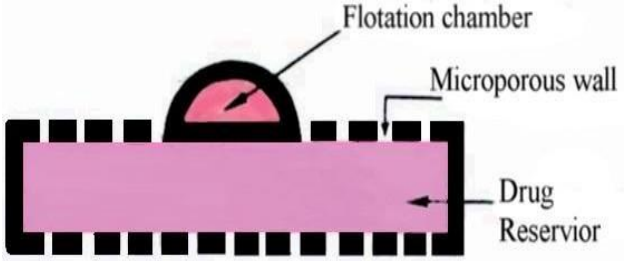


Fig.No 5: Intra gastric floating gastrointestinal drug delivery device

ii. Inflatable gastrointestinal delivery systems

These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix. It automatically inflates and retains the drug reservoir compartment in the stomach. The drug is continuously released from the reservoir into the gastric fluid (Figure).

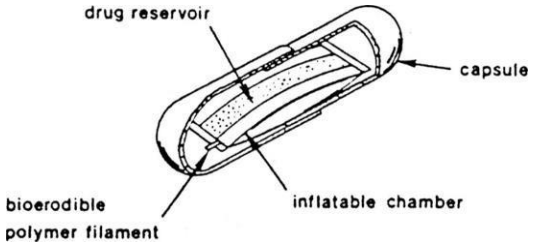


Fig.No. 6: Inflatable gastrointestinal delivery system

iii. Intragastric osmotically controlled drug delivery system

The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapors and liquid and has a drug delivery orifice. It contains an osmotically active salt and is enclosed within a semi-permeable housing. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.

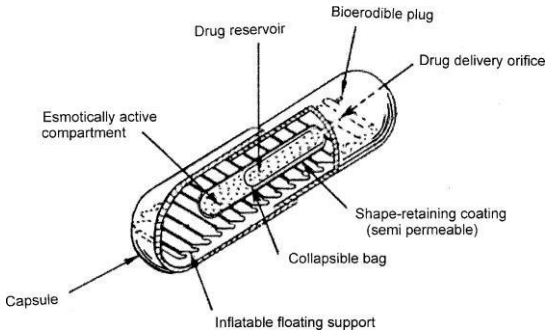


Fig.No. 7: Intragastric osmotically controlled drug delivery system.

I.1.2Matrix Tablets:

They are formed by intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

I.2. NON-EFFERVESCENTFLOATING DRUG DELIVERY SYSTEM[1, 8]:

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1.

I.2.1. HYDRODYNAMICALLY BALANCED SYSTEMS:

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxy propyl methyl cellulose (HPMC) is the most commonly used excipient. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (Figure).

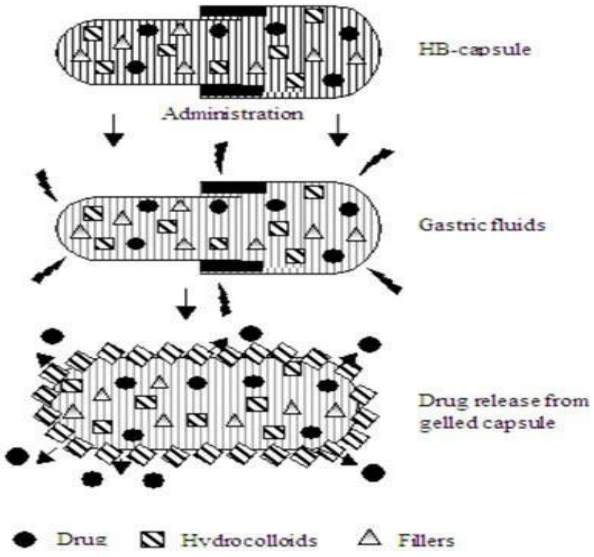


Fig. No. 8: Working Principle of Non-Effervescent type (HBS-Hydro dynamically balanced system) of FDDS

I.2.2. HOLLOW MICROSPHERES:

Multiple-unit microspheres by emulsion solvent diffusion technique were prepared with drug and acrylic polymer. These were dissolved in an ethanol- dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio.

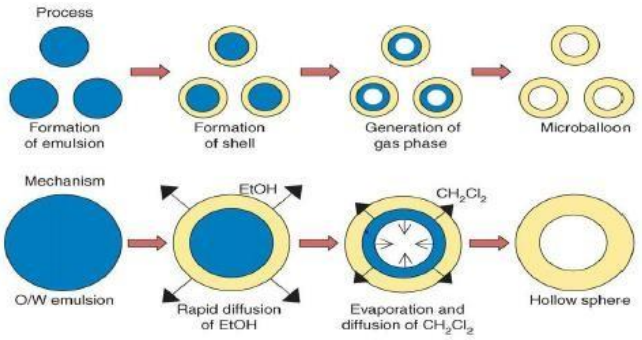


Fig .No.9: Hallow microspherses

I.2.3. ALGINATE BEADS:

Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5mm diameter can be prepared by dropping sodium alginate into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hour. These floating beads gave a prolonged residence time of more than 5.5 hour

I.2.4. LAYERED TABLETS:

It can be formulated in a single layer matrix table by implementing bicarbonates in the matrix forming hydrocolloid gel agent or in a dual layer matrix along with gas generating matrix together as an individual layer. The drug acts as the second layer. There is a possibility of triple layer matrix tablet. However now the gas generating matrix is one layer and rest two are drug layers.

II.NON-FLOATING SYSTEM:

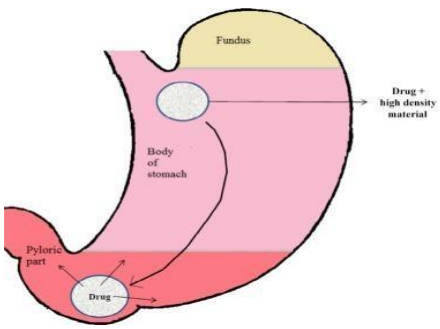


Fig.No.10: GRDDS based on high density.

II.1. BIO/MUCO-ADHESIVE SYSTEMS [9]

Bio/muco-adhesive systems, bind to the gastric epithelial cell surface or mucin, which extends the GRT of drug delivery system in the stomach. The ability to provide adhesion of a drug delivery system to the gastrointestinal wall provides longer residence time in a particular organ site, it improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three categories:

(i) Hydration-mediated adhesion:

Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bio adhesive properties.

(ii) Bonding-mediated adhesion:

It include physical-mechanical bonding and chemical bonding. Physical-mechanical bonding can result from the insertion of the adhesive material into the folds or crevices of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e., Vander Waals interactions) and stronger specific interactions such as, hydrogen bonds.

(iii) Receptor-mediated adhesion:

Certain polymers bind to specific receptor sites on the cell surfaces, thereby enhancing the gastric retention of dosage forms. Various investigators have proposed different mucin-polymer interactions, [45] such as:

- Wetting and swelling of the polymer to permit intimate contact with the biological tissue.
- Formations of weak chemical bonds.
- Sufficient polymer is mobility to allow spreading.
- Water transport followed by mucosal dehydration.

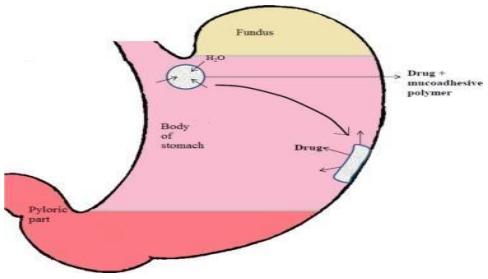


Fig.No.11: GRDDS based on muco-adhesive systems

II.2. MAGNETIC SYSTEMS:

The incentives from external is used as magnetic field in these systems for targeted drug delivery, the compound that are active magnetically are added in these systems to attain the targeted drug delivery.

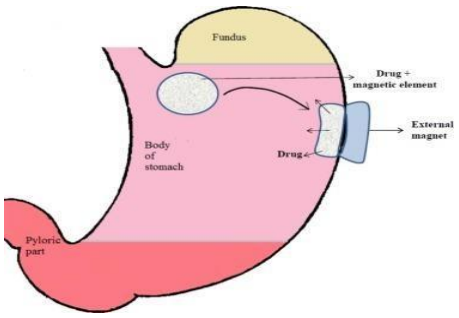


Fig.No.12: GRRDS based on application of magnetic force

II.3. High density systems:

In these systems the pallets are coated, having the greater density than the contents of the stomach (1.004 gm/cm3). The preparation of these type of tablet is done on the basis of high-density tablet is based on hypothesis that dense pellets will stay in stomach for longer time. Such polymers are, Zinc oxide, Barium Sulphate, Iron powder, Titanium dioxide.

II.4. Swelling type system:

In these systems contain the ingredients those have swelling property and they swell to that extent, so they cannot pass out from stomach through pylorus. The name "Plug type system", can also be given to them, so they are logged in pyloric sphincters for greater time. such polymers are, Biodegradable polymers are used, Swelling agents (cross povidone, sodium starch glycolate)

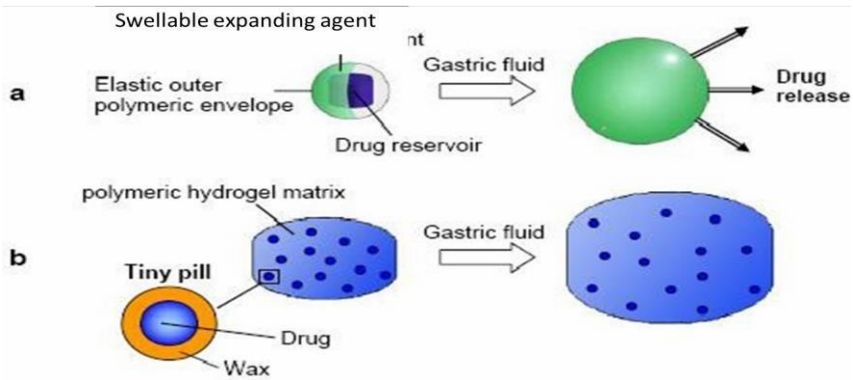


Fig.No.13: Swellable systems, developed by (a) Mamajek and (b) Moyer

II.5. Raft forming System:

Incorporate alginate gel-these have carbonate component and upon reaction with gastric acid, bubbles form in the gel, enabling floating.

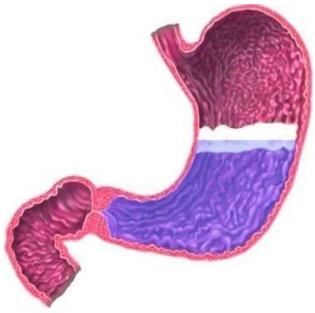


Fig.No.14: Schematic illustration of the barrier formed by a raft-forming system

CRITERIA FOR SELECTION OF DRUG CANDIDATE FOR FDDS

Desirable half-life:

If the drug has a short half-life of less than 2 hours, the dosage form may contain a prohibitively large quantity of the drug.

High therapeutic index:

Drugs with low therapeutic index are not suitable for incorporation in controlled release formulations.

Small dose:

The dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undermined

Aqueous solubility:

Drugs with aqueous solubility make good candidates for controlled release dosage form.

Stability to wide pH range, GI enzymes and flora:

Stability of the drug in the GI contents is important to ensure a complete and reproducible drug input into the body. Typically the drug must be stable in the pH range of 1 to 8.

First pass clearance:

Delivery of the drug to the body in desired concentration is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release form. Saturable hepatic metabolism may render a drug unsuitable because systemic availability for such drug is highly reduced when the input rate is small[20]

Table 3: Marketed Products of GRDDS[11]

Brand name	Delivery system	Drug (dose)	Company name
Almagate Flot-Coat®	Antacid tablet preparation	Al – Mg antacid	Roche, USA
Topalkan®	Floating liquid alginate Preparation	Al – Mg antacid	Pierre Fabre Drug, France
Valrelease®	Floating capsule	Diazepam (15mg)	Hoffmann-LaRoche, USA
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide (25mg) and L-Dopa (100mg)	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithKline, India
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM[12]:

1. Improves patient compliance e.g. Furosemide
2. Enhanced bioavailability.
3. Increased Gastric retention time.
4. Enhanced absorption of drugs which is solubilize only in stomach.
5. Drug releases in controlled manner for prolonged period.
6. To Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage form - no risk of dose dumping.
8. Avoids gastric irritation in stomach.
9. Better therapeutic effect of short half-life drugs can be achieved.

DISADVANTAGES OF GRDDS [13]

1. Need for increased level of fluids in the stomach.
2. Unsuitable for such drugs as:
    - Problematic with solubility in gastric fluid
    - Causing G.I irritation
    - Inefficient in acidic environment
3. Drugs intended for selective release in the colon.
4. Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.
5. GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.
6. The ability of the drug to remain in the stomach depends upon the subject being positioned upright.
7. Hydrogel based swelling system takes longer time to swell.
8. Gastric emptying of floating forms in supine subject may occur at random ad becomes highly on the diameter size. Therefore patients should not be dosed with forms just before going to bed.

Limitations of the Techniques of Gastro/Intestinal retention[14]

- The adequate amount of the fluid must be present in the stomach, for the administration of the floating dosage forms requires normally 200-250ml fluid in the stomach [10], to retain the buoyancy outcome effect of the formulation
- Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti-inflammatory drugs.
- Drugs degraded by first pass effect and have good absorption in the whole gastric tract are not right choice for the floating drug delivery system due to their ability to reduce the gastric emptying that in turn reduce the bioavailability systematically.
- More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions
- For Intestinal retention, dosage form has to cross gastric conditions intact, which is not easily achievable.
- Not suitable for drugs that are unstable in the strong acidic or basic environment.
- These systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastro intestinal tract.

POLYMERS AND OTHER INGREDIENTS USED IN GRDDS TABLETS[15]:

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

1. Hydrocolloids (20%-75%):

They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives.

E.g. Acacia, pectin, Chitosan, agar, casein, bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan Gum (Gel rite®), Sodium CMC, MC, HPC.

2. Inert fatty materials (5%-75%):

Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

3. Effervescent agents:

E.g. Sodium bicarbonate, citric acid, tartaric acid, Di- SGC, CG

4. Release rate accelerants (5%-60%):

E.g. lactose, mannitol

5. Release rate retardants (5%-60%):

E.g. Dicalcium phosphate, talc, magnesium stearate

6. Buoyancy increasing agents (upto80%):

E.g. Ethyl cellulose, Polysaccharides.

7. Low density material:

E.g. Polypropylene foam powder.

EVALUATION PARAMETERS FLOATING DRUG DELIVERY SYSTEM[1, 16]

i) Floating time:

The test for floating time is usually prepared in simulated gastric fluid or 0.1 mole .lit^{-1} HCl maintained at 37ºC, by using USP dissolution apparatus containing 900ml of 0.1 molar HCl as the dissolution medium. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or floatation time.

ii) Drug release:

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

iii) Measurement of buoyancy capabilities of the FDDS

The floating behavior was evaluated with resultant weight measurement. The experiment was carried out in two different media like deionized water and simulated meal, in order to monitor possible difference. The results showed that higher molecular weight polymers with slow rate of hydration had enhanced floating behavior and which was more in simulated meal medium compared to deionized water.

iv) Content uniformity, Hardness, Friability (Tablets):

These test are performed as per described in specified monographs.

Resultant weight: The *in vitro* measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage form as a function of time. It operates by force equivalent to the force F required to keep the object totally submerged in the fluid. This force determine the resultants weight of the object when immersed and may be used to quantify its floating or non-floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (F buoy) and gravity (F grav) forces acting on the objects as shown in the equal. In which the F is total vertical force (resultant weight of the object). G is the acceleration due to gravity, d_f if the fluid density, d_s is the object mass and V is the volume of the object.

v) X-Ray /Gamma scintigraphy:

X-Ray /Gamma scintigraphy is a popularly used evaluation parameter for floating dosage form these days. It helps to locate dosage form in the GIT and by which one can predict and correlate the emptying time and the passage of dosage form in the GIT. Here the inclusion of a ratio –opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting ratio nuclide in a formulation allows indirect external observation using γ-camera or scinti scanner.

REVIEW OF LITERATURE

Ramu Bandameedi *et al.*, 2015[17] Developed floating osmotic tablets of Nizatidine, a H2 receptor antagonist, to release the drug as two distinct pulses separated by a lag time that achieve plasma concentration profiles varying in a circadian rhythm fashion, for the chronotherapy of ulcer. Floating osmotic tablets were developed using effervescence method consisted of three different steps viz, preparation of floating sustained release drug containing tablets followed by time-lagged (4 hrs) coating with hydrophobic rupturable polymer, ethyl cellulose (EC), and finally compression coating with immediate release dose of Nizatidine and supporting buoyant layer. Three ratios of Ethyl cellulose to HPMC E15 (32.5:67.5, 50:50, and 67.5:32.5) at three coating levels (5%, 10%, 15%) were used to optimize the lag time (4 hrs). Carbopol 934P, cross povidone and sodium bicarbonate were used in buoyant layer. The developed floating osmotic tablets by effervescence method were evaluated for preformulation parameters, weight variation, thickness, hardness, friability, drug content, content uniformity, *In-vitro* floating properties, and *In-vitro* drug release. The optimized formulation provided expected two-phase release pattern of Nizatidine with initial immediate dose release in 30 min and then lag time 4 hrs of no drug release followed by sustained release for 8hrs in stomach during floating.

Chouresoniya*et al.*, 2015[18] Studied the floating tablet of Nizatidine using the hydrophilic polymer hydroxypropyl and gas generating agent sodium bicarbonate and citric acid by wet granulation method . Nizatidine is H2 receptor antagonist and anti-ulcer having dose 150mg twice daily. The drug excipients compatibility studies were conducted by using FTIR, DSC and visual observations. The granules were prepared by wet granulation method and evaluated for their granules properties. A 3^2factorial design was applied to systemically optimize the drug release profile. The amount of citric acid (X1) and concentration of polymer HPMC K100M (X2) were selected as independent variables. The % drug release at 6 hour (Q6) and drug release at 12 hour (Q12), and t50 % were selected as dependent variables. The results of factorial design indicated that low level of HPMC K100M favours the preparation of floating controlled release of Nizatidine tablets. Effect of hardness on floating tablet revealed that increase in hardness affect buoyancy lag time due to reduction in porosity of

compact mass. Formulations of NFT 7 provided sustained release of Nizatidine over the period of 12 hrs.

Rushikesh K, *et al.*,2014[19] Nizatidine floating tablets was prepared using different grades of HPMC as drug release retarding polymer and sodium bicarbonate as source for carbon dioxide which helps tablets to float. Floating drug delivery system (FDDS) was developed using gas sodium bicarbonate, citric acid and hydrocolloids, hydroxypropyl methylcellulose (HPMC) and Carbopol 940P. The prepared tablets were evaluated their physicochemical properties and drug release, excipient compatibility, density, buoyancy test, mucoadhesion force, swelling study, drug content and vitro release profile.

Xuehua Zhu *et al.*, 2014[20]Studied famotidine-containing floating-bio adhesive cooperative minitablets and investigated the possibility of using those minitablets as a delivery system for promoting the oral bioavailability of famotidine. Nine minitablet formulations were designed using hydroxylpropyl methylcellulose (HPMC K4M) as release retarding polymers, Carbopol 971P as bio adhesive materials and sodium bicarbonate (NaHCO3) as gas formers. The prepared 3 ± 0.02 mm minitablets were evaluated in terms of their swelling ability, floating behaviour, bio adhesion test and in vitro release. The optimized minitablets (F6) containing HPMC K4M (50.00%, w/w), Carbopol 971P (10.00%, w/w) and NaHCO3 (10.00%, w/w) were found to float in 1 min and remain lastingly buoyant over a period of 8 h in vitro, with excellent bio adhesive properties (20.81 g) and sustained drug release characteristics (T50% ¼ 46.54%) followed one-order model. In addition, plasma concentration–time profiles from pharmacokinetic studies in rats dosed with minitablets showed 1.62-fold (p50.05) increased absorption of Famotidine, compared to the market tablets Xin Fading. These studies demonstrated that the multiple-unit floating-bio adhesive cooperative minitablets may be a promising gastro-retentive delivery system for drugs that play a therapeutic role in the stomach.

Gehan Balata *et al.*,2014[21] Formulated a gastroretentive floating tablet of Nizatidine by direct compression technique using hydroxylpropyl methylcellulose (HPMC k4M). The effect of different formulation variables including polymer concentration, incorporation of different concentrations of carbopol934 or sodium alginate as release retarding polymers and concentration of an effervescent mixture (sodium bicarbonate

and citric acid) on drug release and floating properties was investigated. In addition, the optimized formulation (combined excellent floating behaviour and sustained drug release) was compared to conventional Nizatidine tablet for antiulcer activity in rabbits. The optimized formulation containing 175 mg HPMC k4M, 25 mg carbopol934 and 50 mg effervescent mixture showed 80% drug release within 10.6 h±0.3, floating lag time of about 5.00±0.2 min and total floating time of >24 hours. In vivo results proved that Nizatidine floating tablet had more pronounced antiulcer effect than its conventional tablet. The effervescent based floating tablet of Nizatidine could be a promising approach to increase its gastric residence time up to 12 hours, thereby improving its antiulcer efficacy.

Pawan Jalwal, Anupama Diwan[22]*et al.*, 2013Formulated a sustained drug delivery of famotidine is histamine H2 receptor antagonist in treating gastric ulcer, duodenal ulcer, Zollinger Ellison syndrome, gastro oesophageal reflux disease and erosive esophagitis but their main clinical use is as inhibition of gastric acid secretion. It inhibited histamine stimulation and gastrin stimulated acid secretion. It decreases both basal and food stimulated acid secretion by 90% or more, but promote healing of duodenal ulcer. The swelling of the polymers used (HPMC K15M, Ethyl cellulose, Xanthan Gum) were determined by water uptake of the tablet. The percent swelling of the tablet was determined for 12 h at different time intervals. Increase in percent swelling was found with increasing concentration of polymers.

Ashish Kumar Garg,*et al.*, 2012[23] Formulated a floating drug delivery system of an antiulcer drug Nizatidine using different grades of HPMC (K100, K4M, K15M & K100M) and an effervescent agent i.e. sodium bicarbonate. It was found that the release rate of Nizatidine from tablet formulations prepared from HPMC K100LV was very high as compared to that from formulations containing higher viscosity grades namely K4M, K15M and K100M. In the current study, it was also found that overall rate of drug release tends to decrease with increase in concentration of HPMC. These observations are in agreement with the results reported in literature i.e. with the increase in polymer concentration and viscosity grade, the viscosity of gel layer around the tablet also increases leading to enhanced diffusional path length for the drug to follow and thus limits the release of active ingredient.

A Sarat Chandra *et al.*, 2012[24]Developed a floating gastro retentive dosage of Nizatidine using effervescent technique. Nizatidine was used as a model drug because of its short elimination half-life and localized action in the gastric region. Nine batches containing 75mg of Nizatidine per tablet were developed using release modifiers like xanthan gum and HPMC K100M both individually and in 1:1 combination at 30, 40 and 50% concentrations. Sodium bicarbonate and tartaric acid were used as gas generating agents. The drug-excipient compatibility, pre and post compression parameters, buoyancy properties and swelling index were evaluated. *In-vitro* dissolution studies were carried out in 0.1N HCl (pH 1.2) at 37±0.5ºC. Increase in polymer concentration showed significant retardation of drug release and increase in swelling property. Release kinetics were studied by fitting the data into various models and release mechanism, predicted drug release were studied. Best formulation among the designed batches was selected based on cumulative percentage of drug released by the end of twelfth hour and by comparing the predicted and obtained drug releases at the end of 5^{th} and 8^{th} hours respectively.

D. Lohithasu*et al.*, 2014[25]Studied the Lafutidine for the effect of guar gum is an efficient matrix forming agent in floating tablets by generating gas Lafutidine release was diffusion controlled and follows zero order kinetics. In case of F3 formulation non-Fickian diffusion was the drug release mechanism from the prepared Lafutidine floating tablets. Floating tablets containing 10 mg of Lafutidine could be prepared by wet-granulation technique employing guar gum of different grades as floating polymer and release retardant, methocel K100LVCR, methocel K15M as floating enhancers and sodium bicarbonate as a gas generating agent. The measured tapped density was 0.501 to 0.643(g/cm3), bulk density 0.421 to 0.540 (g/cm3), Carr's index(I) 10.88 to 23.04%, thickness 4.33 to 4.38(mm), hardness 4.26 to 5.06 (Kg/cm2), friability 0.24 to 0.46(%) were well within the limits, which indicates good flow potential of the prepared tablets. Angle of repose (θ) values for the granules was in the range 24.19 to 26.950 indicating good flow potential for the tablets and the tablets with guar gum were able to float for more than 12 h.

Satish Patil*et al.*, 2015[26]Studied the effect of Lafutidine a newly developed histamine H2-receptor antagonist having biological half-life of1.92 ± 0.94 h due to its selective absorption from upper part of gastrointestinal tract the development of mucoadhesive sustained release drug delivery system is recommended inorder to enhance the bioavailability. The tablets was developed using the natural polymer, sodium alginate, xanthan gum and karaya gum. The formulation with xanthan gum showed better results. Thus, it may be useful for prolonged drug release in stomach to improve the bioavailability and reduced dosing frequency. Non-fickians release transport was confirmed as the drug release mechanism from the optimized formulation by Korsmeyer–Peppas. The optimized formulation (B3) showed a mucoadhesive strength 435 g. In vivo study was performed using rabbits by X-ray imaging technique. Radiological evidences suggest that, a formulated tablet was well adhered for 410 h in rabbit's stomach. Optimized Lafutidine tablet in vitro dissolution pattern showed, after storage part 40°C temperature75 ± 5% relative humidity for 3 months.

C. V. S. Raghu Kiran*et al.*,2015[27] Developed floating tablets of Lafutidine in order to achieve an extended retention in the upper GIT which may enhance the absorption and improve the bioavailability. The tablets were prepared by gas generation technique using different ratio and concentrations of natural gums like guar gum, gum karaya, hupu gum. Lafutidine a newly developed histamine H2-receptor antagonist. The formulation code F10 showed superior results it may be constructive for prolonged drug release in the stomach to get better the bioavailability and abridged the dose frequency. Optimized floating tablets showed no significant changes in the physical appearance, drug content, total buoyancy time, and also in vitro dissolution pattern after storage at 40°C/75% relative humidity for 3 months.

Vageesh N.M *et al.*, 2017[28]Formulated the Lafutidine by using various polymers were developed. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimised. Then the formulation was developed by using different concentrations of polymers Xanthan gum, guar gum and Sodium Alginate as polymeric substances. Among all the formulations Only Xanthan gum, Sodium Alginate highest

concentrations (60 mg) retards the drug release up to 12 hours and the drug release 96.25%, 95.81% respectively. In this Xanthan gum releases the more drug release when compared to Sodium alginate. So F3 Formulation considered as optimised formulation. Optimised formulation F3 was kept for release kinetic studies. In the graphs it was evident that the formulation F3 was followed the Peppas release mechanism.

Kapoor D *et al.*, 2014[29] Prepared Lafutidine tablet in gas generation technique using different ratio and concentrations of Methocel K 100, Methocel K 15. Polymer with lower viscosity was found to be beneficial than higher viscosity polymer in improving the release properties of gastroretentive FDDS. The formulation code LFT6 having Methocel K15 showed superior results it may be constructive for prolonged drug release in the stomach to get better the bioavailability and abridged the dose frequency. *In-vitro* floatability studies revealed that most of the tablets still floated for more than 9 hours because of their low densities. Lessen in the citric acid level increased the floating lag time but tablets floated for longer duration. An amalgamation of sodium bicarbonate (70mg) and citric acid (20mg) was found to achieve optimum *in vitro* buoyancy. Optimized floating tablets showed no significant changes in the physical appearance, drug content, total buoyancy time, and also *in vitro* dissolution pattern after storage at 40°C/75% relative humidity for 3 months.

Mahboubeh Razavi*etal.*, 2014[30]formulatedthe gastroretentive dosage form of famotidine was modified using tamarind seed powders to prolong the gastric retention time. Tamarind seeds were used in two different forms having different swelling and gelling properties: with husk (TSP) or without husk (TKP). TKP (TKP1 to TKP 6) and TSP (TSP1 to TSP 6) series were prepared using tamarind powder: xanthan in the ratios of 5:0, 4:1, 3:2, 2:3, 1:4, 0:5, respectively. The matrix tablets were prepared by the wet granulation method and evaluated for pharmacopoeial requirements. TKP2 was the optimum formulation as it had a short floating lag time (FLT < 30 s) and more than 98.5% drug release in 12 h. The dissolution data were fitted to popular mathematical models to assess the mechanism of drug release, and the optimum formulation showed a predominant first order release and diffusion mechanism. It was concluded that the TKP2 prepared using tamarind kernel powder: xanthan (4:1) was the optimum formulation with shortest floating lag time and more than 90% release in the determined period of time.

Amit Kumar Nayak*et al.*, 2017[31] **s**tudied various plant polysaccharides have been for their diverse applications as excipients like binders, granulating agents, disintegrants, emulsifiers, suspending agents, gelling agents, mucoadhesive agents, matrix-formers, release retardants, enteric resistant's, *etc.*, in various pharmaceutical dosage forms. Among these, tamarind seed polysaccharide is an emerging excipient, which is be ingested and investigated for the preparation of various dosage forms like suspensions, emulsions, tablets, gels, creams, beads, spheroids, microparticles, nanoparticles, ophthalmic preparations, and buccal patches, *etc*. The current chapter deals with a comprehensive and useful discussion on pharmaceutical applications of tamarind seed polysaccharide with its some important features like source, isolation, chemical composition and properties.

Ruchira Vasant Mahavarkar *et al.*, 2016[32]formulated the matrix tablet of Diclofenac sodium using natural polymer was to modify the release rate. The matrix forming agent like Tamarind seed Polysaccharide show sustained release property in tablet which is obtained naturally from fruit of *Tamarindusindica*L. belonging to Family Leguminosae. The sustained release matrix tablet of Diclofenac sodium were prepared by wet granulation technique using varying concentration of hydrophilic polymer i.e. TSP. OF1 and OF2 both are optimized batch. The *in vitro* dissolution study was carried out for optimized as well as marketed formulation (Voveran- SR). Both the optimized batches at 10 h were found to be 90.27% and 90.18%, respectively. Tamarind seed polysaccharide can be employed in dosage form to sustain the drug release. Tablet formulated with various concentrations of Tamarind seed polysaccharide (TSP) gives release up to 10 h and more. OF1 and OF2 both formulations give comparable release with marketed formulation. From the present work it can be conclude that, the objectives which were set at the beginning of the study got fulfilled.

Kesarla RS *et al.*, 2015[33]developed a sustained dosage form of Ranitidine hydrochloride (HCl) does not prevent frequent administration due to its degradation in colonic media and limited absorption in the upper part of GIT. FT-IR and DSC indicated no significant incompatibility with selected excipients Klucel-LF, POLYOX WSR N 60 K and l-menthol were selected as binder, Polymer and sublimating material, respectively, for factorial design batches after preliminary screening. From the factorial

design batches, optimum concentration to release the drug within 12 h was found to be 420 mg of POLYOX and 40 mg of l-menthol. Stability studies indicated the formulation as stable. Ranitidine HCl matrix floating tablets were formulated to release 90%of drug in stomach within12 h.

Gharti K *et al.*, 2012[34]developed floating tablets of ranitidine using hydroxypropyl methyl cellulose (HPMC) and polyethylene oxide (PEO). The floating tablets were based on effervescent approach using sodium bicarbonate a gas generating agent. The tablets were prepared by dry granulation method. The result of *in vitro* dissolution study showed that the drug release profile could be sustained by increasing the concentration of HPMC K15 MCR and Polyox WSR303. The formulation containing HPMC K15 MCR and Polyox WSR303 at the concentration of 13.88% showed 91.2% drug release at the end of 24 hours. Changing the viscosity grade of HPMC from K15MCR to K100MCR had no significant effect on drug release profile. Sodium bicarbonate and stearic acid in combination showed no significant effect on drug release profile. The formulations containing sodium bicarbonate 20 mg per tablet showed desired buoyancy (floating lag time of about 2 minutes and total floating time of >24 hours). The study showed that polymers like HPMC K15MCR and Polyox WSR303 in combination with sodium bicarbonate as a gas generating agent can be used to develop sustained release floating tablets of Ranitidine hydrochloride.

Khanittha Chawananorasest *et al.*, (2016)[35]investigated the physical and chemical properties of Tamarind Seed polysaccharide (TSP) from tamarind seed with two methods and characterized. Kernel powder of tamarind seeds was slurred into a clear solution, set aside overnight and then centrifuged at 6000 rpm for 20 min to separate all foreign matter. The supernatant was separated and poured into excess 95% ethanol with continuous stirring. The precipitate obtained was collected and dried in the oven and then the dried TSP polymer was stored in a desiccator. The dried TSP was analysed by ^{1}H-NMR, FT-IR and XRD. The results showed TSP from tamarind seeds taken from paddy farmland (A), a waste from the export tamarind juice industry (B) and the export tamarind powder industry(C) gave yields of 31.55%, 26.95% and 17.30%, respectively, using method 1 and 11.15%, 53.65% and 54.65%, with method 2, respectively, but method 2 gave purer TSP than method 1. The FT-IR spectra displayed peaks at 3351.95 cm^{-1}, 2920.76 cm^{-1}, 1018.85 cm^{-1} and 555.16 cm^{-1}. The ^{1}H-NMR showed polysaccharide peaks between δ 3.50–4.20 ppm and XRD diagrams indicated their

amorphous nature. Future works will focus on the quantitative analysis, biological activity and possible use of TSP as a drug delivery system.

Mahammed Raja. *et al.*, (2016)[36]formulated and evaluated hydrodynamically balanced tablets of Ranitidine hydrochloride by direct compression technique with different ratios of polymers like hydroxyproylmethyl cellulose (HPMC K4M), Ethyl cellulose, Xanthan gum and Guar gum. *In vitro* drug release studies showed that the formulation containing HPMC K4M and ethylcellulose had sustained release up to 98% of Ranitidine hydrochloride over a period of 24h

R. Gowri. *et al*., (2015)[37]formulated floating tablets of Ranitidine hydrochloride by wet granulation technique using the polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC K 100 M and HPMC K 15, HPMC E5) and Carbopol. The physiochemical properties of different formulations, total buoyancy lag time and floating time were evaluated. The formulation containing equal concentration of HPMC K 15and HPMC K 100M per tablet have floating lag time of 90 sec and showed 98 % drug release at the end of 24 h with total floating time of more than 24h.Its drug release profile was fitted in various kinetic models and released that it follows zero order drug release following Higuchi model.

Atul Mansing Kadam. *et al.*, (2014)[38]formulated floating tablets of Ranitidine hydrochloride by direct compression method using HPMC K4M, HPMC K100M as a synthetic polymers and Gellan Gum (low acyl) as a natural polymer and evaluated for pre compression and post compression parameters. From the results it was revealed that formulation with drug: polymer ratio 5:4 exhibited sustained release of drug and followed Korsemeyer Peppa's kinetics. Natural polymer (Gellan Gum) showed better results for sustained drug release properties than synthetic polymer. It was concluded that, Gellan gum shows more floating lag time than HPMC K4M and HPMC K100M respectively. The floating lag time was found to be significantly increased with increase in concentration of polymer. The formulation F13, F14, F15 containing combination of polymers Gellan Gum and HPMC K4M shows that the drug release vary from 88.87±2.12% to 94.29±1.73% respectively.

M. Ehsanul H. Chowdhury. *et al*., (2013)[39]prepared floating tablets of Ranitidine hydrochloride by direct compression method, using polymers such as Hydroxy propyl methyl cellulose, Psyllium husk and Carbopol 934 in combination. Sodium bicarbonate

and citric acid was incorporated as a gas generating agent. All the batches showed floating time more than 12 hours. It is also observed that formulation containing highest combination of polymer shows better controlled release behaviour.

K. Kavitha. *et al.*, (2013)[40]formulated floating tablet of Ranitidine with low density polymers like hydroxyl propyl methyl cellulose and gas generating agents. Formulation was optimized on the basis of floating time and *in vitro* drug release. Four different formulations of Ranitidine were formulated by variation in the ratio of hydroxyl propyl methyl cellulose. It was found that Ranitidine incorporated with concentration of 33% of HPMC K15 found to be better formulation by considering all the evaluated parameters like floating lag time, total floating time, hardness, friability and weight variation and percentage drug release 98% drug release was observed in 24h

S. Dhivya*et al.*, (2012)[41]Preparation of floating drug delivery system is to increase the safety of the drug and to extend its duration of action. This novel drug delivery system is essential for the drugs that are degraded in the intestine .This floating drug delivery system is aimed at providing increased bioavailability. Floating drug delivery system can be retained in the stomach for long time by formulating Ranitidine hydrochloride with low density polymers like hydroxyl propyl methyl cellulose and gas generating agents are added to the system to reduce the density of the system. Intimate contact of the drug with the absorbing membrane has the potential to maximize the drug absorption. The tablet was subjected to evaluation for physical characteristics like weight variation, hardness, friability, drug content uniformity, floating lag time and floating time and *in vitro* drug release. Three different formulations of ranitidine hydrochloride were formulated by variation in the ratio of hydroxy propyl methyl cellulose. From the investigation it's found that Ranitidine hydrochloride incorporated with 120mg of HPMC was found to be better formulation by considering all the evaluated parameters like lag time, hardness, friability and weight variation and percentage drug release.

Hindustan Abdul Ahad. *et al.*, (2011)[42]formulated floating matrix tablets of Ranitidine hydrochloride by direct compression technique, using polymers such as hydroxyl propyl methyl cellulose, Carbopol 934 in combination. Sodium bicarbonate, citric acid and calcium carbonate were incorporated as a gas- generating agent. The calcium carbonate had dual action as it produces gas to float the tablets and act as an

antacid. Optimized floating matrix tablets containing hydroxyl propyl methyl cellulose K4M and Carbopol 934 showed no change in physical appearance, drug content or in dissolution pattern after storage at 40°C and relative humidity 75% for a period of 3months

Asnaashari *et al.*, 2011[43]developed metronidazole floating dosage forms that are designed to retain in the stomach for a long time. HPMC, psyllium and Carbopol in different concentrations were used as floating agents, and sodium bicarbonate was added as a gas-forming agent. Formulations containing HPMC as filler showed prolonged lag times for buoyancy. Adding psyllium to these formulations had reduced relative lag times. Overall, selected formulations were able to float immediately and showed buoyancy for at least 8 h. In general, these systems can float in the gastric condition and control the drug release from the tablets.

Prajapati S *et al.*, 2011[44] developed a floating matrix tablet containing Domperidone as a model drug. Polyethylene oxide (PEO) and hydroxypropyl methylcellulose (HPMC) were evaluated for matrix-forming properties. A simplex lattice design was applied to systemically optimize the drug release profile. The amounts of PEO WSR 303, HPMC K15M and sodium bicarbonate were selected as independent variables and floating lag time, time required to release 50% of drug(t50) and 80% of drug (t80), diffusion coefficient (n) and release rate (k) as dependent variables. The amount of PEO and HPMC both had significant influence on the dependent variables. It was found that the content of PEO had dominating role as drug release controlling factor, but using suitable concentration of sodium bicarbonate, one can tailor the desired drug release from hydrophilic matrixes. The linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppa's model, which had a higher value of correlation coefficient (r). The tablets of promising formulation were found to be stable for 3 months under accelerated (40°C / 75% RH) stability testing.

AIM & OBJECTIVES

AIM:

To formulate and evaluate the floating drug delivery of Nizatidine and comparing the effectiveness of polymers by using semi synthetic and natural polymers on the release rate.

OBJECTIVES:

- To study the drug-excipients compatibility by using FTIR analysis.
- To perform physicochemical characteristics of model drug nizatidine.
- To fabricate effervescent floating tablets of Nizatidine by using polymers Tamarind seed Polysaccharide (Natural), and Hydroxy Propyl Methyl Cellulose (Semi-synthetic) as release retardant.
- To perform Pre-formulation characteristics for the all formulations.
- To perform the post formulation characteristics for the all formulation and compare *invitro* drug release study.
- To select the optimized formulation based on the above studies.
- To study the *in vivo* radiography study of prepared floating tablets.
- To perform the accelerated stability studies of the optimized formulation

PLAN OF WORK:

1. Literature survey
2. Construction of standard calibration curve
3. Collection and isolation of gums from of Natural sources
4. Drug excipients compatibility studies using IR/ FTIR spectrophotometer
5. Preparation of nizatidine formulation
6. Pre-compression evaluations
    a. Bulk density
    b. Tapped density
    c. Angle of repose
    d. Hausner's ratio
7. Post formulation evaluation
    a. Weight variation test
    b. Thickness
    c. Hardness
    d. Friability
    e. Drug content
8. *In vitro* buoyancy / floating study
9. Total Lag floating time
10. Swelling Index
11. *In - vitro* dissolution studies
12. Drug release kinetics model
13. *In vivo* radiography study of optimized formulation
14. Accelerated Stability studies

DRUGPROFILE[45, 46, 47]

DRUG CLASS:

Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H2-receptors, particularly those in the gastric parietal cells.

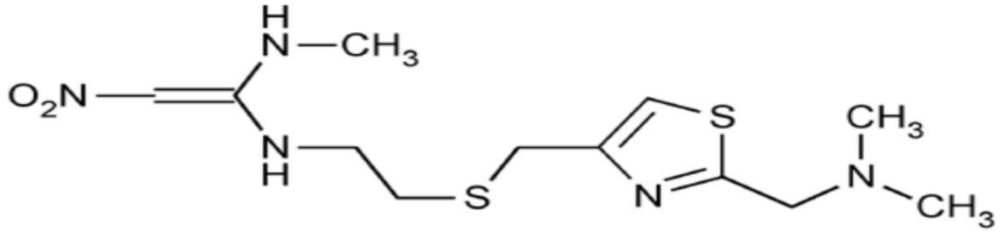
It is inhibits stomach acid production, and commonly used in the treatment of peptic ulcer disease (PUD) and Gastro Esophageal Reflux Disease (GERD).

It is considered a good candidate for incorporation in a gastro-retentive dosage form because this delivery system promotes local delivery of the histamine H2- receptor antagonist to the receptor of parietal cell wall. Local delivery increases the stomach wall receptor site bioavailability of the histamine H2-receptor antagonist to reduce acid secretion. The increase in acid-secretion reducing capacity is described as being advantageous in the treatment of ulcer patients. As its solubility decreases with increase in pH, it would be more beneficial to retain the drug in stomach (acidic environment) for prolonged duration to achieve maximum absorption and receptor site bioavailability.

So, gastro retentive drug delivery system is desirable to prolong the residence time of the dosage form in the stomach until the drug is completely released from the system.

Chemical name: *N*-(2-[(2-[(dimethyl amino) methyl] thiazol-4-yl) methylthio] ethyl) -*N*-methyl-2-nitroethene-1,1-diamine.

Structural formula:



Molecular formula: C12 H21 N5 O2 S2

Molecular weight : 331.46 g/mol.

PHYSICAL PROPERTIES:

Appearance	**:** Almost a white or slight brownish, crystalline powder
Solubility	**:** Shows pH dependent solubility. Water solubility (mg/ml): > 100, 46.1, 26.7 (pH 5, 7, 9), i.e., highly soluble in 0.1N HCl (pH 1.2).
Partition co-efficient	**:** 0.7
Melting range	**:** 130-134^{O}C
Storage	**:** Store at 20-25°C

PHARMACOKINETICPARAMETERS

Bioavailability	**:**	>70%
Protein binding	**:**	35%
Half-life	**:**	1-2hours
Absorption	**:**	Stomach
Metabolism	**:**	Hepatic
Excretion	**:**	Renal
Plasma clearance	**:**	40 to 60 L/hr
C_{max}	**:**	700 to 1,800 µg/L for a 150-mg dose and 1,400 to 3,600µg/L for a 300-mg dose.
T_{max}	**:**	1.5hours
Volume of distribution	**:**	0.8 to 1.5 L/kg.

DOSAGE AND ADMINISTRATION*:*

- **Active duodenal ulcer:**

  The recommended oral dose for adults is 300 mg once daily at bedtime. An alternative dosage regimen is 150 mg twice daily.

- **Maintenance of healed duodenal ulcer:**

  The recommended oral dose for adults is 150 mg once daily at bedtime.

- **Gastro Esophageal Reflux Disease:**

  The recommended oral dose in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily.

- **Active benign gastric ulcer:**

  The recommended oral dosage is 300 mg given either as 150 mg twice daily or 300

mg once daily at bedtime. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

PEDIATRIC DOSING:

- **Erosive esophagitis:**

  For pediatric patients 12 years or older, the dose is 150 mg *b.i.d.* (300 mg/d).

- **Gastro Esophageal Reflux Disease:**

  For pediatric patients 12 years or older, the dose is 150 mg *b.i.d*. (300 mg/day). The maximum daily dose for Nizatidine is 300 mg/day. The dosing duration may be up to eight weeks.

SIDE EFFECTS:

- **Serious reactions:**

  Hepatitis, Thrombocytopenic purpura, Exfoliative dermatitis, leukopenia, Pneumonia.

- **Common reactions:**

  Headache, rhinitis, abdominal pain, nausea and dizziness.

CONTRA INDICATIONS:

Nizatidine is contraindicated in patients with known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H2-receptor antagonists, including Nizatidine, should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.

DRUG INTERACTIONS:

Nizatidine can potentially interact with a few other medicines. Some of the medicines that may lead to Nizatidine interactions include: Aspirin, Atazanavir, Itraconazole, and Ketoconazole.

EXCIPIENT PROFILE

TAMARIND SEED POLYSACCHARIDE[48, 49, 50]

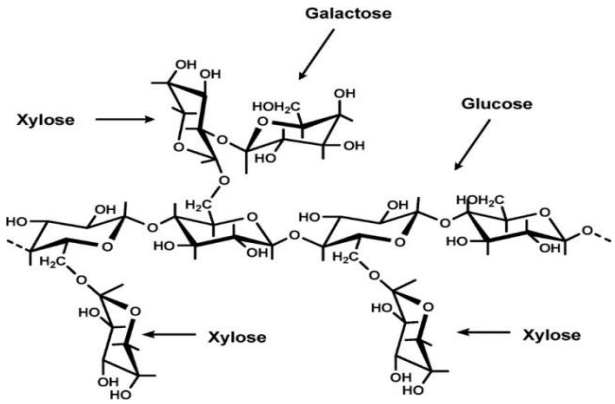
Tamarind, commonly known as *Imli*, is a rich source of tamarind gum or tamarind kernel powder

Synonym: Tamarind Seeds Gum, Tamarind Kernel Powder.

Origin: Tamarind is amongst most common and commercially important large evergreen tree that is grown abundantly in the dry tracks of central and south Indian states, and also in other south East Asian countries. Part of fruit of Tamarinds Indica Family - Leguminosae

Fig .No15: Tamarind seeds

Structure:



Chemical Structure:

Chemically,tamarind kernels powder is a highly branched carbohydrate polymer.Tamarind seeds polysaccharide is a polymer with an average molecular weight of 52350 Dalton's and a monomer of mainly three sugars – glucose, galactose and xylose in a molar ratio of 3:2:1.

A polymer consists of cellulose type spine which carries xylose and galactoxylose substituents. About 80% of glucose residues are substituted by xylose residues (1-6 linked),which themselves are partially substituted by p-1-2 galactose residues.

Chemical Composition:

The composition of tamarind kernels powder, the source of gum resembles cereals with 12.7-15.4% of protein,3-7.5% of oil,7-8.4% of crude fiber,61-72.2% carbohydrates, and 2.45-3.3%of ash. All of this was measured on dry weightbasis.

A polymer with an average molecular weight of 52350 Daltons and monomer of mainly three sugars – glucose,galactose and xylosein a molar ratio of 3:2:1.

A polymer consists of cellulose type spine which carries xylose and galactoxylose substituents.About 80% of glucose residues are substituted by xylose residues (1- 6linked), which themselves are partially substituted by p-1-2 galactoseresidues.Tamarind seed polysaccharides are a branched polysaccharide with a main chain of B-D-1- glucopyrynosyl units with a main chain consisting of single D-xylopyranosyl unit attached to every 2^{nd},3^{rd} and 4^{th} D glucopyrynosyl unit through1-6linkage.

General properties of Tamarind seed polysaccharide

Purified Tamarind seed polysaccharide is a high-molecular- weight, neutral branched polysaccharides consisting of cellulose like backbone that carries xylose and galctoxylosesubstances. It is insoluble in organic solvents and dispersible in warm mater to form a highly viscous gel as a mucilaginous solution with a broad pH tolerance and adhesively.In addition, it is non-toxic and non-irritant with a hemostatic activity. It is a galactoxyloglucan, belongs to the xyloglucan family, and possesses properties such as non-Newtonian rheological behavior, mucomimetic, mucoadhesive and pseudo plastic properties.

Application:

1. A novel polysaccharide named tamarind seed polysaccharide is now being used as an excipient in the hydrophilic drug delivery system because of its properties which include non–carcinogenicity, mucoadhesive and biocompatibility. High drug holding capacity and high thermal stability. There is a need to carry out further research on the efficacy of TSP as an excipient in pharmaceuticalformulation.
2. Tamarind seed polysaccharide could be used as binder for wet granulation and direct compression tabletmethods
3. Tamarind seed polysaccharide is useful for colon specific drug delivery because of biodegradable and hydrophilicnature.
4. Tamarind Seed Polysaccharides is used for production of thickened ophthalmic solutions having a pseudo plastic rheological behavior and mucoadhesive properties.

HYDROXY PROPYL METHYL CELLULOSE (HPMC)[51]

Non-Proprietary name **:BP**-Hypermellose,

USP-Hydroxy propyl methylcellulose

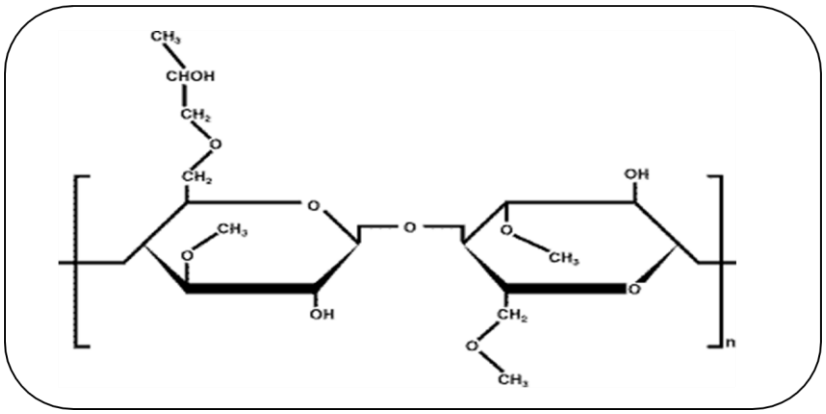
Synonym **:**Methyl hydroxy propyl cellulose, Methylcellulose,

Chemicalname **:**Cellulose 2- hydroxy propyl methylether

Molecularformula **:**$[C_6H_7O_2(OH)_3—(OCH_3)—(OCH_3CH(OH)—CH_3)]_n$

Molecularweight **:**Approximately 86,000Dalton's

Chemical structure



Category **:**Tablet binder, film former, coating agent, suspending agent, and stabilityagent.

Description **:**White (or) yellowish white fibrous (or) granular powder, almost odorless, hygroscopic afterdrying

Solubility **:**Solublein mixtures of ethanol and methylene chloride, practically insoluble in hot water, acetone, ethanol, toluene, and ether. It swellsby cold water forming an opalescent viscous colloidalsolution

Meltingpoint **:**190-200ºC

Acidity/alkalinity **:**5.5- 8.0 for 1% w/w aqueoussolution

Specificgravity **:**1.26w/v

Density **:**0.25- 0.71g/cm^3

Viscosity **:**HPMCK100M 80,000-12,0000 cps
HPMCK4M 3000-5000 cps
HPMCE5 5cps
HPMCE15 15cps

Stability **:** Bulk materials stored in an air tight container and in cold and dryplace.

Increase in temperature decrease the viscosity of the solution.

Safety **:** It was regulated as non-toxic (or) non-irritant although excessive consumption causes laxativeeffect

Application:

1. Used in the treatment of tear deficiency.
2. It was versatile and granular agent.
3. It swells by water and in virtually in all GIT fluids and it may except to retard disintegration and dissolution time of drug in the tablets when wet granulation is employed

Table No.4 : Application of HPMC based on concentration

Uses	Concentration (%)
Extended release matrix formulation	15-35
Tablet binder	2-6
Tablet film coating	2-20

CITRIC ACID[52]

Synonym **:**2hydroxy propane1,2,3,tricarboxylic acidmonohydrate

Non-Proprietary Names **:**BP-Citric acidmonohydrate;

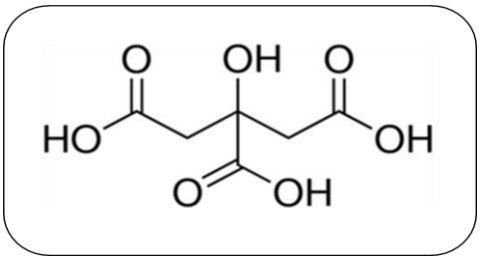
USP **:** Citricacid

ChemicalName **:** 2-hydroxy-1,2,3-propanetricarboxlic acidmonohydrate

Chemicalformula **:** $C_6H_8O_7.H_2O$

Molecularweight **:** 210.14

Chemical structure



Category **:**Acidifying, antioxidant, buffering agent, chelating, flavorenhancer

Description **:**It is colorless (or) transculant (or) as a whitecrystalline efflorescent Powder. It is odorless and has strong acid flavor, the crystal structure is orthorhombic

Solubility **:**Soluble in 1.5 parts of ethanol (95%) and 1 in less than1 partof water, sparingly soluble inether.

Typical properties

Acidity/alkalinity **:** pH 2.2 for a (1% w/v aqueoussolution)

Density **:**1.54g/cm^3

Meltingpoint **:**100ºC

Viscosity (dynamic) **:**65 cps for aqueous solution at 25ºC

Storage **:**The bulk monohydrate (or) anhydrous material should be stored in airtight container in a cool, dryplace

Safety **:** Orally ingested citric acid is absorbed and is generally regarded as a nontoxicmaterial.

Applications:

1. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescenttablets.
2. Citric acid has also been shown to improve the stability of spray-dried insulin powder in inhalationformulations.
3. In food products, citric acid is used as a flavor enhancer for its tart, acidictaste.
4. Citric acid monohydrate is used as a sequestering agent and antioxidantsynergist.

SODIUM BICARBONATE[53]

Synonym **:**Sodium hydrogen carbonate, Monosodium carbonate,Sodium acidcarbonate

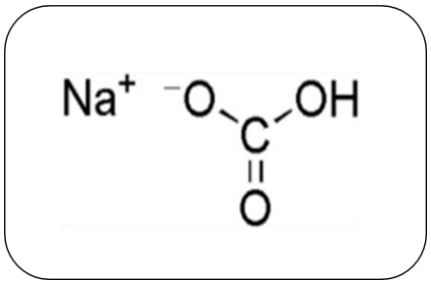
Non-Proprietary name **:**BP-Sodiumbicarbonate

Chemicalname **:**Carbonic acid monosodiumsalt

Chemicalformula **:**$NaHCO_3$

Molecularweight **:**84.01

Chemical structure



Category **:**Alkalizing agent, therapeuticagent

Description **:**Odorless, white crystalline powder, slightly alkaline

Solubility **:** Soluble in water,
practically insoluble in ethanol and ether

Typicalproperties:

Acidity/alkalinity **:**pH 8.3 for a freshly prepared 0.1 M aqueous solution at 25°C alkalinity increase on standing, agitation,(or)heating

Density **:**0.869-2.173g/cm^3

Freezingpointdepression **:**0.381°C

Meltingpoint **:**270°C

Applications:

1. Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets andgranules.
2. It is also widely used to produce or maintain an alkaline pH in apreparation.
3. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaricacid.
4. Sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolicacidosis.
5. Sodium bicarbonate may also be used as a component of oral rehydration salts and as a source of bicarbonate in dialysisfluids.

Table 5: Application of Sodium bi carbonate

Uses	**Concentration (%)**
Buffer in tablet	10-40
Effervescent tablet	25-50
Isotonic injection/ infusion	1.34

MICROCRYSTALINECELLULOSE[54]

NonproprietaryNames	**:** BP: Microcrystalline USP-NF: Microcrystalline Cellulose
Synonyms	**:** Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Tabulose,Vivacel.
Functional Category	**:** Tablet and Capsule diluent, suspending agent, adsorbent, tabletdisintegrant.
Description	**:** White-colored, odorless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties andapplications.
Solubility	**:** Slightly soluble in 5 % w/v NaOH solution, practically insoluble in water, dilute acids and most organicsolvents.
Stability	**:** It is a stable, though hygroscopicmaterial.
Storage conditions	**:** The bulk material should be stored in a well-closed container in a cool and dryplace.
Incompatibilities	**:** Incompatible with strong oxidizingagents.
Safety	**:** It is generally regarded as a nontoxic and nonirritantmaterial.

Applications:

1. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compressionProcesses.
2. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful intableting.
3. Microcrystalline cellulose is also used in cosmetics and foodproducts

MAGNESIUM STEARATE[55]

Non-proprietarynames **:**BP- Magnesium Stearate

JP- Magnesium stearate

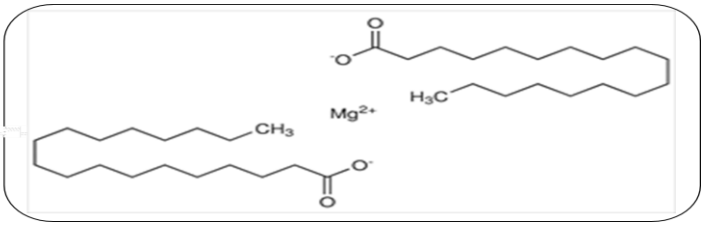
Synonyms **:** Magnesium octadecenoate, octadecanoic acid magnesium salt and stearic acid magnesiumsalt.

Chemical name **:** Octadecanoic acid magnesium salt

Structural formula **:** $[CH_3 (CH_2)_{16}COO]_2Mg$

Molecular weight **:**591.34

Chemical structure



Functional category **:** Tablet and capsulelubricant.

Melting point **:** 117-150^{0}C

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

Solubility **:** It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications **:** It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barriercreams.

Stability & storage conditions: It should be stored in a well closed container in a cool, dryplace.

TALC[56]

Non-proprietarynames **:**BP- Purified talc

USP- Talc

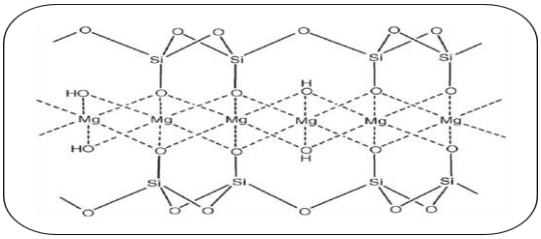
Synonyms **:** Altalc, powdered talc, purified French chalk, Pure talc,soapstone, steatite andSuperior.

Chemical name **:**Talc

Structural formula **:** $Mg_6(Si_2O_5)_4(OH)_4$

Molecular weight **:**379.2

Chemical structure



Functional Category **:**Anticaking agent, glidant, tablet and capsulelubricant

Description **:**Talc is very fine; white to grayish white,odorless,crystalline powder, it adheres readily to the skin and is so soft to touch and free fromgrittiness

Solubility :It is practically insoluble in dilute acids and alkalis,organic solvents and water**.**

Typical properties

Acidity/alkalinity **:**pH 7-10 for a 20 % w/v aqueousdispersion

Stability **:**Talc is a stable material and may be stored by heating at 160ºC for not less than 1hour

Incompatibilities **:** It is incompatible with quaternary ammonium compounds

Storage **:**Talc should be stored in a well closed container in a cool, dry place

Stability & storage conditions **:** It is a stable material and may be sterilized by heating

at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in a well closed container in a cool and dryplace.

Applications:

1. It is used as a diluent, lubricant in tabletformulations.
2. In a novel powder coating for extended-release pellets and as anadsorbent.
3. In topical preparations, it is used as a dusting powder, usedtoclarify liquids.
4. It is also used in cosmetics and foodproducts.

FORMULATION DEVELOPMENT:

1. Isolation of Tamarind seed polysaccharide[49] :

The seeds of Tamarinds indica are washed in water to remove the adhering materials

↓

By heating seeds in sand ratio of 1:4 c

↓

Reddish Testa of the seeds is removed

↓

Seeds are crushed lightly

↓

Crushed seeds are soaked in water for 24 h

↓ Boil for 1 hour

Kept aside for 24hr for the release of mucilage into water

↓

Soaked seeds are squeezed in a muslin bag to remove marc

↓ From the filtrate

Equal quantity of acetone is added to precipitate the mucilage

↓

Separate the mucilage&
Dried at temperature50^0c

↓

Powdered and passed through sieve number 80.

↓

Stored in airtight container at room temperature.

Tamarind seed: sand

Removed Testa

Crushed Seeds

Mucilage

Powder polymer

Stored polymer

Fig.No.16:Isolation of Tamarind seed polysaccharide

FORMULATION OF NIZATIDINE FLOATING TABLET:

Direct compression:

The Nizatidine floating tablets was prepared by effervescent technique used the hydrophilic polymers (HPMC K4M, and Tamarind seed polysaccharides). Sodium bi carbonate & citric acid used as gas generating agent. The polymers were chosen as they are well established in the similar studies and have great swelling and controlled release properties respectively. In direct compression vehicles can be used which are having good free flow properties, no segregating and are have compressible mixture.

Steps involved in preparation of floating tablet by direct compression:

Drug (Nizatidine) + Different polymers in various ratios + NaHCO3+ Citric acid + Talc +Magnesium stearate

↓

Were mixed in mortar with the help of pestle

& add MCC and triturate well

↓

Blended materials compressed on 12.5mm flat round punches

& corresponding dies are used

↓

The Total weight of the prepared tablet was maintained as 500mg

Nizatidine with the other excipients are in concentration & ratio are used for the preparation of tablet were shown in Table. 6

Table.6: Formulation of Nizatidine floating tablets

INGREDIENTS	FORMULATION CODE								
	F1 mg	**F2 mg**	**F3 mg**	**F4 mg**	**F5 mg**	**F6 mg**	**F7 mg**	**F8 mg**	**F9 mg**
Nizatidine	150	150	150	150	150	150	150	150	150
Tamarind polysaccharide (1:0.5, 1:1, 1:1.5)	75	150	225	-	-	-	37.5	75	112.5
HPMC K4 (1:0.5, 1:1, 1:1.5)	-	-	-	75	150	225	37.5	75	112.5
Sodium bicarbonate (10%)	35	35	35	35	35	35	35	35	35
Citric acid (1%)	4	4	4	4	4	4	4	4	4
Talc (1.7%)	6	6	6	6	6	6	6	6	6
Magnesium stearate (4%)	4	4	4	4	4	4	4	4	4
Microcrystalline cellulose (14%)	50	50	50	50	50	50	50	50	50
Lactose (q. s)	176	101	26	176	101	26	176	101	26
Total weight	500	500	500	500	500	500	500	500	500

MATERIALS AND EQUIPMENTUSED

Table. 1: Materials used in the study

S.No.	Name of chemical	Manufacturer/supplier
1	Nizatidine	Central Drug Laboratory, Chennai
2	HPMC K4M	Hi Media Laboratories limited, Mumbai
3	Carbopol	Hi Media Laboratories limited, Mumbai
4	MCC	SD Fine chem. Ltd, Mumbai
5	Sodium bi carbonate	SD Fine chem. Ltd, Mumbai
6	Citric acid	SD Fine chem. Ltd, Mumbai
7	Magnesium stearate	SD Fine chem. Ltd, Mumbai
8	Talc	SD Fine chem. Ltd, Mumbai
9	Conc. Hydrochloric acid	SD Fine chem. Ltd, Mumbai
10	Acetone	Hi Media Laboratories limited, Mumbai
11	Tamarind Seed	Local market, Trichy

Table. 2: Equipment used in the study

S.No.	Equipment	Model no.	Manufacturer
1	Tablet Punching Machine	Mini press-I	Rimek, Ahmedabad
2	Digital Weighing Balance	AX 200	Shimadzu Corporation,,Japan
3	pH Meter	Cyber Scan	EutechInstrument,Singapore
4	Bulk and tapped density apparatus	1951 Digital	Thermonik,Campbell electronics, Mumbai, India
5	Hardness Tester	Monsanto hardness tester	Praveen Enterprises, Bangalore.
6	Vernier caliper	Aerospace 150 mm Digimatic	Linker, Mumbai.
7	Friability (USP)	C-FTA20	Thermonik, Campbell electronics
8	Dissolution Apparatus	6 stage dissolution rate test apparatus IP/BP/USP	TAB Machines, Mumbai
9	UV–Visible Spectrophotometer	UV-1700	Pharmaspec, Shimadzu
10	FTIR Spectrophotometer	FTIR-8400S	Japan
11	Glass ware	Borosilicate	Mumbai, India
12	Heating mantle	-	Sunbim , India

EXPERIMENTAL PROTOCOL

1. Solubility study of Nizatidine in 0.1 N HCl

Nizatidine was placed in 0.1 N HCl in order to determine its solubility. The sample was shaken for 24 hrs at 37 °C in a horizontal shaker. The supernatant was filtered and the filtrate was diluted with the 0.1 HCl and assayed by UV-Visible spectrophotometer at λmax314 nm.

Table No.7: Solubility profile I.P. 1996

Descriptive Term	Parts of Solvent required for 1 part of Solute
Very soluble	>1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1,000
Very slightly soluble	1,000-10,000
Practically insoluble	≥10,000

Preparation of Simulated gastric fluid without enzyme (SGF)

About 2.0g of sodium chloride and 7.0ml of hydrochloric acid (concentrated) were dissolved in small amount of distilled water and made upto to 1000ml with distilled water whose pH 1.2

a. Calibration Curve of Nizatidine in 0.1 N HCl in SGF

Taken into different volumetric flasks and volume were made up to 100 ml with Acid buffer pH 1.2 solution, so as to get concentration of (20-100 μg/ml). The absorbance of these solutions were measured at 314 nm by UV Spectrophotometer. A calibration curve is plotted by taking concentration on X-axis and absorbance on Y-axis to obtain the standard curve.

2. DRUG EXCIPIENTS COMPATIBILITY STUDIES

a. Physical Incompatibility:

Table. No. 8: Ratio for Physical Incompatibility studies

S.NO	INGREDIENTS	DRUG EXIPIENTRATIO
1	Nizatidine	-
2	Drug + Tamarind Polymer	1:1
3	Drug+HPMC	1:1
4	Drug+NaHCO3	1:1
5	Drug+Citricacid	1:1
6	Drug+Talc	1:1
7	Drug+MCC	1:1
8	Drug+MagnesiumSterate	1:1

Chemical Incompatibility:

b. Fourier Transform Infrared (FTIR)Spectroscopy:

Infrared spectroscopic analysis was performed to check out the compatibility between the drug (Nizatidine) and the hydrophilic polymers (HPMC K4M) and Tamarind seed polysaccharides used in the formulation of floating matrix tablets. IR spectrum of the pure drug and the physical mixtures of drug with polymers of optimized formulation were studied.

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3. PRE FORMULATION

a. Angle of repose:

Angle of repose is define as the maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose is designated θ is given by equation:

$$\theta = \tan^{-1} (h/r)$$

Where, h is height of pile in cm,

r= radius of pile in cm,

θ = angle of repose.

The fixed funnel method is to measure the angle of repose. The funnel height is maintained approximately 2 - 4 cm from the top of the powder pile in order to minimize the impact of falling powder on the tip of the cone. The blend carefully pored through the funnel. The height *'h'* of the pile from base and radius '*r'* of the base of the conical pile is measured.

TableNo.9: Range for Angle of repose

Angle of repose (θ) (degrees)	**Flow Type**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

c. Bulk density (D_b):

It is the ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particle. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and

volume was measured 'as it as' which is called initial bulk volume. It is expressed in gm/ml and is given by,

$$D_b = M / V_0$$

Where,

M is mass of a Powder

V_0 is the bulk volume of the powder

d. Tapped density:

Ten gram of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 250 times from a constant height and the tapped volume was read. It is expressed in gm/ml and given by,

$$D_t = M / V_t$$

Where,

M is mass of powder

V_t is the bulk volume of the powder

e. Compressibility index (or) Carr's Index (I)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. It indicates the ease with which a material can be induced to flow powder flow properties. It is expressed in percentage and given by,

$$I = D_t - D_b / D_t \times 100$$

Where,

I is the Compressibility index,

D_t is the tapped density of the powder and

D_b. is the bulk density of the powder.

Table. No. 10 Range for Compressibility index (%)

Compressibility index (%)	Type of flow
5-15	Excellent
12-18	Good
18-23	Fair
23-35	Passable
35-38	Poor
>38	Very poor

e. Hausner's ratio:

It indicates the flow properties of the powder. The ratio of Tapped density to bulk density of the powder or granules is called Hausner's ratio.

$$H = Dt / Db$$

Where,

H is the Hausner's ratio,

Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table. No. 11 Range for Hausner's ratio

Hausner's ratio	Type of flow
1- 1.11	Excellent
1.12- 1.18	Good
1.19- 1.25	Fair
1.26- 1.34	Passable
1.35- 1.45	Poor
1.46- 1.54	very poor
>1.60	very very poor

4. POST - COMPRESSION PARAMETERS

a. General appearance:

The formulated tablets are evaluated for general appearance. Viz., color, odour, shape.

b. Thickness and Diameter:

They are measured by using Vernier calliper. Five tablets were selected randomly from each batch and thickness and diameter were measured .It was expressed in (mm).

c. Hardness Test:

The Monsanto tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjust to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness of about 6.26 to 7.2 was considered to be minimum for uncoated tablets for mechanical stability. It was expressed in kg/cm^2

d. Friability Test:

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 resolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets. Compressed tablets should not loss more than 1% of their initial weight. The % friability was then calculated by;

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

e. Weight Variation as Per IP:

Randomly selected twenty tablets were weighed individually and together in a single electronic pan balance. The average weight was noted and calculated standard deviation. The percentage weight variation as per Official limits are as shown in the Table. No. It can be calculated by,

$$\mathbf{PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100}$$

Where,

PD= percentage deviation,

W_{avg} =Average weight of tablet,

$W_{initial}$ = Individual weight of tablet

Table No. 12: Official limits for weight variation

Average weight of Tablet (mg)	Percentage Deviation (%)
80 or less	10
80 to 250	7.5
More than 250	5

f. Drug content uniformity:

Ten tablets are weighed and taken in a mortar and crushed to make powder form. A quantity of powder weighing equivalent to 10mg of drug is taken in a 100ml volumetric flask and Acid buffer PH 1.2 is added. The solution is filtered using membrane filter (0.45µm) and 10 ml of filtrate is taken into 100 ml volumetric flask and made up to final volume with Acid buffer PH 1.2. Then its absorbance is measured at 314 nm using UV Visible spectrometer. The amount of drug present in one tablet is calculated using standard graph.

g. Swelling index:

The swelling of the polymers can be measured by their ability to absorb water and swell. The water uptake study of the tablet was done using beaker containing respective medium and it was maintained at 37 ±0.5° C throughout the study. After a selected time interval at 8hrs, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of tablets were expressed in terms of water uptake. The percentage of swelling index was calculated by,

$$S.I\ (\%) = \frac{\text{Weight of the swollen tablet - Initial weight of the tablet}}{\text{Initial weight of the tablet}}$$

5. IN VITRO BUOYANCY DETERMINATION:

a. Floating properties of the tablet (Floating lag time and total floating time):

The time taken for tablet to float on surface of medium is called the floating lag time (FLT) and duration of the dosage form to constantly remain on surface of medium is called the total floating time (TFT). The *in vitro* buoyancy was determined by floating lag time total floating time. The tablets were placed in a 100 ml beaker containing SGF pH 1.2. The time required for the tablet to rise to the surface and float was determined as floating lag time and total floating time.

6. IN VITRO DRUG RELEASE STUDIES:

Dissolution characteristics of the formulated floating tablets of Nizatidine are carried out using USP Type II (paddle) dissolution test apparatus for 12hrs.

Method:

900 ml of acid buffer pH 1.2 was filled in dissolution vessel and temperature of the medium is set at 37°C ± 0.5°C. One tablet of different batch is placed in each dissolution vessel and the rotational speed of paddle was set at 75rpm. 5ml of sample is withdrawn at pre-determined time interval of every one hour for up to 12 hours and same volume of fresh medium is replaced immediately. The withdrawn sample is diluted to 10ml in volumetric flask and filtered through 0.45µ membrane filter. The resultant samples are analyzed for drug content at 314 nm using UV-Visible spectrophotometer. Parameters for *in vitro* studies are shown in **Table. No.13**

Table. No. 13 Parameters Performed *in vitro* studies

Parameter	Specifications
Dissolution Medium	Buffer 0.1N hydrochloric Acid
Temperature	37.0 ± 0.5 ℃
Initial Volume	900ml
Rotation Speed	75rpm
Drawn Volume	5ml
Running Time	12 hrs. in 0.1N hydrochloric Acid

7. *IN-VITRO* DRUG RELEASE KINETICS [66]

To analyze the *In-vitro* release data various kinetic models were used to describe the release kinetics. The zero-order rate describes the systems where the drug release rate is independent of its concentration. The first order describes the release from the system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion. The Koresmeyer- Peppa's describes the mode of release of drug from swellable.

Table. No.14: Equations of Release Kinetics Model

Release Kinetics Model	Equation
Zero Order	Qt = Q0 + K0.t
First Order	In Qt = In Q0 + K0.t
Higuchi model	Q = KH. t1/2
Korsmeyer – Peppa's	Mt / M0 = a.tn

Where,

Qt is amount of drug release at time t,

M_t is drug release at time t,

M_0 is total amount of drug in dosage form,

F is fraction of drug release at time t,

$K_0$is zero order release rate constant,

$Q_0$is Initial amount of drug in the solution (Most times, Q_0=0)

KH is Higuchi's square root of time release rate constant,

Km is constant depend on geometry of dosage form and

n is diffusion exponent values indicating the mechanism of drug release.

Fitness of release profiles to linear equations is assessed by comparing the coefficients of determination (regression) values.

Table. No. 15.Diffusion exponent values indicating drug release mechanism

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.5	Fickian release
2	0.5 to 1.00	Non-Fickian transport
3	1.00	Case II transport
4	> 1.00	Super case II transport

The *in-vitro* release data are fitted to the above mathematical models and the applying data are,

- Cumulative % drug release vs. time for zero order kinetic.
- Log cumulative of % drug remaining vs. time for first order kinetic.
- Cumulative % drug release vs. Square root of time for Higuchi model.
- Log cumulative % drug release vs. log time for Korsmeyer- Peppa's model.

8. SELECTION OF BEST FORMULATION:

Selection of best formulation were depends on best fit parameters of FLT, TFT, Swelling index, in vitro drug release, in vitro kinetic release

9. *IN VIVO* X-RAY STUDIES:

a. Animal and diet:

- The male albino rabbit (2 - 2.5kg) are housed in the polypropylene cages at temperature 22 ± 2°c. The animal is fasted overnight but allowed to take water *ad libitum* (Londhe S *et al*., 2010).
- Then 30 ml of 5 % dextrose solution is given immediately before administering the tablet by using stomach tube (No. 12 French Catheter) and 20 ml syringes.
- The experiment protocol of the study was approved by Institutional Animal Ethical Committee (Registration No. KMCRET/M. Pharm/01/2018-2019)

b. *In vivo* X-ray of optimized formulation:

- The *in-vivo* X-ray studies were performed in healthy male albino rabbit.
- After performing physicochemical characteristics. *In- vitro* buoyancy, *In vitro* drug release and swelling index, among all formulations, F8 formulation containing combination of tamarind seed polysaccharides & HPMC K4M polymer(1:1)have shown best and satisfactory results.
- Hence, this formulation was selected for further *In vivo* evaluations. The optimized formulation was prepared using 25% of drug was replaced with barium sulphate are made opaque, with no changes in other ingredients.
- The *in-vivo* radiographic studies were performed in healthy male albino rabbit in the abdominal region, and photographs are taken at 0, 2, 4, 6, 8, 10 & 12 hrs by using x-ray machine.
- The *in-vivo* radiographic studies were performed in healthy male albino rabbit at appropriate periodic time intervals by using x-ray machine.

- .After administration of tablet. At hourly intervals 30 ml of 5% dextrose solution is given to maintain optimum fluid level in the stomach. The gastric residence time is observed.

10. EVALUATION OF ACCELERATED STABILITY STUDIES BEST FORMULATION (F8):

Stability studies were carried out by using selected formulation i.e. F8. The formulation is kept in accelerated stability condition at temperature 40˚C/75% relative humidity for a period of 2 months as per International Conference on Harmonization guidelines.

The samples were withdrawn after 60 days intervals and evaluation was carried out for appearance, thickness, hardness, buoyancy lag time, drug content and *In-vitro* release studies (60days) were performed**.**

1. SOLUBILITY OF NIZATIDINE

Nizatidine is highly soluble in 0.1 N HCl, having quantitative solubility99.20 mg/ml.

a. CALIBRATION CURVE OF NIZATIDINE in 0.1 N HCl (pH 1.2)

Scanning of the volumetric solution to nizatidine in ultraviolet range (200-400nm) against 0.1N HCl blank gave the λ_{max} at 314nm. The standard concentrations of Nizatidine (20-100 µg/ml) prepare as 314 nm and there absorbance are shown in **Table. No.16** The standard concentrations of Nizatidine (20-100 µg/ml) showed good linearity with R^2 value of 0.9998, were shown in **Fig.No.**which suggests that it obey the Beer-Lamberts law.

Table.No.16: Absorbance of Nizatidine in 0.1 N HCL (pH 1.2)

Concentration (µg/ml)	Absorbance
0	**0**
20	**0.073**
40	**0.138**
60	**0.203**
80	**0.268**
100	**0.339**

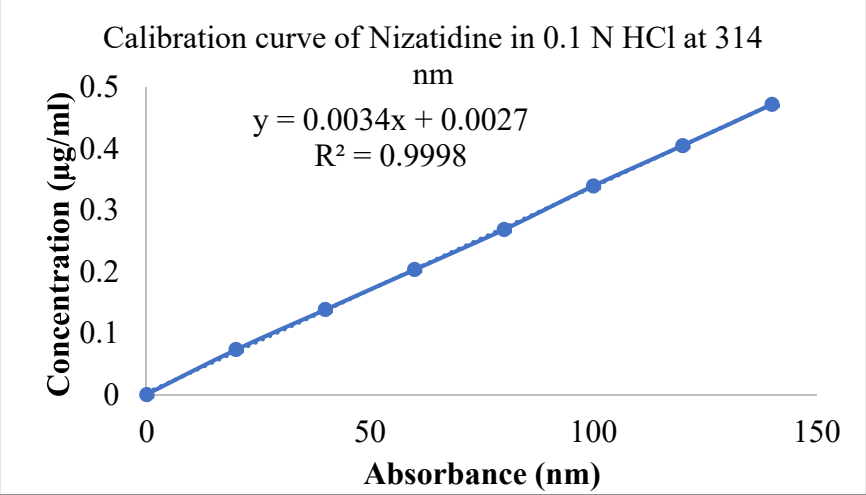


Fig. No. 31Calibration curve of Nizatidine in 0.1 N HCl at 314 nm

2. DRUG EXCIPIENTS COMPATIBILITY STUDIES

a. Physical Incompatibility:

There is no interaction between drug and excipientsbased on the physical appearance and the result werementioned in **Table. No:17**

Table.No.17: Physical Incompatibility

S.NO	INGREDIENTS	DRUG EXIPIENTRATIO	OBSERVATION
1	Nizatidine	-	Off white crystalline powder
2	Drug + Tamarind Polymer	1:1	Off white crystalline powder
3	Drug+HPMC	1:1	Off white crystalline powder
4	Drug+NaHCO3	1:1	Off white crystalline powder
5	Drug+Citricacid	1:1	Off white crystalline powder
6	Drug+Talc	1:1	Off white crystalline powder
7	Drug+MCC	1:1	Off white crystalline powder
8	Drug + Magnesium Sterate	1:1	Off white crystalline powder

b. Chemical Incompatability:

Fourier Transform Infrared (FTIR) Spectroscopy:

From the **Fig. No**. the majors peaks were obtained at 765, 1226 , 1393 and 3000-2968/ cm-1 for pure drug of some functional groups of N-H, C-N, C=C, CH_3 of respectively. Ranges were shown in **Table.No.18**

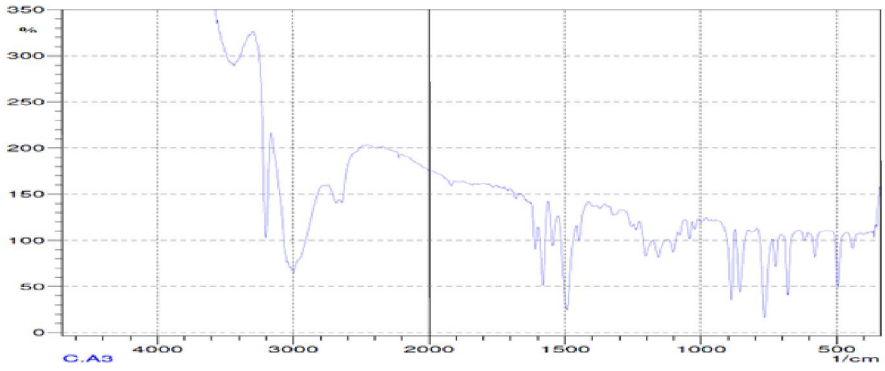


Fig.no.32 FT-IR Spectra of Nizatidine pure drug

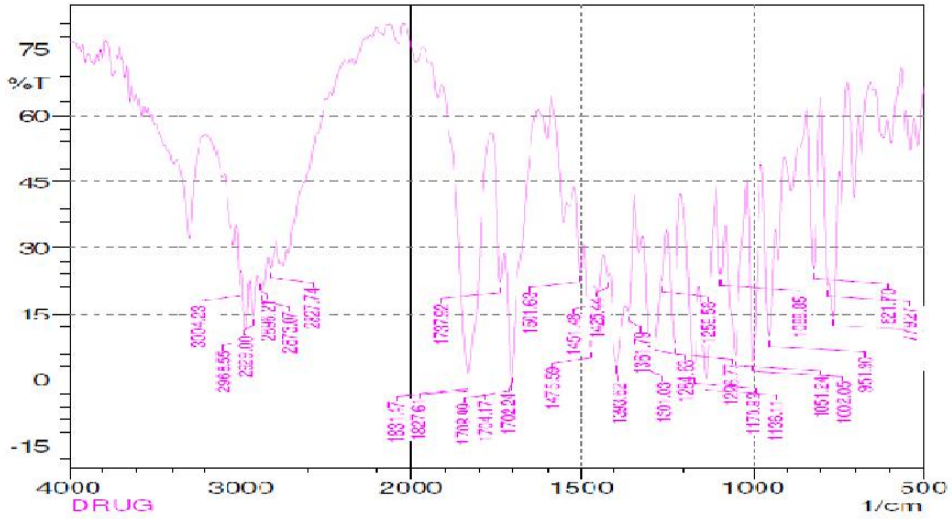


Fig.no. 33.FT-IR Spectra of Nizatidine + Tamarind polysaccharide

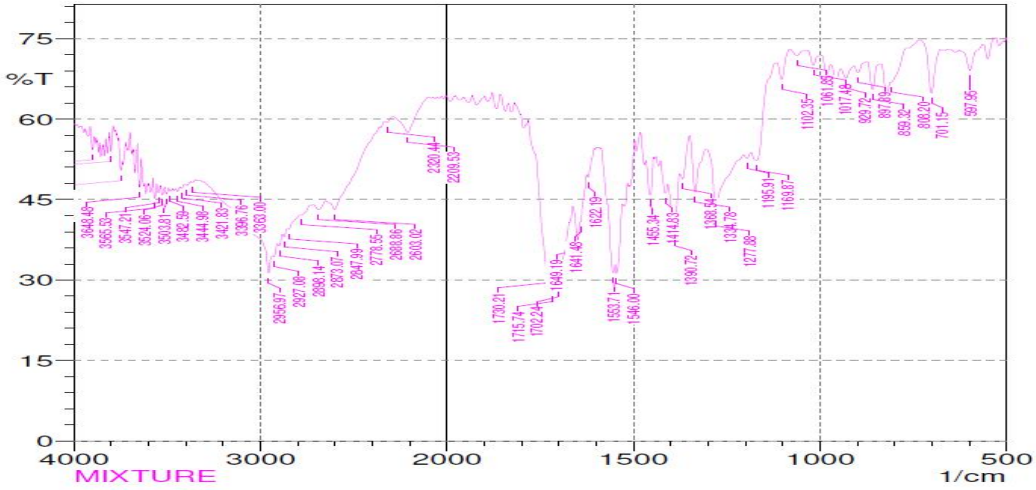


Fig.no.34. FT-IR Spectra of Nizatidine + HPMC K4

Table No.18: FTIR SPECTRA OF DRUG AND EXCIPIENTS

Specified functional group	Nizatidine	Nizatidine + Tamarind	Nizatidine +HPMC
CH_3	2968	2956	2968
NH	3300	3306	3300
N-O	1393	1390	1395
C-S	765	751	769
C-N	1301	1334	1330
C=C	1393	1390	1380

The major peaks obtained a pure drug in the same characteristic bands drug in excipients also shown, without any significant spectral changes thus there is no interaction between the drug and excipients used in the formulations.

3. PRE-FORMULATION

a. Angle of repose:

The Angle of repose for all formulations was in the range of $25^0$42' to $28^0$72'whichindicates good flow of the powder,were shown in **Table. No.19**

b. Bulk density (D_b):

The Bulk density of the powder was in the range of 0.66 to 0.74 gm/cc, which indicatesthe powder

were shown in **Table.No**.19

c. Tapped density (D_t):

The Tapped density of the powder was in the range of 0.74 to 0.83 gm/cc, were shown in **Table.No**.19

d. Compressibility index (or) Carr's Index(I):

The Compressibility index(or) Carr's Index was found to be in range 9.2 to 11.96% , which support fact that these formulation has excellent flow and compaction propertieswere shown in **Table .No.**19

e. Hausner's ratio:

The Hausner's ratio was found to be in the range of 1.102 to 1.135 which was supports the fact that the formulation has good and excellent flow abilitywere shown in Table No.19

All formulation were exhibit good flow property and compressibility which is very essential for direct compression and hence tablets were prepared by using direct compression technology.

Table No.19: Pre-Formulation (Pre-Compression)

Formulations	Angle of repose ± SD	Bulk density (gm/ml) Avg ±S.D	Tapped density(gm/ml) Avg ±S.D	Carr's index (%)	Hausner's ratio
F1	$25^0$42' ± 1.11	0.742± 0.002	0.818± 0.002	9.24	1.102
F2	$25^0$69' ± 1.51	0.660± 0.002	0.740± 0.002	10.810	1.121
F3	$27^0$47' ± 1.63	0.731± 0.003	0.821± 0.003	10.962	1.123
F4	$26^0$94' ± 0.56	0.714± 0.004	0.789± 0.003	10.504	1.105
F5	$26^0$05' ± 1.48	0.740± 0.003	0.823± 0.002	10.085	1.112
F6	$28^0$68' ± 1.82	0.721± 0.002	0.818± 0.002	11.858	1.134
F7	$26^0$29' ± 0.51	0.734± 0.002	0.810± 0.002	9.382	1.103
F8	$25^0$60' ± 0.92	0.728± 0.004	0.826± 0.002	11.86	1.134
F9	$28^0$72' ± 1.48	0.736± 0.004	0.836± 0.002	11.96	1.135

4. POST-COMPRESSION PARAMETERS

a. Generalappearance:

The formulated tablets were evaluated for general appearance. Viz., color, odour, shape were good as shown in **Table. No.20**

b. **Thickness and Diameter:**

The Thickness of tablet were measured using venier caliper. The Thickness was found to be 4.12 to 4.29 mm and diameter were in 11mm as shown in **Table. No.20**

c. Hardness Test:

The measured hardnessof all batches of tablet was found to be in the range of 6.26 to 7.2 kg/ cm^2as shown in Table. No.20These ensure good handling characteristics of tablets.

d. Friability Test:

The maximum friability of the formulation was found to be 0.89%. The minimum friability of the formulation was found to be 0.82% were shown in **Table.No**.20 The friability was less than 1% in all the formulations ensuring that the tablets were found mechanically stable.

e. Weight Variation as Per IP:

All the formulated tablets passed the percentage weight variation as per IP limits of ±5% to the weight as shown in **Table. No.20** The weights of the all the formulated tablets were found to be uniform. The prepared formulation complies with the weight variation test.

f. Drug content uniformity:

The drug estimation data for all the formulated tablets were found to be within the limit and the result as shown in **Table. No.20**

g. **Swelling index:**

Swelling index for all formulations was carried out in the 0.1N HCl. F8 were shown maximum Swelling in 8hr with highest swelling index when compare to other all formulations as shown in **Table. No.20**

Table No.20: POST FORMULATION STUDIES

Formulations	Average Weight(mg) Avg ±S.D	Thickness (mm) Avg ±S.D	Hardness kg/cm^{2}Avg± S.D	Friability (%w/w)	Diameter (mm)	Drug Content uniformity (%)
F1	472.3±0.862	4.12±0.11	6.66±0.378	0.829±0.03	11	97.18±0.35
F2	470.1±0.340	4.13±0.08	6.76±0.251	0.853±0.02	11	98.39±0.34
F3	483.5 ±0.055	4.20±0.12	6.79±0.264	0.826±0.13	11	98.39±0.34
F4	482.5 ±0.068	4.18±0.13	6.62±0.458	0.895±0.12	11	98.19±0.34
F5	480 ±0.0529	4.16±0.14	6.86±0.378	0.833±0.06	11	97.39±0.34
F6	472.5 ±0.155	4.23±0.11	6.96±0.321	0.826±0.04	11	98.29±0.6
F7	481.5 ±0.570	4.16±0.10	6.92±0.350	0.84±0.03	11	97.19±0.34
F8	485.5 ±0.755	4.25±0.11	7.01±0.251	0.856±0.02	11	98.59±0.35
F9	480 ±0.895	4.29±0.11	7.0±0.251	0.896±0.03	11	97.19±0.34

5. *IN VITRO* BUOYANCY DETERMINATION:

a. Floating Lag Time:

The time taken to emerge on the surface of the liquid after adding to the dissolution medium at pH 1.2 with 50 sec of F8 least Floating lag time when compare to the other formulations.

At 0 second **At 20 second** **At 30 second** **At 40 second**

At 45 second **At 48 second** **At 50second**

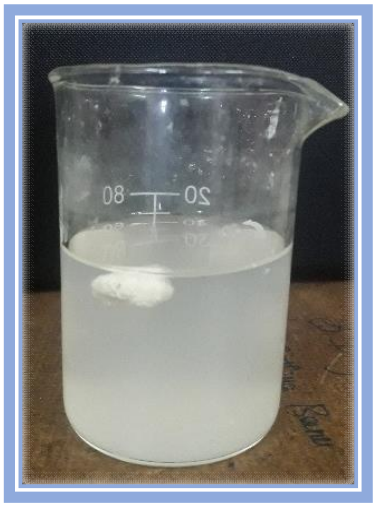
Fig. 35.Floating lag time of F8 formulation

b. **Total floating time:**The time taken by the tablet to float constantly on the surface of the gastric fluid at pH 1.2 in 100ml beaker were observed as shown **Fig.No.22.**

2 hour

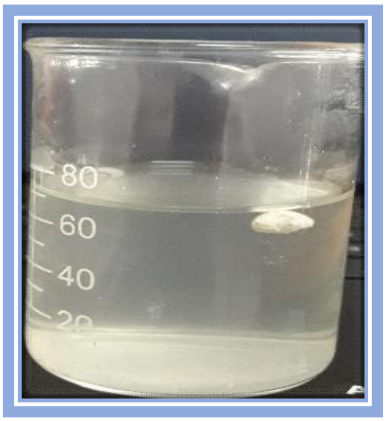
4 hour

6 hour

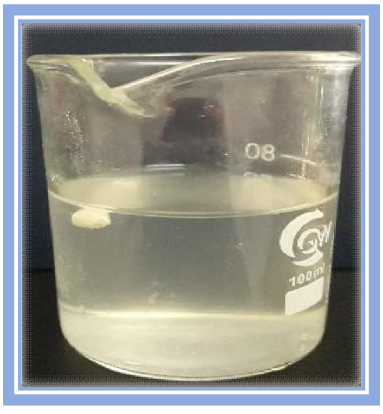


8 hour

9 hour



10 hour



11:30 hour

FigNo.22 Total floating time of F8 best formulation

6. *IN VITRO* DRUG RELEASE STUDIES:

*In vitro*dissolution studies of all the formulations of floating tablets of Nizatidine were carried out in Acid buffer (0.1 N HCl).The study was performed for 12 hour, and cumulative drug release was calculated at different timeintervals.

Effects of various ingredients and their concentration on drug release were studied. It was observed that the type of polymer influences the drug release pattern. The *in vitro* drugrelease was observed that as the concentration of polymer is increased in formulations (F1 to F9) the time of drug release was decreased.

The *in-vitro* drug release profiles for the formulations (F1-F12) were tabulated in **Table.No**.21The plot of cumulative drug release (vs) time (hr) was plotted (F1-F3) and depicted as shown in Fig.37

Controlled release profiles were observed in the following order, Tamarind seed polysaccharide and HPMC K4M > Tamarind seed polysaccharide > HPMC K4M irrespective of the type of polymer.

The *in-vitro* dug release of F8 (TSP 15% & HPMC 15%) effervescent technique was the best formulation (F8) when compare with other formulations. The results as shown in Table**. No.21, Fig.No.**

Among all the formulations, F8 (Tamarind seed polysaccharide - 15 % & HPMC K4M - 15%) had the best formulation on the basis of *in vitro*drug release, floating lag time, total floating time and swelling index. It showed maximum drug release in a Controlled release manner (98.28% in 12hrs) because the formation of strong viscous gel layer that slowed down the rate of diffusion of medium into the tablet.

Table. No.21:*In vitro*Release data of Nizatidine floating tablets

Time (Hrs)	Percentage of cumulative release F1 – F9								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.28	17.4	18.99	19.12	16.94	18.21	16.42	15.22	14.96
2	27.52	20.24	17.91	25.12	21.42	23.15	24.63	19.98	21.93
3	28.64	29.54	26.87	33.92	29.54	33.12	32.84	23.16	30.24
4	35.97	37.95	35.83	46.23	31.54	37.45	41.05	37.93	42.65
5	42.63	49.42	40.79	55.12	38.54	42.15	49.27	48.69	55.12
6	56.29	60.23	53.74	59.22	46.15	55.72	56.15	52.13	62.82
7	62.94	68.57	62.70	67.42	52.19	61.21	65.69	58.92	67.31
8	68.26	75.42	71.66	79.12	58.49	66.15	73.90	64.52	73.75
9	77.64	82.24	80.62	83.52	78.21	70.43	82.29	71.57	78.24
10	94.12	88.5	89.57	96.99	80.23	78.12	94.11	85.94	82.92
11	94.12	93.12	91.53	96.99	85.29	87.65	94.11	90.41	90.87
12	94.12	96.21	95.21	96.99	96.21	95.92	94.11	98.28	95.25

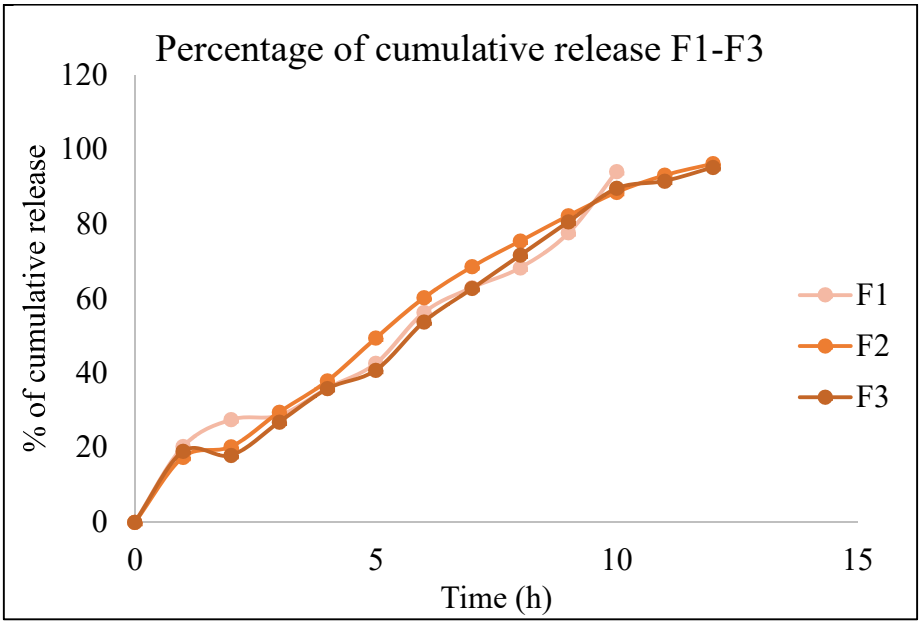


Fig.No.*37.In vitro*Release data of Nizatidine floating tablets F1 – F3

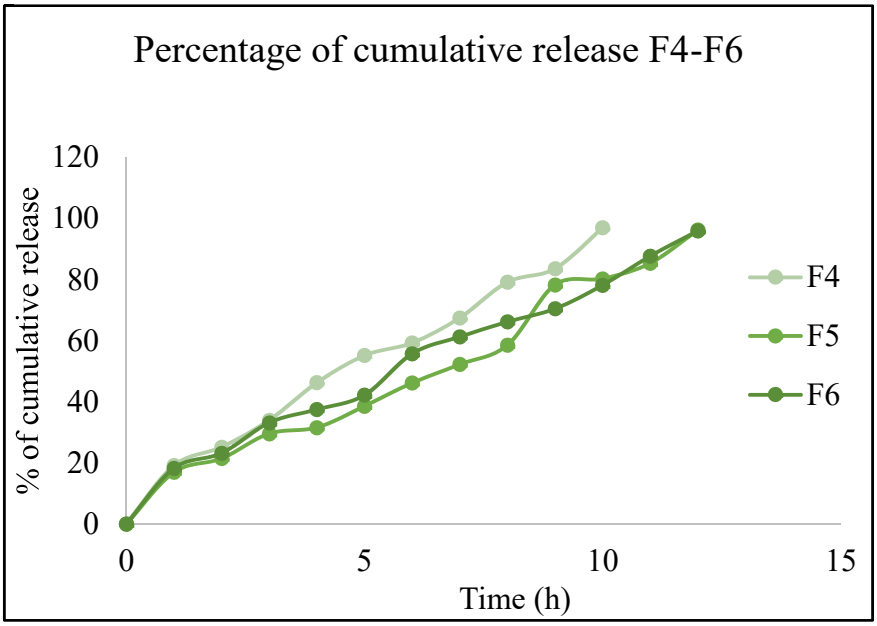


Fig.No.*38.In vitro*Release data of Nizatidine floating tablets F4 – F6

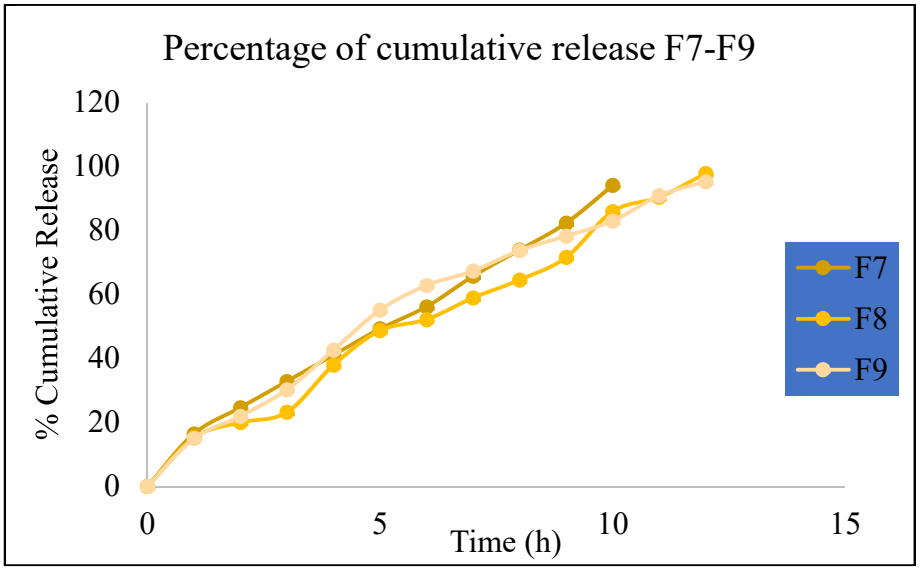


Fig.No.*39.In vitro*Release data of Nizatidine floating tablets F7 - F9

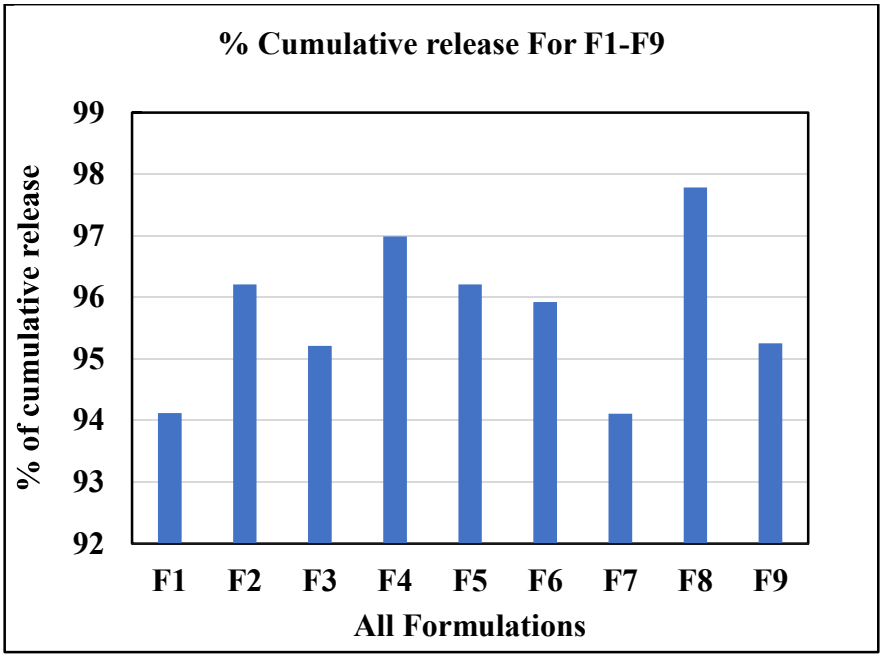


Fig.No.40.Comparatives*In vitro*Release data of Nizatidinefloating tablets F1 – F9

7. *IN VITRO* RELEASE KINETICSSTUDIES:

The*In vitro* release kineticsstudies were Studies done by using software "DD Solver". The release data (1-12hrs) wasanalyzed as per Zero order, First order, Higuchi's and Peppa's equation models to know the pattern of drug release and mechanism of drug release from the tablet.

Korsmeyer Peppa's model was found to be the best fitted in all dissolution profile having higher correlation coefficient (R2 value). The values of n (diffusion exponent) were estimated by linear regression of log cumulative % drug release Vs log time (t) of different formulations. The 'n' value could be used to characterize different release mechanisms as follows,

Table .No.22:Characterize different release mechanisms

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.5	Fickian release
2	0.5 to 1.00	Non-Fickian transport
3	1.00	Case II transport
4	> 1.00	Super case II transport

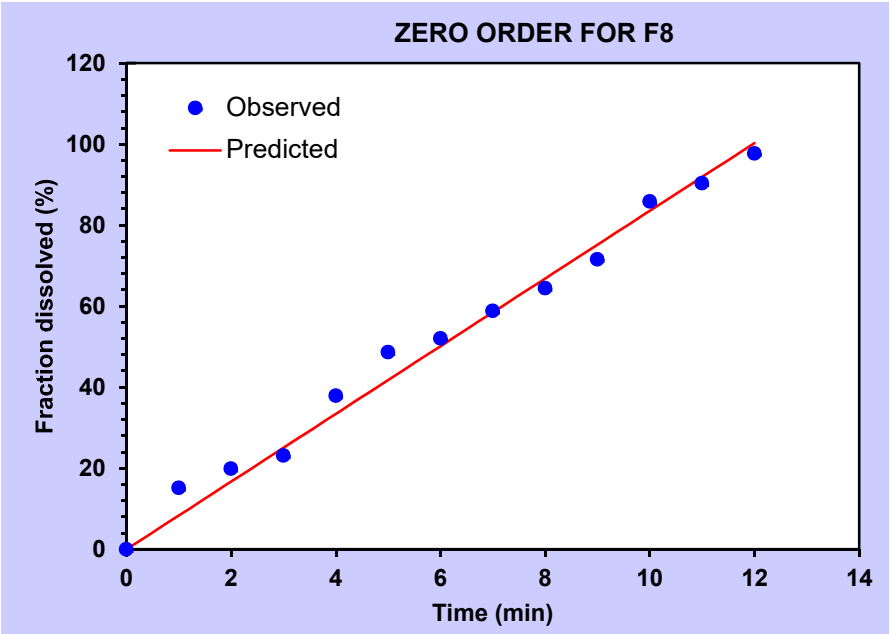
The 'n' value of Koresmeyer-Peppas model of all formulations was between 0.929 to 0.998. The R2 value of best formulation F8 was 0.998. Therefore, the most probable mechanism that the release patterns of all formulations followed was Non-fickian diffusion.

The drug release mechanism was controlled by both diffusion as well as polymer relaxation process. The rate of drug permeation out of the matrix was supposed to be proportional to the rate of solvent entry and broadening of the diffusion path length due to swelling of the matrix as a result of polymer hydration and subsequent strand relaxation.

The kinetic studies of all the formulations showed that the Zero order plots were fairly linear as indicated by their high regression values compared to Zero order plots. Therefore it was as certained that drug release from the all formulations followed Zero order kinetics (0.991 to 0.997). Formulation F4 showed the closest linearity to unity (r^2= 0.996). The regression co efficient value (r^2) and 'n' values of all batches (F1 to F9) were depicted in the release kinetics of data of all formulations were showed in **Table. No, Fig.No.**

Table. No.23.*In vitro*kinetic model for the floating tablet of Nizatidine (F1-F9)

Formulations	**Zero order**	**First order**	**Higuchi model**	**Korsmeryer - peppa's model**	
	r^2	**r^2**	**r^2**	**r^2**	**n**
F1	0.9881	0.9255	0.8894	0.9722	0.867
F2	0.9915	0.9517	0.9181	0.9913	0.806
F3	0.9929	0.9271	0.8862	0.9865	0.890
F4	0.9941	0.9570	0.9271	0.9931	0.799
F5	0.9911	0.9158	0.8709	0.9795	0.829
F6	0.9936	0.9564	0.9281	0.9913	0.783
F7	0.9971	0.9546	0.9131	0.9904	0.850
F8	0.9952	0.9357	0.8911	0.9950	0.890
F9	0.9865	0.9745	0.9402	0.9919	0.740



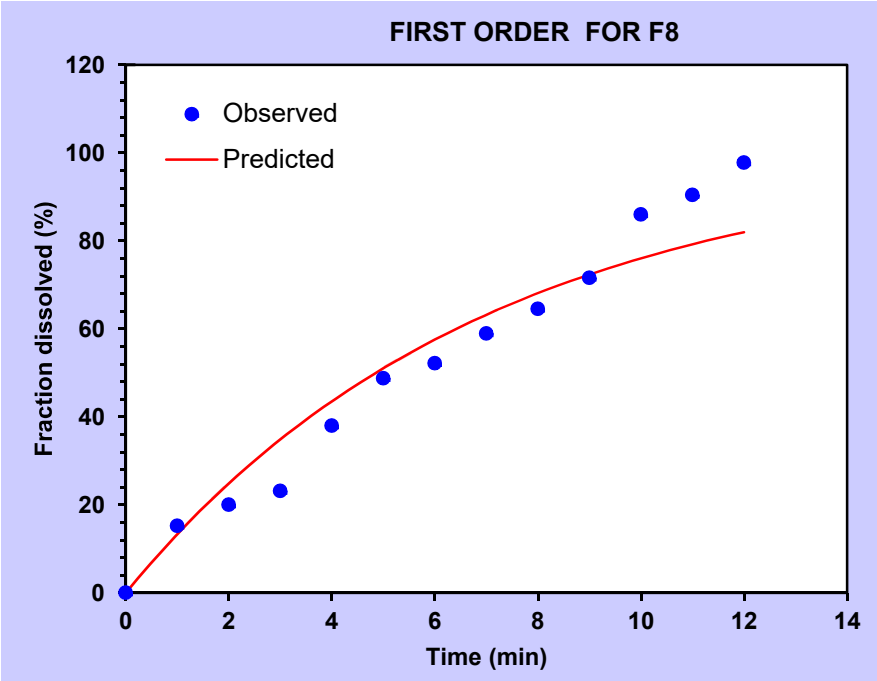
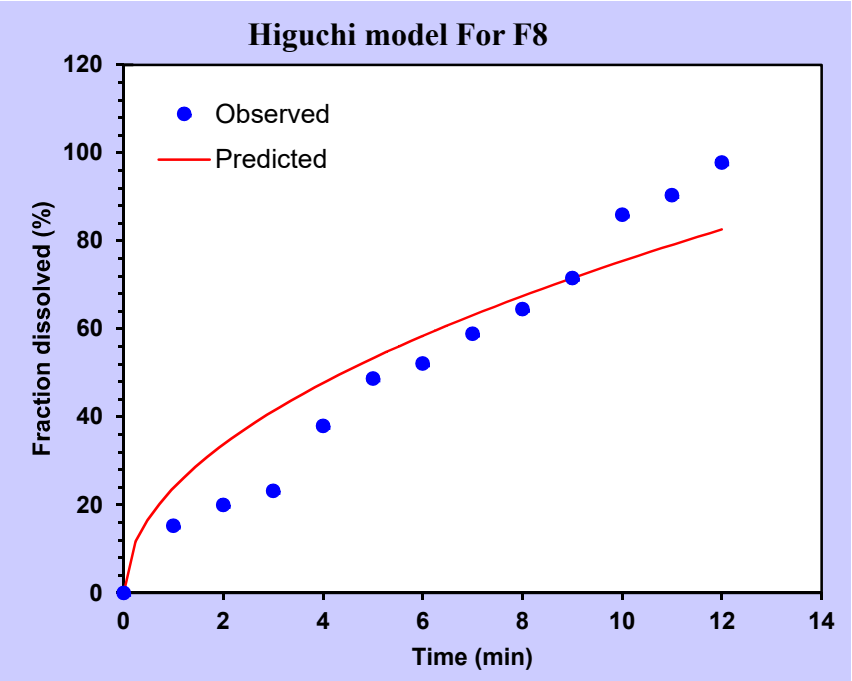


Fig 41.In the comparative kinetic model for the Formulation F8 is best fit to Zero order kinetics



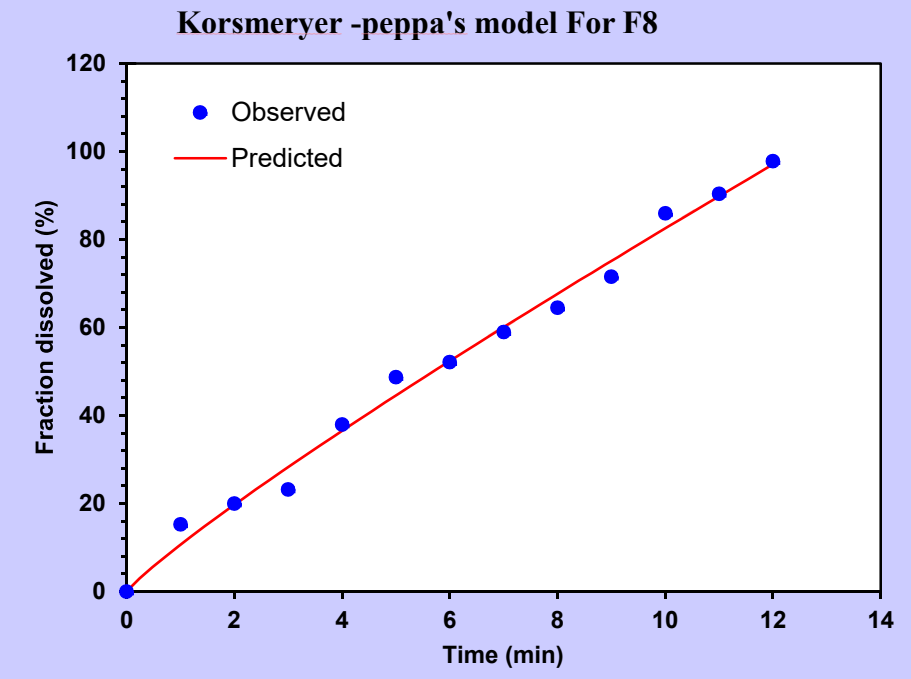


Fig. No. 42. In the comparative kinetic model for the Formulation F8 is best fit to Korsmeryer -peppa's model kinetics

Table. No.24.Comparative kinetic model for the Formulation F8 is best fit to Korsmeryer -peppa's model kinetics

Formulation code	Zero order	First order	Higuchi model	Korsmeryer -peppa's model	
	r2	r2	r2	r2	n
F8	0.9951	0.9747	0.8911	0.9909	0.8898

8. SELECTION OF BESTFORMULATION:

From the above results, F4 was selected the best formulation based on following character,

i. Floatinglag time : 50 seconds.

ii. Totalfloatingtime : up to 12hrs.

iii. Swellingindex : 65.57 % (8hrs).

iv. *In-vitro* releaseprofile : 98.28% (12hrs).

v. *In-vitro*releasekinetics : Zero order kinetics (r^2=0.996).

9. *IN-VIVO* X-RAY STUDIES :

***In vivo*X-ray for optimized formulation:**

- X-ray studies were conducted to find out the gastric retention of tablet.

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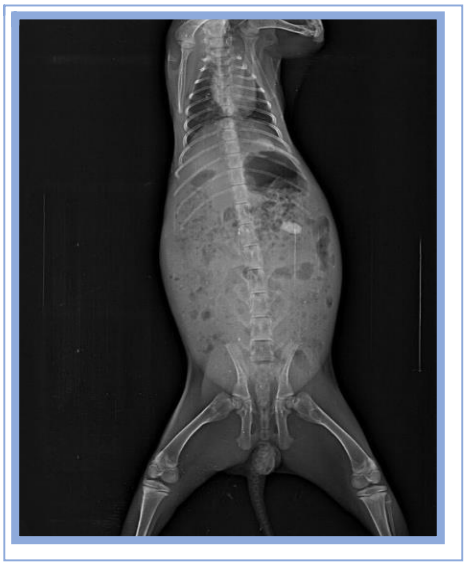
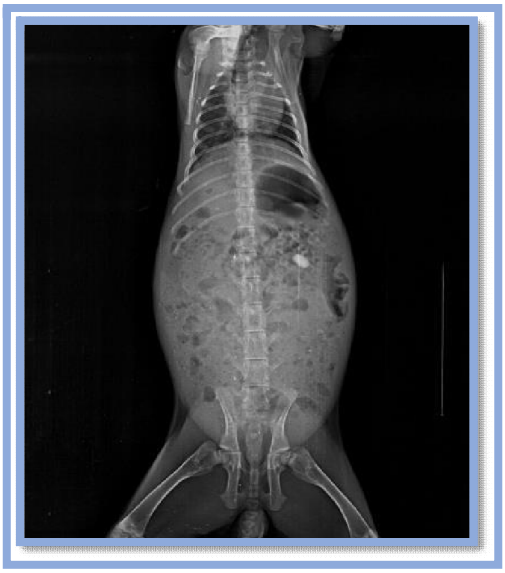
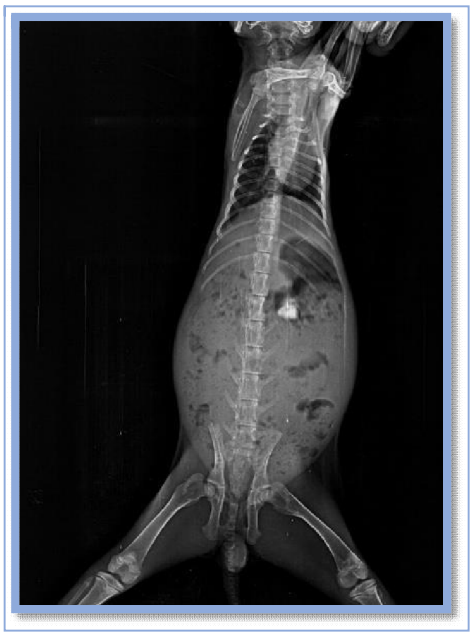
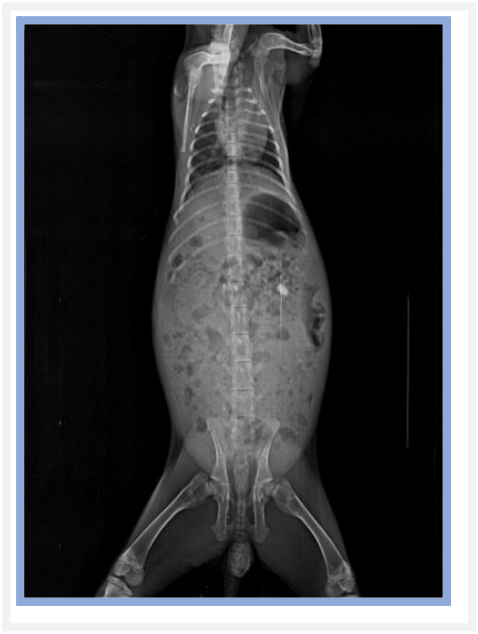
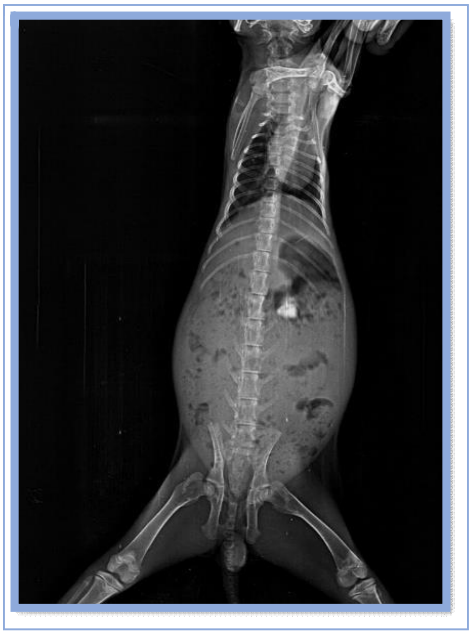
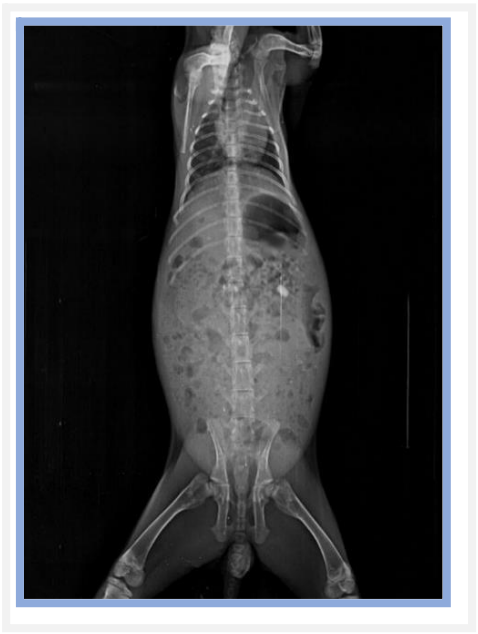
2nd hour 	**4th hour** 
8th hour	**9 th hour**







10 th hour



12 th hour

Fig.No.43.*In-Vivo* X-Ray Studies of Floating Tablet Of Nizatidine (Best FormulationF8)

10. EVALUATION OF ACCELERATED STABILITY STUDIES BEST FORMULATION (F8)

Stability studies were carried out by using selected formulation i.e. F8. The formulation is kept in accelerated stability condition atF temperature **40˚C/75%** relative humidity for a period of **2 months** as per International Conference on Harmonization guidelines.

The samples were withdrawn after **60 days** intervals and evaluation was carried out for appearance, thickness, hardness, buoyancy lag time, drug content and *In-vitro* release studies (60days)

Table.No. 25.Evaluation of nizatidine floating tablets for best formulation (F8)

Formulation Parameters	Initial	60days
Average weight (mg)	498.46	498.44
Thickness (mg)	4.39	4.38
Hardness (kg/cm2)	7.24	7.16
Diameter (mm)	11	11
Floating lag Time(sec)	14sec	15sec

Swelling Index (8 Hours) (%)	64.21	64.20

Table. No.26.*In vitro*% drug Release of Nizatidine (F8) after 2 months stability studies

S.No	Time (hrs)	Cumulative % Drug Released ± SD at 40±2ºC/75±5%RH	
		1st Day	60th Day
1	0	0	0
2	1	15.22 ±1.2	14.20 ±1.3
3	2	19.98 ±1.4	17.90 ±1.8
4	3	23.16±1.3	22.14±1.9
5	4	37.93 ±1.9	36.91±1.9
6	5	48.69 ±2.0	48.68±1.6

7	6	52.13 ±1.5	52.09 ±1.7
8	7	58.92 ±1.2	57.88 ±1.2
9	8	64.52 ±1.6	62.49 ±1.8
10	9	71.57 ±1.7	73.51 ±1.4
11	10	85.94 ±1.8	83.89 ±1.8
12	11	90.41 ±1.7	89.40 ±1.9
13	12	98.28 ±1.9	96.27 ±2.0

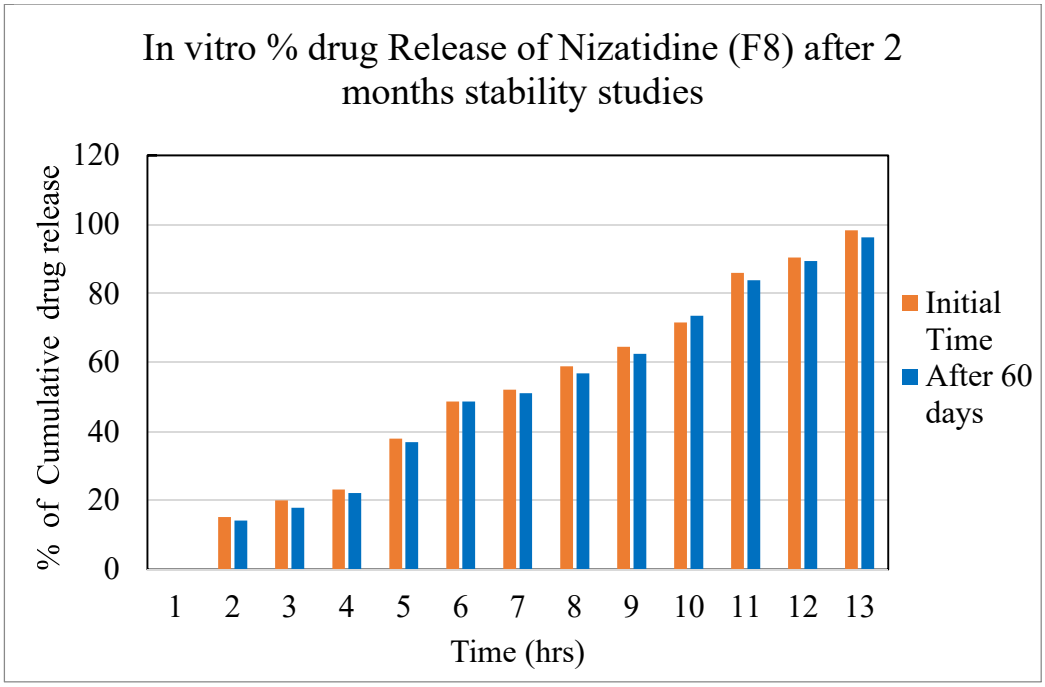


Fig. 44.*In vitro*% drug Release of Nizatidine (F8) after 2 months stability studies

1. Drug delivery through the numerous gastroretentive approaches has opened a new horizon for effective way of increasing patient compliance and increasing bioavailability of variety of drugs through oral rout. Many approaches with use of different polymers and other constituents can produce different range of gastroretentive systems. Especially the floating drug delivery system is the most widely used in gastroretentive dosage forms. However a lot of work is still needed to be done to overcome the different physiological and pharmaceutical barriers to develop the more effective gastroretentive dosage forms.
2. Nizatidine floating tablets were successfully prepared with hydrophilic polymers like HPMC K4M and Tamarind seed polysaccharide.
3. All formulations were evaluated for Compressibility Index, Angle of repose and Hausner ratio. The results indicated that the final blend had good flow and suited for direct compression technique.
4. From the pre-formulation studies for drug excipient compatibility it was observed that Nizatidine, doesn't show any physical or chemical incompatibility between the drug and other excipients.
5. All formulations were tested for post compression parameters like hardness, thickness, weight variation, friability and drug content. All estimated parameters were found to be within the limits. This indicated that all the prepared formulations were good
6. All formulations were tested for buoyancy properties like floating lag time & total floating time. Almost all the formulations showed satisfactory results.
7. All formulations were tested for *in vitro* drug release. The optimized formulations among HPMC K4M and Tamarind seed polysaccharide are F8. It contains combination of polymer with tamarind seed polysaccharide and HPMC K4M (1:1)ratio which exhibit least floating lag time in 50 sec and with maximum rate of drug release of 98.28% So, this formulation was considered to be the optimized formulation.
8. Comparitively kinetic model obtained for the floating tablet of nizatidine best formulation F8 and for other formulation are r^2 in Zero order kinetics and mechanism is fit to Kormeyer –Peppa's model.
9. The F8 formulation was chosen as the best formulation among all the other formulations. So stability studies are performed after one month also the formulation is stable.
10. Use of Tamarind seed polysaccharides enhanced the floating lag time, maintained the

Controlled release of drugs.

CONCLUSION

It can be concluded that the combination of tamarind seed polysaccharide and HPMC in ratio of (1:1) can be used to develop controlled release floating tablets of Nizatidine by incorporating sodium bicarbonate and citric acid for gas generation. However, clinical experiment on the human should be concluded with optimized formulation F8 in order to correlate *in vivo* performance with its *in vitro* behaviour.

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