

**FORMULATION AND EVALUATION OF NIZATIDING FLOATINCE
TABLETS**

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LIST OF ABBREVIATIONS

GIT	:-	Gastro Intestinal Tract
CR-GRDF	:-	Controlled Release Gastroretentive Dosage Form
NAW	:-	Narrow Absorption Window
GRT	:-	Gastric Residence Time
GRDF	:-	Gastro Retentive Dosage Form
CYP	:-	Cytochrome P
P-gp	:-	Pearmeability glycoprotein
CR	:-	Controlled Release
MMC	:-	Migrating Myloelectric Cycle
KSI	:-	kilo pounds per square inch
FDDS	:-	Floating Drug Delivery System
HPMC	:-	Hydroxy Propyl Methyl Cellulose
HEC	:-	Hydroxyl Ethyl Cellulose
Na CMC	:-	Sodium Carboxy Methyl Cellulose
HPC	:-	Hydroxyl Propyl 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)
MPas	:-	milli Pascal seconds
MCC	:-	Micro Crystalline Cellulose
UV	:-	Ultra-Violet

1. INTRODUCTION¹

Currently, in the field of pharmaceutical technology, great efforts are being directed towards the refabrication of existing drug molecules in a fashion, capable of solving problems related to poor water solubility, poor bioavailability, dosing problem, stability, toxicity, etc. This trend of working has led to development of new drug delivery system.

Basic goal of drug therapy is to provide therapeutic amount of drug to proper site in the body to promptly achieve and then maintain desired drug concentration. This idealized objective points to two aspects most important to the drug delivery, namely, spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ or tissue while temporal delivery refers to controlling rate of drug delivery to that specific organ or tissue.

Despite tremendous advancement in drug delivery, oral route remains preferred route for administration. Even today, conventional drug delivery systems are primary pharmaceutical products commonly seen in prescriptions and 'over the counter' market place. They provide prompt release of the drug but in order to achieve as well as maintain drug concentration within therapeutically achieved range, it is often necessary to administer it several times a day. This results in significant fluctuations of drug concentration in systemic circulation causing either lethal effect or no therapeutic action.

Oral controlled release dosage forms have been developed over past three decades. These drug delivery systems have a great potential of solving problems associated with conventional multiple dosing system like strict adherence to timely dosing, plasma concentration fluctuations, associated side effects due to systemic accumulation of drug. Thus, there are numerous advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience, reduction in health care cost, etc.

However, this approach is facing problems with several physiological difficulties such as inability to restrain and locate controlled drug delivery system within the desired region of GIT, due to variable gastric emptying and motility. Furthermore, the relative brief gastric emptying time in humans which normally averages 2-3 hours through major absorption zone i.e., stomach and upper part of intestine can result in incomplete drug release from drug delivery system leading to low bioavailability and thus reduced efficacy of administered dose.

It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in GIT is to control gastric residence time.

Control of placement of drug delivery system in specific region of GIT offers advantage for variety of important drugs characterized by narrow absorption window in GIT or drugs with stability problem. These considerations have led to development of unique oral controlled release dosage form with gastro retentive properties i.e., dosage form could be retained in the stomach for several hours and release the drug there in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption site in the upper GIT.

1.1. GASTRORETENTIVE DRUG DELIVERY SYSTEM

Gastroretentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastroretentive systems retain in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or drugs which are unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach. Prolonged gastric retention of the drugs may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of dosage size.

Suitable drugs for gastro retentive drug delivery systems²

- ❖ Narrow absorption window in GI tract
e.g., riboflavin, levodopa, para-aminobenzoic acid, furosemide.
- ❖ Primarily absorbed from stomach and upper part of GI tract
e.g., calcium supplements, chlorthalidone and cinnarizine.
- ❖ Drugs that act locally in the stomach
e.g., antacids and misoprostol.
- ❖ Drugs that degrade in the colon
e.g., ranitidine HCl and captopril.

❖ Drugs that disturb normal colonic bacteria
e.g., antibiotics against *Helicobacter pylori* (amoxicillin trihydrate).

Incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors.

1.2 PHARMACOKINETIC ASPECTS³

1.2.1. Absorption window

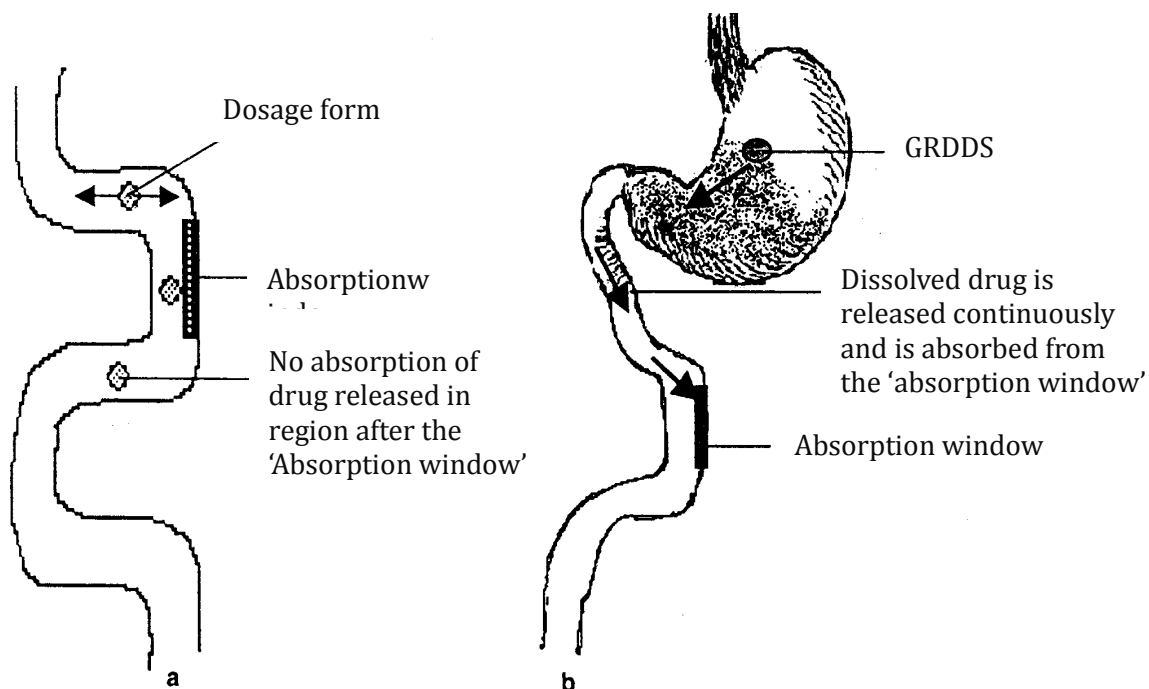


Figure 1.1: Drug absorption in the case of (a) conventional dosage forms and (b) gastroretentive drug delivery systems

Some of the drugs are characterized by a narrow absorption window (NAW) at the upper part of the GIT. This is because the proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time (GRT) of a NAW drug may significantly improve the net extent of its absorption.

1.2.2. Enhanced bioavailability

Once it has been ascertained that the compound in question is defined as NAW, there is a possibility for improving oral bioavailability by continuous administration of the compound to the specific site. The bioavailability of riboflavin and levodopa CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations.

1.2.3. Enhanced first pass biotransformation

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

1.2.4. Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, CR-GRDF may elevate absorption compared to the immediate and CR dosage forms.

1.2.5. Reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

1.2.6. Targeted therapy for local ailments in the upper GI tract

The prolonged and sustained administration of the drug from the GRDF to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

1.3. PHARMACODYNAMIC ASPECTS

1.3.1. Reduced fluctuations of drug concentration

Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

1.3.2. Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

1.3.3. Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

1.3.4. Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as β -lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

1.3.5. Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for β -lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to development of microorganism's resistance.

Table 1.1: List of drugs formulated as single and multiple unit forms of GRDDS ⁴

S.NO	Dosage form	Drugs
1	Microspheres	Metformin hydrochloride, Ketoprofen, Aspirin, Verapamil, Griseofulvin, p-nitroaniline, Ibuprofen, Terfenadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Prednisolone.
3	Films	Cinnarizine
4	Capsules	ChlordiazepoxideHCl, Diazepam, Furosemide, L-Dopa and Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine.
5	Tablets/Pills	Phenytoin, 5-fluorouracil, Furosemide, Ciprofloxacin, pentoxyfillin, Atenolol, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnarizine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, p-amino benzoic acid, Piretanide, Prednisolone, Quinidine gluconate.

Table 1.2: Marketed Products of GRDDS

Brand name	Delivery system	Drug (dose)	Company name
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
Topalkan [®]	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Convicon [®]	Colloidal gel forming FDOS	Ferrous sulphate	Ranbaxy, India
Cytotech [®]	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA

1.4. PHYSIOLOGICAL CONSIDERATIONS

It is recognized that there are many physiological constraints, which may limit development of such delivery systems. Factors such as pH, enzymes, nature and volume of secretions, residence time and effective absorbing surface area of the site of delivery play an important role in drug liberation and absorption. Nevertheless, *in vivo* studies of certain systems have shown promising results.

1.4.1. Stomach physiology

The stomach is divided into 3 anatomic regions: fundus, body, and antrum (pylorus). The part made of fundus and body act 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, due to its size, plays a major role in gastric residence time of GRDF.

The stomach volume is about 1.5 L after a meal and in range of 250 - 500 mL in interdigestive phases, it produces 2 L among the 8 L of all liquid present in gastro intestinal tract.

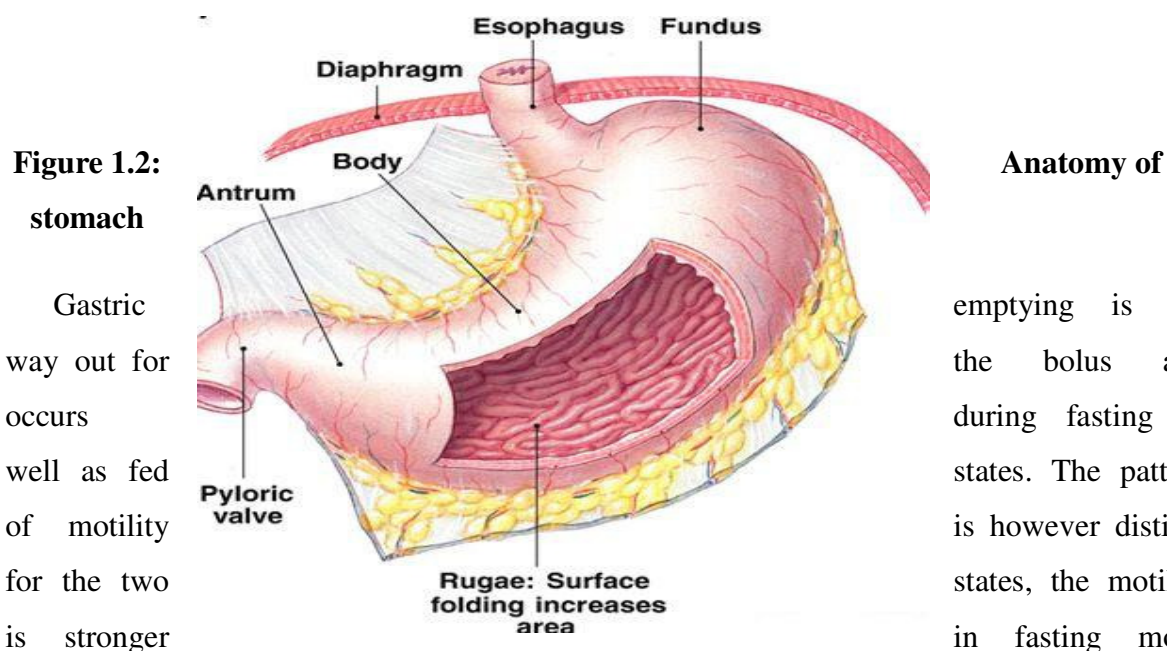


Figure 1.2:
stomach

Gastric
way out for
occurs
well as fed
of motility
for the two
is stronger

Anatomy of

emptying is the
the bolus and
during fasting as
states. The pattern
is however distinct
states, the motility
in fasting mode

than in fed mode. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 h. This is called the interdigestivemyoelectric cycle or migrating myoelectric cycle (MMC). which is further divided into following 4 phases.

- Phase I (basal phase) lasts from 30 to 60 min with rare contractions.

- Phase II (preburst phase) lasts from 20 to 40 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 10 to 20 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV lasts for 0 to 5 min is a transition period of decreasing activity until the next cycle begins.

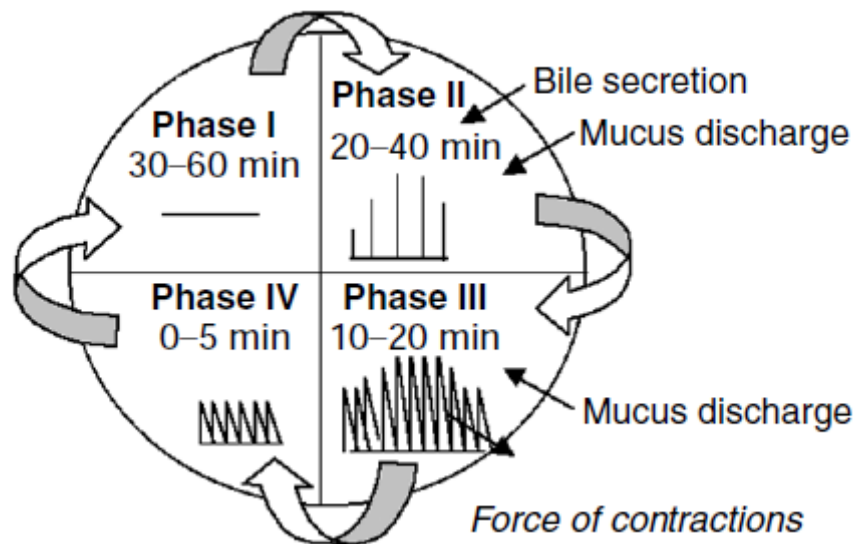


Figure 1.3: Schematic representation of interdigestive motility pattern

Table 1.3: 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

1.4.2. Gastric pH

The gastric pH is not constant rather it is influenced by various factors such as diet, disease, presence of gases, fatty acids and other fermentation products, however, the reported mean value of gastric pH in fasted healthy subjects is 1.1 ± 0.5 and in fed state basal gastric secretion in women is slightly lower than that of men (Mojooverian and Chan, 1988). The pH in the proximal duodenum may rise as high as 4 pH units from the stomach. This increase in pH is caused by the bicarbonate secreted by the pancreas and the duodenal mucosa that neutralize acidic chyme peristalsis from the stomach. The mean pH value in fasted duodenum has been reported to be 5.8 ± 0.3 in healthy subjects while the fasted small intestine has been observed to have a mean pH of 6.0 ± 0.14 . Passing from jejunum through the mid small intestine and ileum, pH rises from about 6.6 to 7.5.

1.5. FACTORS AFFECTING THE GRDDS⁵

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system.

- **Density** – Gastric retention time (GRT) is a function of dosage form buoyancy, which is dependent on the density.
- **Size** – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Shape of dosage form** – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content** – GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Biological factors** – Diabetes and Crohn's disease, etc.
- **Concomitant drug administration** – Anti-cholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.

1.6. ADVANTAGES OF GRDDS

Gastro retentive drug delivery systems have numerous advantages listed below.

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the

gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows:

1. Enhanced bioavailability
2. Sustained Drug Delivery / reduced frequency of dosing
3. Site-Specific Drug Delivery
4. Reduced fluctuations of drug concentration
5. Minimized adverse activity at the colon
6. Absorption Enhancement

1.7. DISADVANTAGES OF GRDDS

Gastro retentive drug delivery systems have some disadvantages listed below:

1. There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems.
3. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.
4. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately.
5. Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed.
6. High variability in gastric emptying time due to variations in emptying process.

1.8. LIMITATIONS

Gastro retentive drug delivery systems have some limitations listed below:

1. The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However, this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach
2. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
3. The dosage form should be administered with a minimum of glass full of water (200-250 mL).
4. The drugs, which are absorbed throughout gastro-intestinal tract, which under go first-pass metabolism (e.g., nifedipine, propranolol etc.) are not desirable candidates.
5. Some drugs present in the floating system causes irritation to gastric mucosa.

1.9. APPROACHES TO GASTRIC RETENTION⁶

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include:

- Floating Drug Delivery System (FDDS), with low density providing sufficient buoyancy to float over the gastric contents.
- Bioadhesive systems, enabling the localized retention of the system in the stomach.
- Swelling and expanding systems, preventing transit from the gastric sphincter.
- High density system, remaining in the stomach for longer period of time by sedimenting to the folds of stomach.
- Superporous hydrogels.

- Modified-shaped system.

A number of other methods like use of passage-delaying agents, magnetically controlled systems and combination methods like floating-bioadhesive systems were also tried.

1.9.1. 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.

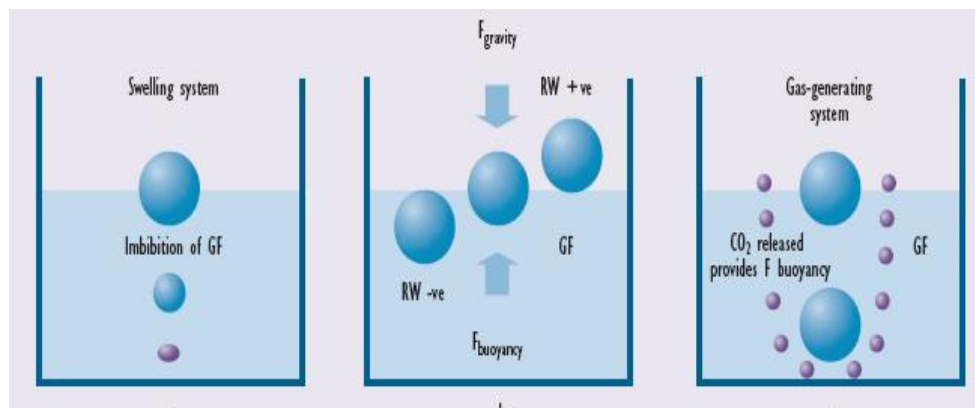


Figure 1.4: Mechanism of floating system

Formulation of this device must comply with the following criteria:

- It must have sufficient structure to form a cohesive gel barrier.
- It must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010).
- It should dissolve slowly enough to serve as a drug reservoir.

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.

- 1) Non- Effervescent FDDS
- 2) Effervescent FDDS

1.9.1.1. Non-Effervescent FDDS

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrixforming 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 . The air entrapped within the swollen matrix imparts buoyancy to the dosage form. Thus formed swollen gel-like structure, acts as a reservoir and allows sustained release of drug through the gelatinous mass.

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, although hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), sodium carboxy methyl cellulose (NaCMC), agar, carrageenans or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatine capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. 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 1.5).

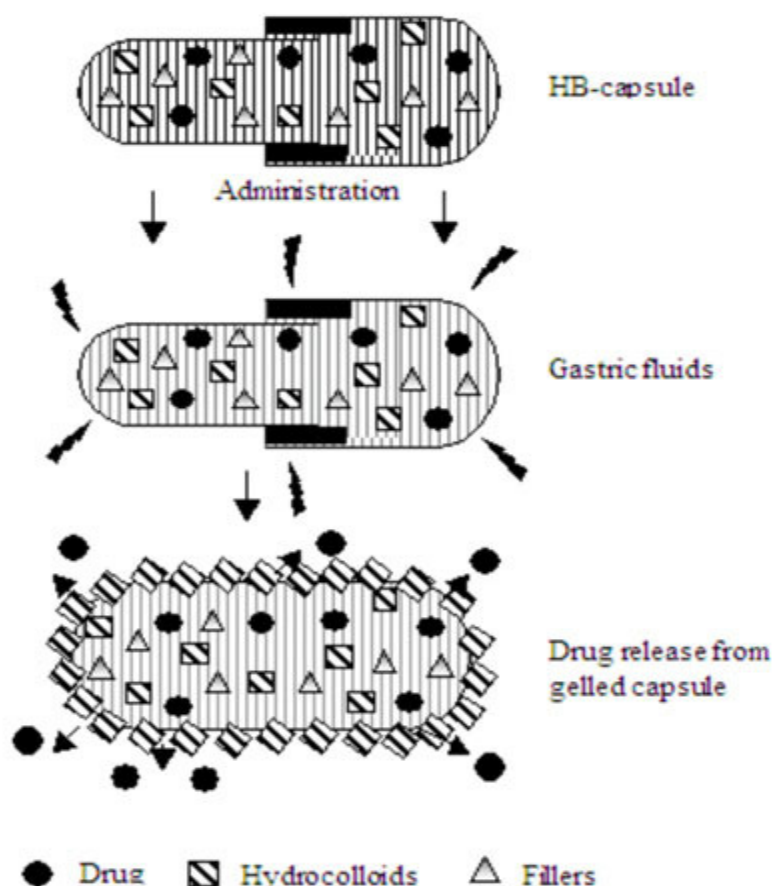


Figure 1.5: Working Principle of Non-Effervescent type (HBS-Hydrodynamically balanced system) of FDDS

1.9.1.2. Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it to float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produces gas due to evaporation at body temperature.

These effervescent systems further are classified into two types:

- A. Gas generating systems
- B. Volatile Liquid/Vacuum Containing Systems

A. Gas Generating Systems

These are matrix type of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO₂ is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms.

In single unit systems, such as capsules or tablets, effervescent substances are incorporated in the hydrophilic polymer, and CO₂ bubbles are trapped in the swollen matrix (Figure 1.6 a). *In vitro*, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 hours. *In vivo* experiments in fasted dogs showed a mean gastric residence time increased up to 4 hours. Bilayer or multilayer systems have also been design. Drug and excipients are formulated independently and the gas generating unit can be incorporated into any of the layers (Figure 1.6 b). Further refinements involve coating the matrix with a polymer which is permeable to water, but not to CO₂ ((Figure 1.6 c). The main difficulty of such formulation is to find a good compromise between elasticity, plasticity and permeability of the polymer.

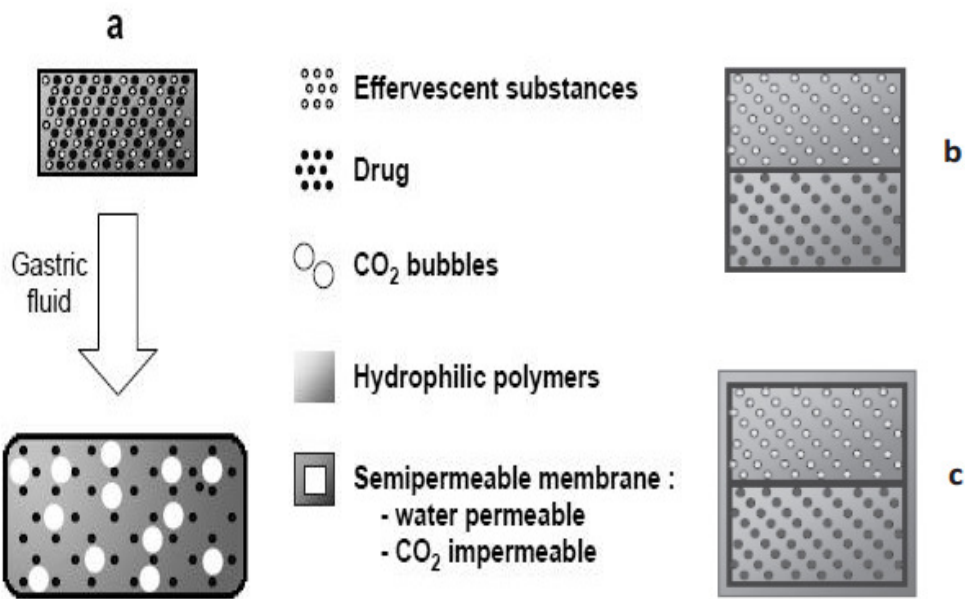


Figure 1.6: Gas-generating systems. Schematic monolayer drug delivery system (a) and Bilayer gas-generating systems, with (c) or without (b) semipermeable membrane

Multiple unit systems avoid the “all or nothing” emptying process. However, it is essential that the units remain dispersed and suspended individually in the gastric fluid and not agglomerate into a mass floating at the top of the stomach a double layered coated system

in the form of granules (Figure 1.7). It comprised an inner effervescent layer (bicarbonate and tartaric acid) and an outer swellable membrane (polyvinyl acetate and shellac). The system floated completely within 10 min and 80% remained floating over a period of 5 hours. *In vivo* studies have been carried out in beagle dogs and humans in the fed state using granules loaded with barium sulphate as a radio opaque marker. Most floated in the stomach within 10 min and remained so for at least 3 hours as observed by X-ray photography.

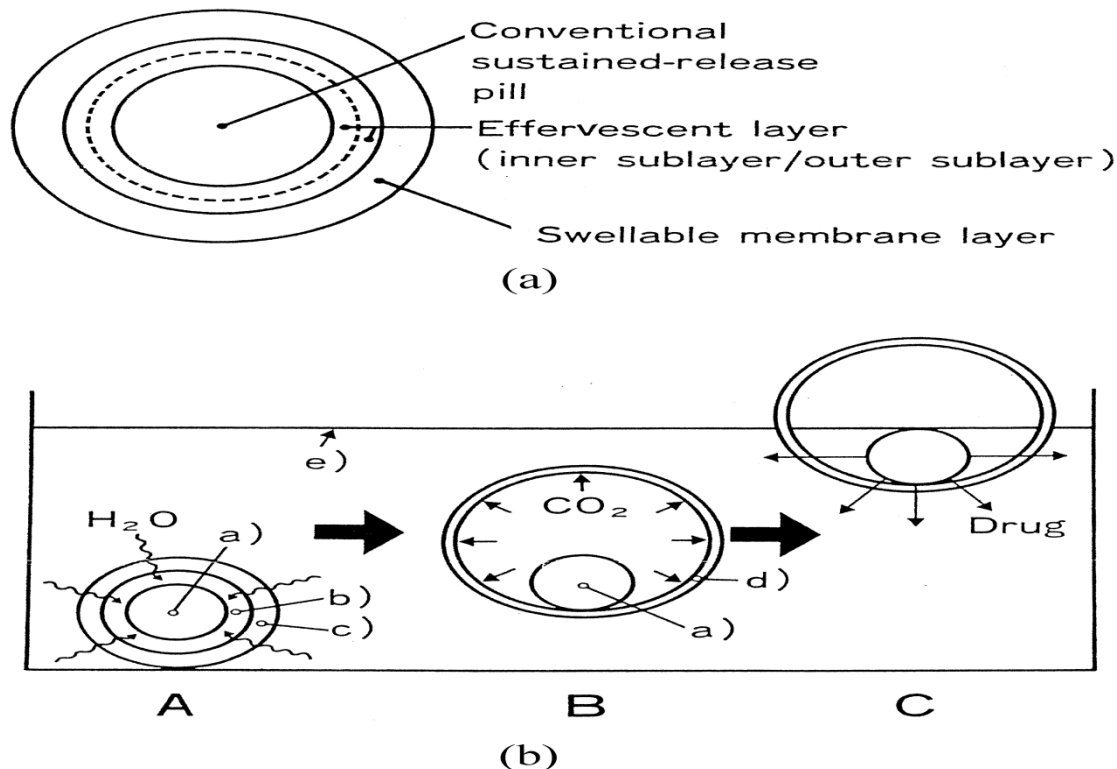


Figure 1.7: Schematic representation of “floating pill” (a),The penetration of water into effervescent layer leads to a CO₂ generation and makes the system to float (b).

A) Penetration of water into the device; B) generation of carbon dioxide and floating; and C) dissolution of the drug. Key: a) Conventional sustained release core; b) effervescent layer; c) swellable layer; d) expanded swellable membrane layer; e) water (37°C) surface in the beaker.

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO₂. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place, that resulted in CO₂ generation, thereby carrying beads towards the top of gastric contents and producing a floating layer of resin beads. The *in vivo* behavior of the coated and uncoated

beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).

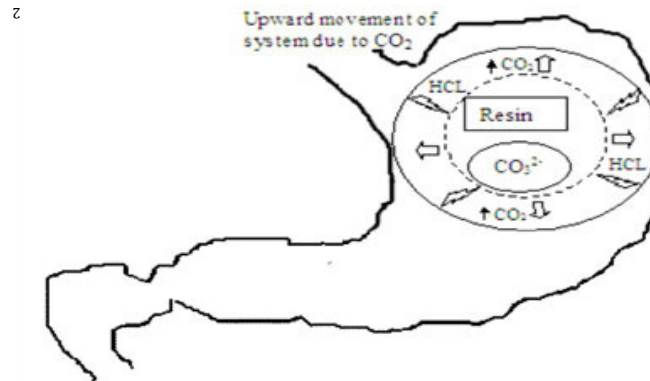


Figure 1.8: Pictorial presentation of working of effervescent floating drug delivery system based on ion exchange resin

B. 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 (Figure 1.9).

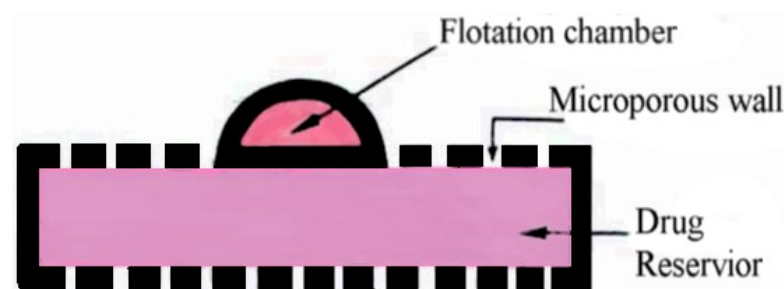


Figure 1.9: Intra gastric floating gastrointestinal drug delivery device

ii. Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug impregnated polymeric matrix, encapsulated in a gelatin capsule. After oral

administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is continuously released from the reservoir into the gastric fluid (Figure 1.10).

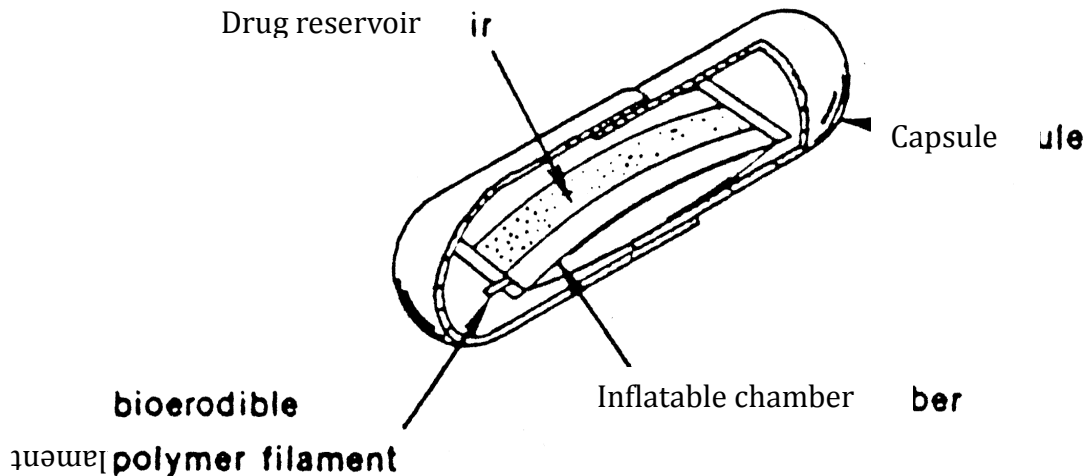


Figure 1.10: Inflatable gastrointestinal delivery system

iii. Intra-gastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. 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 vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. 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.

The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

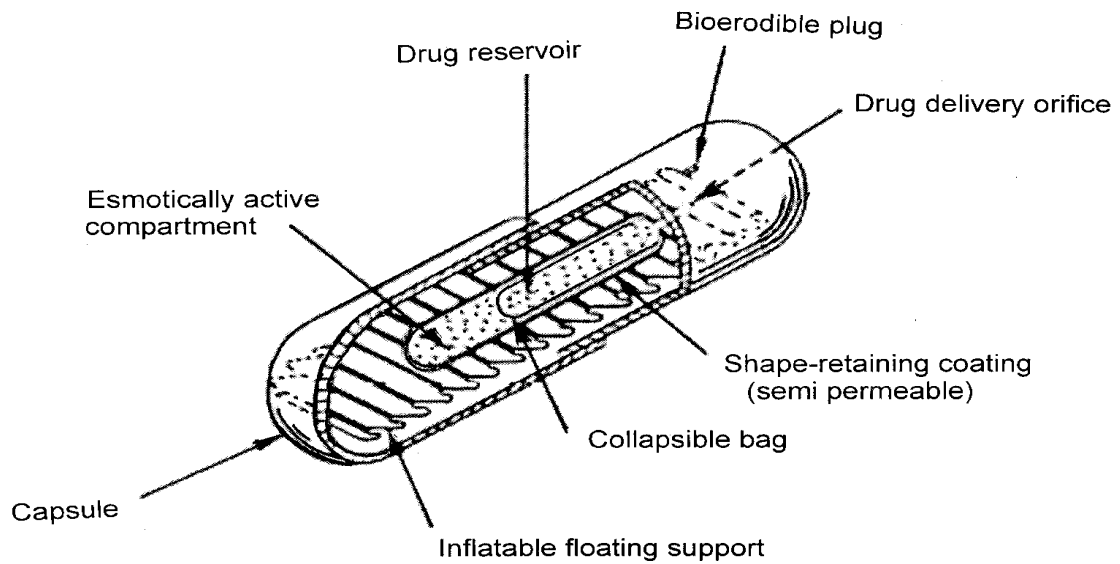


Figure 1.11:Intragastric osmotically controlled drug delivery system.

1.9.2. Bio adhesive systems⁷

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach . Thus, they improve the prolongation of gastric retention.



Figure 1.12: Schematic illustration mucoadhesive systems

1.9.3. Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles on contact with gastric fluid (Figure 1.13). Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon (GlaxoSmithkline).



Figure 1.13: Schematic illustration of the barrier formed by a raft-forming system

1.9.4. High density systems

Gastric contents have a density close to water (1.004 g /cm³). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm³ seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

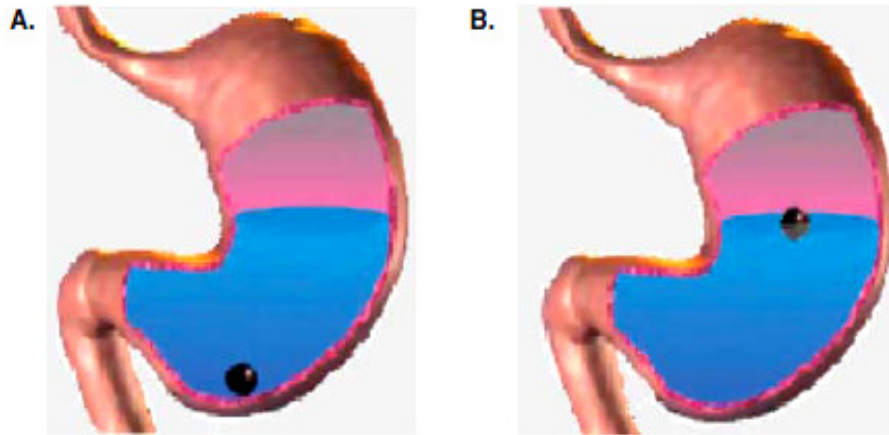


Figure 1.14: Illustration representing (A): the systems based on high density, (B): the systems based on low density

1.9.5. Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems ($<1 \text{ g/cm}^3$) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called “microballoons” because of the low-density core. Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.

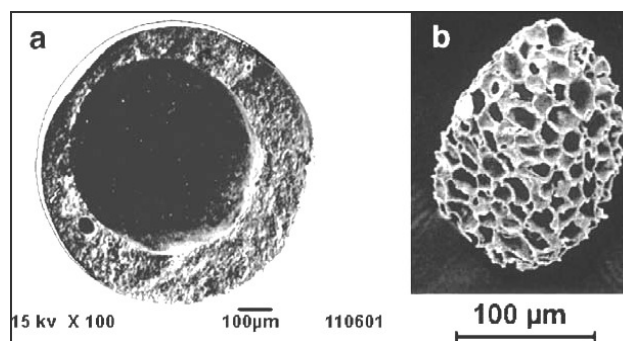


Figure 1.15: (a) Microballoons and (b) Foam-particles

1.9.6. Expandable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastro retentive form and a final small form enabling evacuation following drug release.

Expandable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. different geometric forms (tetrahedron, ring or planar membrane, 4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule (Figure 1.16).

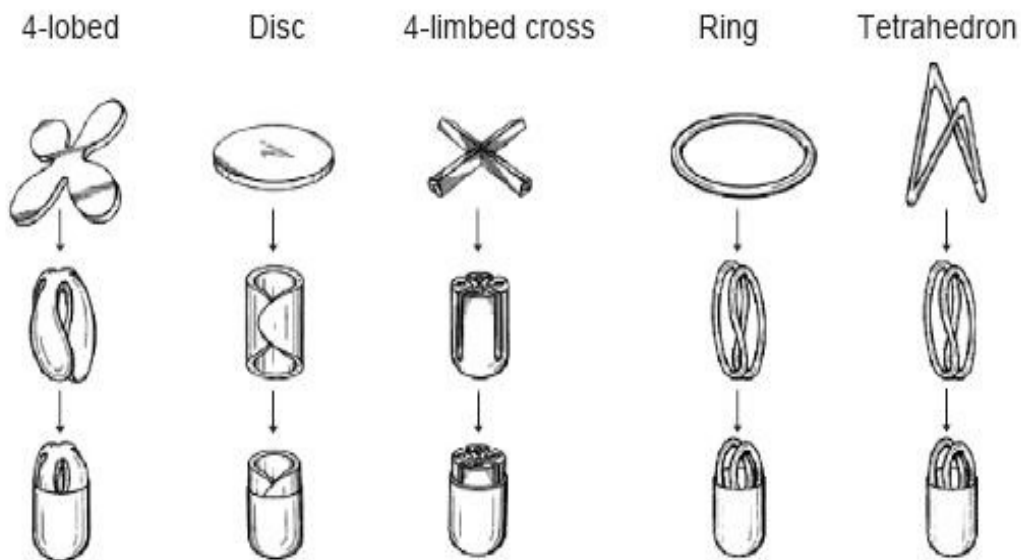


Figure 1.16: Different geometric forms of expandable systems

1.9.7. Swellable System

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a 'fed' state, suppressing housekeeper waves.

Mamajek and Moyer patented drug reservoirs, surrounded by a swellable expanding agent. Urquhart and Theeuwes developed a system containing tiny pills, with a very high

swelling ratio enabling up to 50 fold volume increase. They were coated by wax to control drug release and dispersed in a matrix of polymeric hydrogel (Figure 1.17).

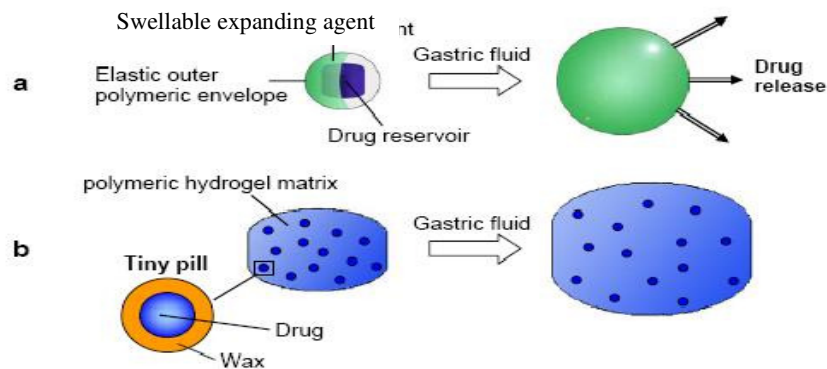


Figure 1.17: Swellable systems, developed by (a) Mamajek and Moyer, and (b) Urquhart and Theeuwes

1.9.8. Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10 nm and 10 μm . Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogel, average pore size $> 100 \mu\text{m}$, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size (swelling ratio 100 or more) (Figure 1.18) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co- formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium).

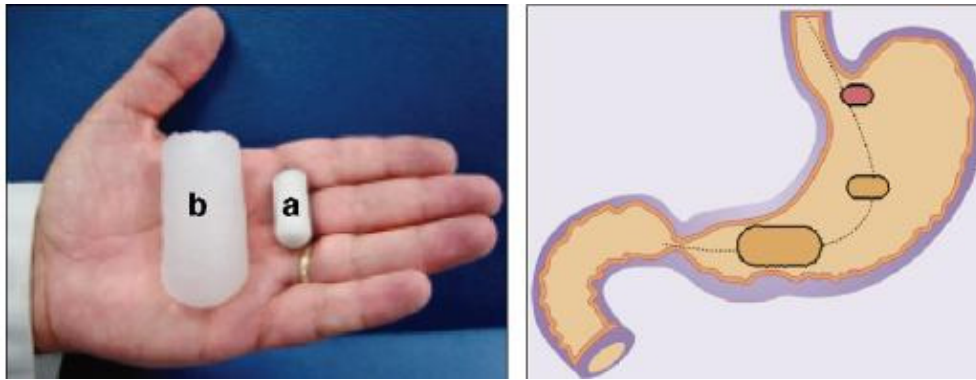


Figure 1.18: On

the left, (a) superporous hydrogel in its dry and (b) water-swollen state. On the right, schematic illustration of the transit of superporous hydrogels

1.9.9. Magnetic system

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

LITERATURE REVIEW

Muralidhar Mama et al⁸ 2008: Developed hydrodynamically balanced delivery system of Clarithromycin (CLA) which, after oral administration should have the ability to prolong gastric residence time with the desired in vitro release profile for the localized action in the stomach, in the treatment of Helicobacter pylori (H.pylori) mediated peptic ulcer. By applying wet granulation technique floating tablets of Clarithromycin were prepared. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. In vivo radiographic studies were performed with Barium sulphate loaded formulation to justify the increased gastric residence time of the dosage form in the stomach, based on the floating principle. The formulation developed using 66.2% Clarithromycin, 12% HPMC K4 polymer, 8% sodium bicarbonate gave floating lag time less than 3 min with a floating time of 12 h, and an in vitro release profile very near to the desired release. X-ray studies showed the enhanced gastric residence time of the tablet to 220±30 min.

Patil UK et al⁹ 2008: Developed Amlodipine besylate effervescent floating tablets in ten different formulations (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameter buoyancy studies, dissolution parameters and drug release mechanisms. F10 formulation showed maximum floating time of 24 hours and gave slow and maximum drug release of Amlodipine besylate spread over 24 hours and whereas Amlodipine besylate released from marketed tablet was rapid and maximum within 12 hours.

Mohamad Abdul Kalam Azad et al¹⁰ 2009 described the preparation and in vitro evaluation of gastro retentive floating tablet of theophylline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of theophylline on drug release profile and floating properties were investigated. Tablets were prepared by direct compression technique. Formulations were evaluated for in vitro buoyancy and drug release study was evaluated for eight hours using USP XXII paddle-type dissolution apparatus using 0.1HCl as dissolution medium. The release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be governed by polymer and floating agent content. The content of active ingredient was also a vital factor in controlling drug release pattern. It was found that polymer content and amount of floating agent significantly affected the mean.

Atul C. Badhan et al¹¹ 2009: Designed and optimized of sustained release gastro retentive matrices of amoxicillin by using central composite design. Effect of amount of xanthan gum, rate controlling polymers (HPMC K100M CR/PEO coagulant (1:1)), carbopol 974P, and gas generating couple (sodium bicarbonate/citric acid (3:1)) was studied on dependent (response) variables, i.e., buoyancy lag time, drug release at 1 h, time required for 95% drug

release, swelling index, and strength. Minimatrices were prepared by non aqueous granulation method using solution of PVP K30 in isopropyl alcohol. All the formulations were found to contain 99.2% to 100.9% of amoxicillin per minimatrix. Optimum formulation (Formulation number AGT09) containing high level of independent variables was having buoyancy lag time of 7 min and drug release at 1 h was 32.5%. It required 9.39 h for 95% drug release while swelling index and bio adhesive strength were 341 and 17.9 dyn/cm², respectively. This formulation was said to be optimum because it has minimum buoyancy lag time, requires maximum time for 95% drug release, and has high bioadhesive capabilities. In vitro results of an optimized formulation indicate its sustained drug release and gastric retention capability, which may be very useful for effective treatment of H. pylori infection.

Sharad Shinde et al¹² 2010: Developed the floating matrix tablets Salbutamol Sulphate. Tablets were prepared by wet granulation method and were characterized using the official method. Hydroxypropyl methylcellulose was used as a release retardant material. Sodium bicarbonate and Citric acid was incorporated as a gas-generating agent. The effects of citric acid on drug release profile, floating properties and matrix integrity of tablet were investigated. Addition of Citric acid caused the enhancement in drug release and disintegration of tablet that was retarded by incorporation of stearic acid in the formulation. Addition of high level of HPMC K100M didn't significantly retard the burst effect and tablet disintegration produced by citric acid but addition of stearic acid was necessary to retard the same. Formulations were evaluated for in vitro drug release profile, swelling characteristics. The similarity factor, dissolution kinetics, and *t*₅₀ were used as parameters for selection of the best batch.

ChandraShekar B et al¹³ 2010: Designed and developed a gastro retentive drug delivery system of Ketoconazole by direct compression technology. HPMC K100LV, HPMC K15M, Ethyl Cellulose and effervescent sodium bicarbonate formed the floating tablet. The prepared tablets exhibited satisfactory physico-chemical characteristics. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radically and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 20-24 h. Final formulation released approximately 89.21% drug in 24 h *in vitro*, while the floating lag time was not more than 35 Sec and the tablet remained floatable throughout all studies. The tablets with HPMCK15M were found to float for longer duration as compared with formulations containing HPMCK 4 M. The release Ketoconazole was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The optimized formulation was found to be buoyant for 24 h in stomach. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

P. N. Kendre, R.K.Godge et al¹⁴ 2010: Developed and characterized a single unit controlled delivery system of Theophylline and was formulated as floating matrix tablet by direct compression method using gas generating agent (sodium bicarbonate) and various viscosity grades of hydrophilic polymers (HPMCK15M, K4M; HPC and Carbapol 934P).

Formulation was optimized on the basis of buoyancy and in vitro drug release profile. Also tablets were tested for various tests like hardness, thickness, weight variation, friability, Swelling index and erosion index. The tablets swelled and eroded upon contact with release medium (0.1 N HCl) at 37 °C. The release rate could efficiently be modified by varying the matrix forming polymer, the use of polymer blends and the addition of water soluble or water insoluble fillers (such as dicalcium phosphate, lactose or mannitol). Fitting the in-vitro drug release data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

N. B. Santha sheela et al¹⁵2010: Formulated floating sustained release tablets of Clarithromycin, by using a combination of hydrophilic polymers (different grades of hydroxypropyl methylcellulose), Kollidon SR and an effervescent substance (sodium bicarbonate). The formulations were evaluated to study the effect of sodium bicarbonate concentration on the floating lag time, total duration of floating, in vitro dissolution release profile and the effect of different fillers and ethyl cellulose concentration on the release profile of drug. It was found that among all the formulations, formulation F4 (HPMC K15M, Avicel 102 pH and sodium bicarbonate) was found to be the optimum formulation as it had good swelling property, floating time and drug release. The drug release of optimized formulation was found to follow Zero order, Higuchi and Korsmeyer-Peppas kinetic models.

R. Margret chandir et al¹⁶ 2010:

Designed and developed of hydro dynamically balanced tablet of cefuroxime axetil to enhance the bioavailability and therapeutic efficacy of the drug. Cefuroxime axetil is classified as a second-generation cephalosporin antibiotic and beta lactum antibiotics based on spectrum activity. Tablets are prepared by the direct compression technique by using HPMC K4M and mannitol as polymers along with sodium bi carbonate as gas generating agent. Formulation were evaluated for in vitro buoyancy and drug release study using up dissolution apparatus using 0.1N Hcl as a medium. The result indicate that floating tablets of dissolution cefuroxime axetil containg 45mg HPMC K4M provides a better option for control release action and improved bioavailability.

Deepak Jain et al¹⁷ 2010: Designed and optimized of Gastro retentive floating drug delivery systems (GFDDS) of furosemide, an loop diuretic drug, with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) using 3² full factorial design. Hydroxypropyl methyl cellulose of different viscosity grades (K4M and K100M) was used as the polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. The tablets were prepared by direct compression method. Estimation of furosemide in the prepared tablet formulations was carried out with 0.1N HCl and measuring the absorbance at 271 nm. The prepared formulations were further evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, In-vitro drug release pattern, short-term stability and drug excipient interactions. Majority of the designed formulations displayed nearly first order release kinetics, releasing more than 80% drug in 10

hours and remained buoyant more than 24 hours. The optimized formulation containing furosemide 80 mg, HPMC (K4M) 100 mg and sodium bicarbonate 30 mg has displayed almost zero order release kinetics with a floating lag time of only 2.9 minutes. This formulation released more than 90% drug in 9 hours. This study proves that GFDDS of furosemide can be designed using HPMC K4M as matrix polymer, which provides nearly zero order release kinetics and thus possible enhancement of oral bioavailability of the drug.

I. Sarath Chandiran et al¹⁸ 2010: Formulated and developed salbutamol sulphate as a floating matrix tablets and control the drug release up to 24 h for administration as once daily dose. Salbutamol Sulphate is a short acting bronchodilators which have short biological half life about 2 - 4 h. Floating matrix tablets were formulated by using swelling polymer like Methylcellulose, Hydroxy propyl methyl cellulose (K100M, K4M) with different concentration 25, 50, 75 % w/w of the polymer were used for the preparation of the floating matrix tablets. The formulation variables like hardness, polymer concentrations, and shape of the tablets were optimized to achieve the floating nature of the tablet in stomach for 24 h. In addition stearic acid included in this formulation to evaluate their release characteristics. From this the hydrophilic floating matrix control the release up to 12 h with HPMC K100M at 75 % w/w of the polymer concentration. The formulations, which have stearic acid retards the drug release by controlling the water penetrations in to the floating matrix tablets, sustained their drug release above 12 h. The floating matrix tablets with minimum hardness of 5 kg/cm² and round shaped tablets exhibited better

Jadav mayur et al¹⁹ 2010: Formulated and developed floating tablets of Famotidine were prepared by employing polymers like Guar gum and Xanthan gum by effervescent technique. The tablets were prepared by direct compression method. The polymers were used individually as well as in combination to formulate floating tablets. Sodium bicarbonate was incorporated as a gas generating agent. The floating tablets were evaluated for physicochemical parameters such as hardness, weight variation, percent friability, floating properties (floating lag time, total floating time and matrix integrity), swelling studies, drug content, stability study and In vitro drug release. The drug polymer interaction was studied by DSC thermal analysis. The physicochemical parameters of formulated tablets were found to be within normal range. The floating lag time of all the formulations was within the prescribed limit (<10 minutes). All the formulations showed good matrix integrity and retarded the release of drug for ten hours except the formulations F1, F2 and F3. The release pattern of Famotidine was fitted to different models based on coefficient of correlation (r). The swelling studies of all the formulations showed that formulations containing combination of Guar gum and Xanthan gum has higher swelling indices than individual Guar gum and Xanthan gum. Optimized formulation (F7) of Famotidine floating tablet was found to be stable for storage at 40°C/75% relative humidity for 3 months.

K. Karunakar et al²⁰ 2011: Developed Floating matrix tablets of Lamivudine to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone

leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methyl cellulose (HPMC E15), Ethyl cellulose and Xanthan gum combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of different concentrations of HPMC, EC and Xanthan gum on drug release profile and floating properties were investigated. Comparable release profiles between the commercial product and the designed system were obtained. The model fitting showed that the optimized formulation F2 formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

Pramod Patil et al²¹ 2011: Developed and designed floating tablets of Ofloxacin which prolong the gastric residence time after oral administration. Ofloxacin is a fluoroquinolon antibacterial agent which is highly effective against gram positive and gram negative bacteria. Ofloxacin floating tablets were prepared by wet granulation method incorporating natural polymer like guar gum, locust bean gum, either alone or in combination with HPMC K100M as swelling polymers, with sodium bicarbonate as gas generating agent and were evaluated for parameters such as Weight variation, Hardness, Friability, Drug content, Swelling index, *in vitro* buoyancy study, *in vitro* drug release study. All the formulation showed compliance with pharmacopieal standards. Based on the evaluation results, F3 and F6 formulations were selected as the best formulations and were checked for stability as per ICH guidelines. These results indicated that the selected formulations were stable. The drug release profile of the best formulations was well controlled and uniform throughout the dissolution studies. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation.

Gada et al²²2011: Designed and developed floating tablets by using direct compression technique using polymers like HPMCK4M, HPMCK15M and HPMCK100M for their gel forming properties. The scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. Floating tablets are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs.

Mahalaxmi Rathnanand et al²³ 2011: Formulated and evaluated (*in vitro*) of floating pulsatile tablets of Nizatidine, a H₂ receptor antagonist, which conceptualizes a specific technology, based on combining principles of both the floating and pulsatile principles to deliver a programmed dose of drug from the developed delivery system anticipated for chronotherapy of excessively secreted gastric acid and for promoting healing of duodenal ulcers. Accordingly floating pulsatile Nizatidine tablets were developed in three different steps viz, preparation of immediate release drug containing core tablets, time-lagged film coating by a hydrophobic rupturable polymer, ethyl cellulose (EC), and compression coating

of a buoyant layer using gel forming polymers like carbopol 934P, poly (ethylene oxide) and sodium bicarbonate for the generation of carbon dioxide which is responsible for the floating behaviour of the tablet on the gastric contents. The obtained tablets were evaluated for weight variation, thickness, hardness, disintegration, *in vitro* floating properties (buoyancy studies) and *in vitro* dissolution studies. Stability studies of the optimized formulation was carried out as per ICH guidelines at $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$ for one month and it was found to be stable.

Apparao et al²⁴ 2011: Developed and optimized a controlled- release floating tablet of highly water soluble drug Nizatidine in an effort to increase its gastric retention time in the stomach. The tablets were prepared by direct compression method by using a Hydroxypropyl methylcellulose (HPMC) of different viscosity grades, Carboxymethyl cellulose Sodium (NaCMC) were incorporated as retarding polymers. Sodium bicarbonate was incorporated as effervescent agent. Formulations were evaluated for weight variation, thickness, hardness, percentage swelling, friability, and *in vitro* drug release, and floating lag time, total duration of floating, dissolution efficacy and *in vivo* Mean Residence Time (MRT) in the stomach. The formulation F6 with HPMC K 4M exhibited floating lag time of less than 1min and floating time of more than 12 hrs. The drug release of the optimized formulation followed Higuchi kinetic model ($R^2=0.9832$) and the mechanism of drug release was found to be supercase II according to Krosmeyster-Peppas (n value is 0.60). *In vivo* nature of tablet was observed at different time intervals with help of radiographic pictures in healthy human volunteers and MRT in the stomach was found to be 320 minutes.

Srinivas Pannala et al²⁵ 2011: Developed and evaluated (*in vitro*) Nizatidine immediate release tablets. The developed drug delivery system delivers a programmed dose of drug intended for excessively secreted gastric acid and for promoting healing of duodenal ulcers thereby spontaneously delivering the drug when exposed into GIT for producing an anti-ulcer effect. Accordingly, immediate release drug-containing core tablets of Nizatidine were prepared by wet granulation method. The obtained tablets were evaluated for weight variation, thickness, hardness, drug content, disintegration and *in vitro* dissolution studies. Stability studies of the optimized formulation was carried out as per ICH guidelines at $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$ for one month and it was found to be stable.

Kurnal patel M et al²⁶ 2011: Formulated and developed gastro retentive drug delivery system of Mebendazole. Chitosan and hydroxypropyl methyl cellulose of various viscosity were used. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. The specific study was carried out formulate such a dosage form that can neutralize the acidity locally in the stomach. The granulation was formed by Fluidized bed processor in which top spray technique was adopted for forming the granules.

Afaser c.shaikh et al²⁷ 2011: Formulated floating-bio adhesive tablets of Tramadol by direct compression method using varying amounts Carbopol 971P (CP) and Hydroxypropyl methylcellulose (HPMC), along with other requisite excipients. *In vitro* drug release profile,

floatation characteristics and *ex vivo* bio adhesive strength using texture analyzer were determined, and systematically optimized using a 32 central composite design (CCD). The studies indicated successful formulation of gastro retentive compressed matrices with excellent controlled release, mucoadhesion and hydrodynamic balance. Comparison of the dissolution profiles of the optimized formulation, with optimal composition of CP: HPMC: 80.0:125.0, with that of the marketed controlled release formulation.

Sonia dhiman et al²⁸ 2012: Developed controlled release floating type gastro retentive tablets using Famotidine as a drug and HPMC K15M as a polymer. This targeted delivery of the drug provides an effective and safe therapy with reduced dose and duration of therapy. A floating controlled-release drug delivery system of Famotidine was developed by effervescent approach using varying concentrations of HPMC K15M and sodium bicarbonate. The matrices are fabricated using sodium bicarbonate (NaHCO₃) and citric acid as gas formers so that upon contact with gastric fluid, carbon dioxide is liberated that is entrapped in the jellified hydrocolloids, which produces an upward motion of the dosage form and maintain its buoyancy.

Ajay Bagherwal et al²⁹2010: Formulated and developed ciprofloxacin floating tablet as sustained release dosage form. HPMC and carbomer are the polymers, used as suspending agent, viscosity increasing agent and tablet binder coating agents. In the present study, it was aimed to formulate floating tablet of ciprofloxacin HCl with HPMC and carbomer in different proportion (4%, 8% and 12%) by direct compression techniques using polymers lactose, magnesium Streate and talc with sodium bicarbonate. All the prepared formulation were found to comply with the official tests like precompression parameter like angle of repose and post compression parameters like Shape, tablet dimensions, hardness, friability test, weight variation test, floating test, content uniformity and *in-vitro* dissolution study. *In-vitro* release studies were carried out using USP XXII dissolution test apparatus. The mean percentage of ciprofloxacin released at various time intervals was calculated and plotted against time. The mechanism of drug release with all the formulations was dominantly diffusion and followed zero order kinetics. It was observed that the integrity of the drug is not affected by formulation procedure. The results revealed the drug polymer ratio showed greater drug release than other formulations.

Ayesha naz et al³⁰ 2011: Formulated and designed Nizatidine floating tablets were prepared by effervescence method using Sodium bicarbonate as a gas generating agent. The tablets were formulated using direct compression technology by employing semi synthetic polymers like various grades of HPMC such as HPMC K4M, K15M, K100M and natural polymers like xanthan gum and kondagogu gum. The prepared tablets were evaluated for various physicochemical parameters such drug-excipient interaction by FTIR and DSC, flow properties, hardness, weight variation, friability, *in vitro* buoyancy (floating lag time, total floating time), swelling studies, drug content and *in-vitro* drug release. The *in vitro* drug release pattern of Nizatidine floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics with non fickian diffusion mechanism. Out of all formulations the one prepared with combination of HPMC K4M and K15M was optimised based on desired sustained release time (12hrs) and acceptable floating properties.

The optimised formulation was evaluated for *in vivo* floating time in rabbits, which showed the floating property in stomach up to 5 hours. The FTIR and DSC study revealed that there is no drug-excipient interaction.

A.m.rao et al³¹2011: Formulated and evaluated floating tablets of pioglitazone employing calcium starch, a new modified starch in comparison to HPMC K15M, a synthetic cellulose derivative. Floating tablets of pioglitazone were prepared employing calcium starch and HPMC, K15M as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer and the tablets were evaluated for *in vitro* buoyancy and drug release characteristics. Tablets formulated employing calcium starch (50%), sodium bicarbonate (10%) and bees wax (10%) exhibited floating over 36 hours with a floating lag time of 5 – 10 min. Pioglitazone release from the floating tablets formulated was slow, spread over more than 24 h and depended on the polymer used and its strength and concentration of sodium bicarbonate in the tablets. Drug release was diffusion controlled and followed first order kinetics. Fickian diffusion was the drug release mechanism from all the tablets formulated. Calcium starch gave slow, controlled and complete drug release in 24 h, Whereas HPMC; K15M gave slow but incomplete drug release. Calcium starch was found to be a better matrix former than HPMC for floating tablets.

Burpate S. S et al³² 2011: Developed floating tablets of Nizatidine employing two different grades of HPMC; these grades of HPMC were evaluated for their gel forming properties. The other polymer carbopol was added for controlled release of drug from the formulation. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of content, hardness, friability, *in vitro* buoyancy, floating lag time, dissolution studies and also for short term stability studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies.

Singh L. P et al³³ 2011::Developed a dosage form to prolong the release of drug from dosage form and improve drug absorption in upper GIT and stomach and to optimize using full factorial design. HPMC K100M (water swellable release retarding polymer), gas generating agent NaHCO₃ and citric acid were used to evaluate the release of the drug. 3² factorial design was implemented at 25, 30 and 35 % concentration of the release retarding polymer and 11.25, 13.75 and 16.25% concentration of gas generating agent to correlate with the release pattern of the drug. Process variables like floating lag time, cumulative percent release and swelling index were investigated. The results showed excellent adaptability in absorption of the drug from narrow therapeutic window with improved gastric retention. Based on the results, formulation of dosage form with optimum concentration of polymer and gas generating agent was possible to fulfil the desired need.

Amul N. Mishra et al³⁴ 2011: Formulated and evaluated of floating tablets of Ranitidine Hydrochloride. Two different grades of hydroxy propyl methylcellulose namely Methocel K 100 M and Methocel K 15 M were used. It was observed that viscosity had a major influence

on drug release from hydrophilic matrices as well as on floating properties. Dissolution profiles were subjected various kinetic drug release equations and found that drug release from hydrophilic matrices occurred via different mechanism following square root of time profile (Higuchi equation). Prepared tablets were evaluated for Hardness (Kg/cm²), Thickness (MM), Average weight (mg), Weight variation, Hardness (Kg/cm²), Friability (%), Drug content (mg/tab.), Floating Lag Time (Sec.), and total floating time (hr.). The granules were characterized for Angle of repose, Bulk Density (gm/cm³), Tapped density (gm/cm³), Carr's index (%), and Hausners ratio, loss on drying and porosity. In vitro drug release study of these tablets indicated controlled sustained release for Ranitidine HCL and 70 to 93% at the end of 10m hrs. Hence, it is evident from this investigation that gas powered floating matrix tablets could be promising delivery system for RHCL with sustained release action and improved drug availability. The formulations were found to be stable at Rt/60o/75% +5%RH for the period of three weeks.

A. K Pathak et al ³⁵2011: Developed a bi-layer tablet of Metoprolol tartrate using disintegrant starch for the fast release layer and HPMC K grade polymers for the sustaining layer. In vitro dissolution studies were carried out in an Indian Pharmacopoeia dissolution testing apparatus II (paddle method). The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. The *In-vitro* release study of this tablet indicated sustained release for Metoprolol tartrate and followed zero order release and 95% drug in 24h *in vitro* and it follow Fickian diffusion.

N. Damodharan et al³⁶ 2011: Developed Bi-layered floating tablets of Theophylline were using wet granulation technique. The current study aims at formulation and evaluation of bi-layered floating tablets of Theophylline. The floating tablets of theophylline were formulated using polymers namely hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, methyl cellulose and the tablets were evaluated. Two layered tablet formulations were designed with an immediately releasing layer consisting of Theophylline with lactose as diluents and sustained release layer with slow releasing swellable matrix consisting of theophylline in hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose and methyl cellulose alone or in combination. The formulations were tested for drug release, floating time, floating lag time and drug content. Tablets formulated employing a combination of hydroxyl propyl methyl cellulose and methyl cellulose provide slow release of Theophylline over a period of 9 hours and were found suitable for maintenance portion of bi-layered floating tablets. Theophylline release from these tablets was diffusion controlled and followed first order kinetics. The tablets exhibited good floating behavior in the stomach for 9 hours.

Anitha Kakkerle et al³⁷2011: Developed and designed Floating matrix tablets of Alfuzosin hydrochloride were to prolong gastric residence time. Alfuzosin hydrochloride was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression and melt granulation technique, using polymers such as

hydroxy propyl methyl cellulose K15M, sodium carboxy methyl cellulose, compritol 888 ATO and either alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics hardness, % friability, floating capacity, weight variation, content uniformity, in-vitro release characteristics for 12 hours and in-vivo gastric retention time. In-vitro release mechanism was evaluated by linear regression analysis. The calculated regression coefficients value of Higuchi and Korsmeyer (0.998, n value 0.520) for optimized formulation F2 and the drug release mechanism was found to be non-Fickian diffusion. No drug-polymer interaction was observed by Fourier Transform Infrared Spectra Analysis. In-vivo studies showed that the tablets retained in stomach for 6 hours. It was concluded that, HPMC K15M alone retarded the drug release for highly water soluble drug (Alfuzosin hydrochloride) for a period of 12 hours.

Anil G, Satyanarayana T et al³⁸ 2011: Formulated and evaluated gastro retentive floating tablets of venlafaxine hydrochloride, which releases the drug in a sustained manner over a period of 12 hours. Three different viscosity grades Hydroxypropylmethylcellulose (HPMC) namely K4M, K15M, and K100M were used for the preparation of tablets. The tablets were prepared by direct compression and evaluated for tablet thickness, weight variation, tablet hardness, friability, in vitro buoyancy test, in vitro drug release and Fourier transform infrared (FT-IR) spectroscopy. Formulation F3 can be considered as an ideal or optimized formulation for gastro retentive floating tablet of venlafaxine HCl. The optimized formulation showed sufficiently sustained drug release and remained buoyant on the surface of the medium for more than 12 hours. As the concentration of HPMC increases in the formulation the drug release rate was found to be decreased. It can be concluded that floating drug delivery system of venlafaxine HCl can be successfully formulated as an approach to increase gastric residence time and there by improving its bioavailability.

Arun M, Mahale et al³⁹ 2011: Developed a new drug delivery system for a water-soluble beta-blocker drug, Metoprolol Succinate, utilizing both the concepts of adhesiveness and of flotation, in order to obtain a unique drug delivery system which could remain in the stomach for a much longer period of time. Floating-Mucoadhesive tablets of Metoprolol Succinate were developed to prolong its release and improve bioavailability by avoidance of first pass metabolism during the treatment of chronic hypertension. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, HPMC K15M, Sodium CMC and Carbopol 940P and were evaluated for buoyancy test, mucoadhesion force, swelling study, drug content, *Ex vivo* mucoadhesion strength and *in vitro* release profile. Sodium bicarbonate was used for producing effervescent base for buoyancy of tablets. Result indicated that release of Formulations best fitted square root kinetics. The swelling properties were increased with increasing polymer concentration and contributed to the drug release from the tablet matrix. No significant change was observed in physical appearance, drug content, floatability or *in vitro* dissolution pattern after storage at 45 °C / 75% RH for three months.

Anilkumar Jet al⁴⁰ 2011: Formulated an oral floating tablet of cephalexin (CEF) using the hydrophilic polymer 2 hydroxy propyl methyl cellulose (HPMC), gas generating agent

sodium bicarbonate and citric acid. A 3 factorial design was applied systematically; the amount of citric acid (X1) and amount of HPMC K100M (X2) were selected as independent variables. The time required for 50% drug release (t_{50}), percentage drug release at 12hr (Q_{12}) and 50% drug release at 6 hr (Q_6) were selected as dependent variables. The results of factorial design indicated that high level of HPMC K100M and citric acid favors preparation of floating sustained release tablet of cephalexin. The granules were prepared by wet granulation method and evaluated for their granular properties. Tablets were compressed by KBr press and evaluated with different parameters like diameter, thickness, average weight, hardness, friability, drug content, in vitro buoyancy study, swelling characteristics, scanning electron microscopy, kinetic release data. Hardness was found to be in the range of 13 ± 0.23 to 13 ± 0.40 kg/cm, the percent friability was in the range of 0.0010 ± 0.02 to 0.0027 ± 0.01 , and tablets showed 99.63 ± 0.12 to 115.73 ± 0.13 of the labelled amount of cephalexin indicating uniformity content. The tablets containing CEF released 72.28 to 99.461 % of drug at the end of 12 hr by in vitro release.

Y and Zakir et al⁴¹ 2011: Formulate and evaluate hydro dynamically balanced controlled drug delivery system of Glipizide. This dosage form is associated with many advantages especially increased bioavailability and reduction in dosing frequency. The formulation was designed adopting optimization technique, which helps in setting up experiments in such a manner that the information is obtained as efficiently and precisely as possible. Initially, considering buoyancy as the main criteria, blank tablets were compressed for different formulae with various polymers like Carbopol-940p, HPMC, Citric acid and sodium bicarbonate. The formula selected for design had a combination of Glipizide, Carbopol-940p, HPMC, Citric acid. The tablets were prepared by direct compression method and evaluated for Glipizide content, in vitro release profile and buoyancy. The dissolution study was carried out in simulated gastric fluid using USP dissolution test apparatus employing paddle stirrer. Duration of buoyancy was observed simultaneously when the dissolution has carried out. The variation in weight was within the range of $\pm 3\%$ complying with pharmacopoeial specifications ($\pm 7.5\%$). The drug content varied between 9.127 ± 0.1317 mg and 9.923 ± 0.0183 mg in different formulations indicating content uniformity. The in-vitro release was found to be in the range of 50.28% to 99.65%. The Glipizide content in the formulation varied between 91–100%. The optimized formulation F9 exhibited responses that were comparable with that of the predicted values of the design in optimization technique. This indicates the suitability of the technique chosen for the present dosage form.

Madhusudan Rao Y et al⁴² 2012: Developed gastro retentive formulation cefuroximeaxetil with the low bioavailability (30-40%) and short biological half life (1.5 hours) oral administration favours. Gastro retentive floating matrix tablets of Cefuroxime Axetil were successfully prepared with hydrophilic polymers like HPMC K4M and HPMC K15M. From the Preformulation studies for drug excipients compatibility it was observed that there was no compatibility problem with the excipients used in study. The drug release from most of the formulations follows fickian diffusion. From vivo X-ray studies, it was clearly observed that the floating tablets showed a gastric residence of nearby 6 hrs in fed state.

3. AIM

- To design and formulate gastro retentive drug delivery system for Nizatidine.

OBJECTIVES.

1. Development of effervescent floating matrix tablets of Nizatidine with different polymers.
2. To evaluate the physicochemical characteristics of all formulations and to carryout *in vitro* drug release studies using USP type 2 apparatus.
3. To select the best formulation based on the above studies.
- 4.To carry out the stability studies to the best formulation.

4. PLAN OF WORK

In order to meet the objective the present work was planned in the following manner:

- Preparation of calibration curve of Nizatidine in 0.1 N HCl (pH 1.2).
- Solubility study of Nizatidine in 0.1N HCl (pH 1.2).
- Stability study of Nizatidine in 0.1N HCl (pH 1.2).
- To determine the flow properties of the final blend.
- Determination of drug-excipient compatibility using FTIR and DSC studies.
- Formulation of Nizatidine floating tablets with HPMC K4M, Polyox WSR 1105.
- Evaluation of Nizatidine floating tablets for weight variation, thickness, hardness, friability, drug content, floating lag time and total floating duration time.
- Theoretical release pattern.
- *In vitro* drug release studies of prepared floating tablets in 0.1 N HCl (pH 1.2) by using USP dissolution apparatus, rotating paddle type and selection of best formulation.
- Stability study of the best formulation.

5. MATERIALS AND EQUIPMENT USED

Table. 5.1: Materials used in the study

Name of chemical	Source
Nizatidine	VIVIMED LABS LIMITED
HPMC K4M	VIVIMED LABS LIMITED
Polyox WSR1105	VIVIMED LABS LIMITED
MCC (Avicel PH 102)	VIVIMED LABS LIMITED
Sodium bi carbonate	VIVIMED LABS LIMITED
Magnesium stearate	VIVIMED LABS LIMITED
Talc	VIVIMED LABS LIMITED
Conc. Hydrochloric acid	VIVIMED LABS LIMITED

Table. 5.2: Equipment used in the study

Equipment	Model no.	Manufacturer
Rotary tablet machine	RDD3	Riddhi, Ahmedabad.
Digital weighing balance	AUX 220	Shimadzu, Japan.
Pfizer hardness tester	CMTT R/1342/98	Cadmach, Ahmedabad.
Friabilator (USP)	EF2	Electro Lab, Mumbai.
Dissolution apparatus	TDT 06P	Electro Lab, Mumbai.
UV-Visible Spectrophotometer	SL 159	Elico Pvt. Ltd., Hyderabad.
FTIR spectrophotometer	BX I	Perkin Elmer, USA.
Differential Scanning Calorimeter	DSC 822 e/200	Mettler Toledo, Switzerland.
Glass ware		Borosil & Schott Duran.

5.1.1. DRUG-EXCIPIENT PROFILE

5.1.1.1. DRUG PROFILE⁴³

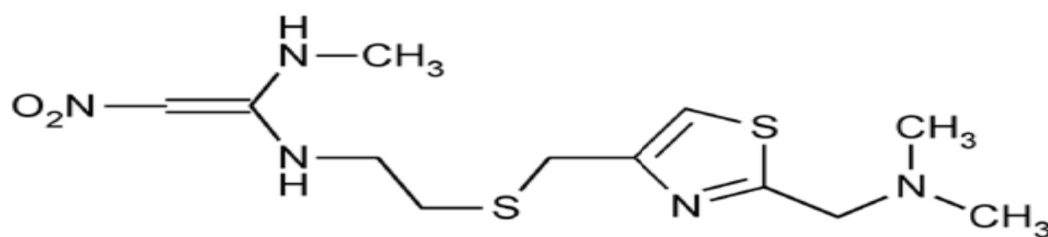
Nizatidine is a histamine H₂-receptor antagonist that inhibits stomach acid production, and commonly used in the treatment of peptic ulcer disease (PUD) and Gastro Esophageal Reflux Disease (GERD).

Nizatidine 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: $C_{12}H_{21}N_5O_2S_2$

Molecular weight : 331.46 g/mol.

PHYSICAL PROPERTIES

Description: It is a white to off-white crystalline powder

Solubility: Freely soluble in methanol.

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° C

PHARMACOKINETIC PARAMETERS

Bioavailability : >70%

Protein binding : 35%

Half-life : 1-2 hours

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} : 1.5 hours

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.

DRUG CLASS AND MECHANISM

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

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, Ketoconazole.

5.1.1.2. EXCIPIENT PROFILES⁴⁴

5.1.1.2 (a) HYDROXYPROPYLMETHYLCELLULOSE (HPMC)

Nonproprietary Names:

BP: Hypromellose

JP: Hypromellose

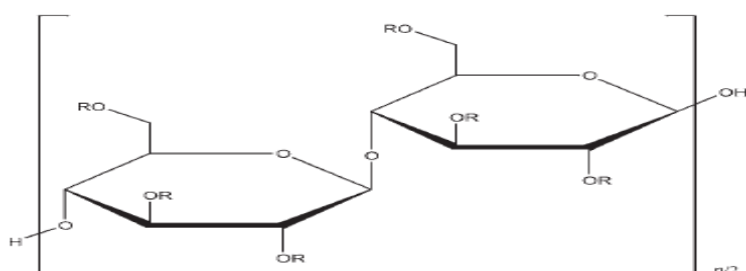
PhEur: Hypromellose

USP: Hypromellose

Synonyms: Benecel MHPC; E464; hydroxyl propyl methylcellulose; HPMC; hypromellosum; methocel; methylcellulose propylene glycol ether; methyl hydroxyl propylcellulose; metolose; MHPC; pharmacoat; tylopur; tylose MO.

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether.

Structural Formula:



Where R is H, CH₃, or CH₃CH(OH)CH₂

Physical and chemical properties:

Molecular weight : 10,000 – 15, 00,000

Color : White to creamy-white

Nature : Fibrous or granular powder

Odor : Odorless

Taste : Tasteless

Density : 0.3-1.3 g/ml

Specific gravity : 1.26

Solubility: Soluble in cold water, practically insoluble in chloroform, ethanol (95%) and ether but soluble in mixture of ethanol and dichloromethane.

Viscosity: 4,000 mPas (HPMC K4M, 2% solution).

Melting point: Browns at 190-200C, chars at 225-230°C, Glass transition temperature is 170-180°C.

Functional category: Bioadhesive material, coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Applications:

- In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.
- HPMC is widely used in oral and topical pharmaceutical formulation.
- Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution.
- HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products. In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating, thus inhibiting the formation of sediments.

Stability and storage: It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place.

5.1.1.2 (b) POLYETHYLENE OXIDE

Nonproprietary Names: USP-NF: Polyethylene Oxide.

Synonyms: Polyox; polyoxiante; polyoxirane; polyoxyethylene.

Chemical Name: Polyethylene oxide

Structural Formula: $(\text{CH}_2\text{CH}_2\text{O})_n$

Physical and chemical properties:

Molecular weight	:	9, 00,000
Color	:	White to off-white
Nature	:	Free-flowing powder
Odor	:	Slight ammoniacal odor
Density (true)	:	1.3 g/mL

Solubility: Soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.

Viscosity: 8,800 – 17 600 mPas (5% solution).

Melting point: 65 – 70°C.

Functional category: Mucoadhesive; coating agent; tablet binder; thickening agent.

Applications:

- Polyethylene oxide can be used as a tablet binder at concentrations of 5–85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach.
- Excellent mucoadhesive polymer.
- Low levels of polyethylene oxide are effective thickeners, although alcohol is usually added to water based formulations to provide improved viscosity stability.
- Polyethylene oxide films demonstrate good lubricity when wet. This property has been utilized in the development of coatings for medical devices.
- Polyethylene oxide can be radially cross-linked in solution to produce a hydrogel that can be used in wound care applications.

Stability and storage: Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

5.2.1.1.2 (c) SODIUM BICARBONATE

Non-proprietary names:

BP: Sodium Bicarbonate

JP: Sodium Bicarbonate

PhEur: Sodium Hydrogen Carbonate

USP: Sodium Bicarbonate

Synonyms: Baking soda, E-500, monosodium carbonate, Effer-soda, Sal de Vichy, sodium hydrogen carbonate, sodium acid carbonate.

Chemical Name: Carbonic acid monosodium salt.

Structural Formula: NaHCO_3

Physical and chemical properties:

Molecular weight: 84.01

Color : White

Nature : Crystalline powder

Odor : Odorless

Taste : Saline/slightly alkaline

Density : 0.869-2.173 g/cm³

Solubility: Soluble in water, practically insoluble in ethanol (95%) and ether.

Osmolarity: 1.39% w/v aqueous solution is iso-osmotic with serum.

Melting point: 270 °C (with decomposition).

Category: Alkalizing agent, therapeutic agent.

Applications:

- Used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.
- Used to produce or maintain an alkaline pH in a preparation, like solution of erythromycin, lidocaine, and niacin etc.
- Used to produce a sodium salt of the active ingredient that has enhanced solubility.

- Used as a freeze-drying stabilizer and in toothpaste.
- Used as a gas forming agent in alginate raft system and in floating drug delivery system.
- Used as component of oral rehydration salts and isotonic injection/infusion.

Stability and storage: Sodium bicarbonate is stable in dry air but slowly decomposed in moist air and should therefore be stored in well-closed container in a cool & dry place.

5.1.1.2 (d) MICROCRYSTALLINE CELLULOSE

Non-proprietary names:

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Applications: MCC is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulation where it is used in both wet and dry granulation processes. In addition to its use as a binder/diluents, MCC also has some lubricant and disintegrant properties that make it useful in tableting.

Description: Microcrystalline cellulose (MCC) is purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles.

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

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

5.1.1.2 (e) MAGNESIUM STEARATE

Nonproprietary names :

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

Empirical formula: $C_{36} H_{70} Mg O_4$

Functional category: Tablet and capsule lubricant.

Applications: It is widely used in cosmetics, food and pharmaceutical formulations. Primarily used in capsule and tablet manufacture at a concentration in between 0.25% to 5.0%.

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

Solubility: Practically insoluble in ethanol (95%), ether and water. Slightly soluble in warm benzene and warm ethanol (95%).

Incompatibilities: Incompatible with acids, alkalis, and iron salts.

5.1.1.2 (f) TALC

Nonproprietary names:

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

Empirical formula: $Mg_6(Si_2O_5)_4(OH)_4$

Functional category: Anticaking agent, glidant, tablet and capsule diluent; tablet and capsule lubricant.

Application in pharmaceutical technology: It is generally used in oral solid dosage forms as a lubricant and diluents. It is also used in topical preparations as a dusting powder.

Use	Concentration (%)
○ Dusting powder	90-99
○ Glidant and tablet lubricant	1-10
○ Tablet and capsule diluent	5-30

Description: Talc is very fine, white to grayish-white colored, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin, is soft to the touch, and free from grittiness.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents and water.

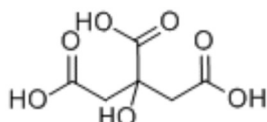
Incompatibilities: Incompatible with quaternary ammonium compounds.

5.1.1.2(g) CITRIC ACID:

Synonyms: Citro; E 330;F 4020, CheMfill, Aciletten

Empirical formula: C₆H₈O₇

Molecular formula: 192.12



Citric acid

Chemical Properties: White crystalline powder

Description: Colorless, odorless crystals with an acid taste. Denser than water.

Density : 1.542

Storage temp. : Store at RT.

Solubility: H₂O:1 M, clear, colorless.

Water Solubility: 750 g/L (20 °C)

Sensitive :Hygroscopic

Stability: Stable. Incompatible with bases, strong oxidizing agents, reducing agents.

Citric acid is a very useful and effective preservative, obtained from naturally occurring organic acids. It exists in many different fruits and vegetables, but is especially concentrated in lemons and limes. Although it is also produced in refineries by using cane sugar, molasses, and dextrose, the citric acid stocked by Mountain Rose Herbs comes from the fermentation of crude fruit sugars. Citric acid is used extensively in the food, beverage, cosmetic, and pharmaceutical industries. It has been recognized as safe by all major national and international food regulatory agencies, and is also approved by the US Food and Drug Administration and in Europe for use in food. Citric acid is used for many different reasons, including (but not limited to):

- Antioxidant and preservative properties
- prevents rancidity and bacteria growth
- Astringency and Acidity

- Used in sourdough bread for an extra tart taste (known as "sour salt" among bakers)

5.2. EXPERIMENTAL PROCEDURES:

5.2.1. PREFORMULATION STUDIES⁴⁵

5.2.1.1 Solubility study of Nizatidine in 0.1 N HCl

Excess amount of 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 λ_{max} 314 nm.

5.2.1.2. Stability study of Nizatidine in 0.1 N HCl

Some amount of Nizatidine was placed in 0.1 N HCl in order to determine its stability. In predetermined time points like 0.5, 1, 2, 3, 4, 6, 8, 10 & 24 hours samples were assayed by UV-Visible spectrophotometer at λ_{max} 314 nm.

5.2.1.3. DRUG EXCIPIENTS COMPATIBILITY STUDIES

5.2.1.3(a) PHYSICAL INCOMPATABILITY

S.NO	INGREDIENTS	DRUG EXCIPIENT RATIO	OBSERVATION	
			INITIAL	40±2C/75%RH AFTER 1-MONTH
1	Nizatidine	—	Off white crystalline powder	No characteristic change
2	DRUG + HPMC	1:1	Off white crystalline powder	No characteristic change
3	DRUG+POLYOX WSR 1105	1:1	Off white crystalline powder	No characteristic change

4	DRUG+NAHCO3	1:1	Off white crystalline powder	No characteristic change
5	DRUG+CITRICACID	1:1	Off white crystalline powder	Slightly colour changes to brown.
6	DRUG+TALC	1:1	Off white crystalline powder	No characteristic change
7	DRUG+MCC	1:1	Off white crystalline powder	No characteristic change
8	DRUG+MAGNESIUMSTERATE	1:1	Off white crystalline powder	No characteristic change

5.2.1.3(b) CHEMICAL INCOMPATIBILITY⁴⁶

a) Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer. Pure drug, individual polymers and their mixtures were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1} .

b) Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) experiments were carried out to find out the presence of any interaction among drug and the excipients. Pure drug, individual polymers and their mixtures were subjected to the study. 5-15 mg of sample to be analysed was taken in the pierced DSC aluminium pan and scanned in the temperature range of 50–250 °C. The heating rate was 10°C/min; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyser was used for this purpose.

5.2.1.2. EVALUATION OF FINAL BLEND⁴⁷

The Final blend of all formulations was evaluated for Bulk density, Tapped density, Compressibility Index, Hausner ratio and Angle of repose.

a) Bulk Density

About 20gms of material was passed through a sieve no. 40 to break up agglomerates and introduced into a dry 50mL cylinder. Without compacting, the powder was carefully leveled and the unsettled apparent volume, V_o , was read. The bulk density was calculated, in grams per mL, using the following formula:

$$\text{Bulk density} = M / V_o$$

Where, M = Total mass of the material

b) Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a mechanical tapped density tester (Electrolab). The cylinder was tapped until no change in volume and then tapped volume V_f , was measured to the nearest graduated unit. The tapped density was calculated, in grams per mL, using the formula:

$$\text{Tapped density} = M / V_f$$

c) Measures of Powder Compressibility

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed.

$$(1) \text{Compressibility index} = [(V_o - V_f) / V_o] \times 100$$

$$(2) \text{Hausner ratio} = V_o / V_f$$

Where, V_o = Bulk volume

V_f = Tapped volume

Table 5.4: Scale of flowability

Compressibility index (%)	Flow ability	Hausner ratio
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, Very poor	>1.60

d) Angle of Repose⁴⁸

The fixed funnel method was employed to measure the angle of repose. The funnel height was 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 was carefully pored through the funnel. The height ' h ' of the pile from base and radius ' r ' of the base of the conical pile was measured. The angle of repose, α , was calculated using the following formula: $\alpha = \tan^{-1}$

Table 5.5: Flow properties and corresponding angles of repose

Angle of repose (degrees)	Powder flow
25-30	Excellent
31-35	Good
36-40	Fair - aid is not needed
41-45	Passable - may hang up
46 – 55	Poor - must agitate, vibrate
56 – 65	Very poor

5.2.3.

ANALYTICAL METHODS

5.2.3.1. Calibration curve of Nizatidine in 0.1 N HCl⁴⁹

Calibration curve of Nizatidine was plotted in 0.1 N HCl (pH 1.2)

An accurately weighed amount of 100 mg of Nizatidine was transferred separately into 100 ml volumetric flask containing 0.1N HCl and then the volume was made up to the mark with 0.1N HCl. From this, necessary dilutions were made to give concentration ranging from 0-275 µg/ml solutions. The absorbances of these solutions were recorded at λ_{\max} (314nm) of the drug and plotted graphically to give the standard graph of Nizatidine.

5.2.4. PREPARATION OF NIZATIDINE FLOATING TABLETS

Technology Applied: Direct compression.

The key ingredients included in the formulations are:

HPMC Hydrophilic polymer	Modify drug release pattern
Polyox WSR 1105	Mucoadhesive agent
Sodium bicarbonate	Effervescent agent
Avicel PH 102(MCC)	Filler
Talc	Anti adherent
Magnesium stearate	Lubricant

Preparation procedure: Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically. To this required quantity of Nizatidine was added and mixed slightly with pestle. Accurately weighed quantity of sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder was passed through sieve no. 40 and mixed with the drug blend which was also passed through sieve no. 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this talc was added and mixed for 2 minutes, later magnesium stearate was added and mixed for 3 minutes. The mixture equivalent to 500 mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm².

.Table 5.6: Composition of Nizatidine floating tablets containing HPMC K4M&POLYOX WSR1105

Ingredients	Formulations(Weight in mg)						
	F1	F2	F3	F4	F5	F6	F7
Nizatidine	270	270	270	270	270	270	270
HPMC K4M	100	75	80	-	-	-	-
Polyox WSR 1105	-	-	-	80	100	110	115
Sodium bicarbonate	50	60	60	60	60	60	60
Citric acid anhydrous	10	-	-	-	-	-	-
Avicel P^H 102	56	81	76	76	56	46	41
Talc	7	7	7	7	7	7	7
Magnesium stearate	7	7	7	7	7	7	7
Total tablet weight	500	500	500	500	500	500	500

5.2.5. EVALUATION OF NIZATIDINE FLOATING TABLETS⁵⁰

- ❖ Weight variation
- ❖ Thickness

- ❖ Hardness
- ❖ Friability
- ❖ Floating lag time
- ❖ Total floating time
- ❖ Water absorption study
- ❖ Drug content
- ❖ *In vitro* drug release

a) Weight Variation test:

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight.

Table 5.7: Weight variation tolerances for uncoated tablets

Maximum % of weight difference allowed	Average weight of tablets(mg)	
	USP	IP
10	<130	<80
7.5	130 – 324	80-250
5	>324	>250

b) Thickness test:

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using Vernier Calipers. The average thickness and standard deviation were reported.

c) Hardness test:

Tablet hardness was measured using a Pfizer hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm² and the average hardness, and the standard deviation was reported.

d) Friability test:

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dedusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets.

e) *In vitro* buoyancy studies:

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 mL beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and to float was determined as *floating lag time*. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the *total floating time*.

f) Drug Content:

Twenty tablets were taken, powdered and the powder equivalent to one dose each was transferred to a 100 mL volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-Visible spectrophotometer at λ_{\max} 314 nm.

g) *In vitro* drug release studie⁵¹:

The *in vitro* drug release study was performed for all the tablets using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters:

Medium	:	900 mL of 0.1 N HCl
Rotation speed	:	50 rpm
Temperature	:	37 ± 0.5°Cs

Sampling volume : 5 mL

Sampling time : 0.5, 1, 2, 3, 4, 6, 8, 10 hours

At predetermined time intervals samples (5 mL) were collected and replenished with same volume of fresh medium. The drug content in the samples was estimated using UV-Visible spectrophotometer at λ_{\max} 314 nm.

5.2.6. STABILITY STUDIES⁵²

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Design Plan:

The product is subjected to short term studies at $40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$ for 3 months.

6. THEORETICAL DOSE CALCULATION⁵³

The objective of this calculation was to arrive at the theoretical amount of drug that must be present in the floating drug delivery system, being administered once a day and capable of acting up to 12 hours.

The total dose of Nizatidine was calculated with available pharmacokinetic data. As per the zero-order release principle, the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. The release from the dosage form with zero-order kinetics is shown by the equation.

$$K_r^0 = \text{Rate in} = \text{Rate out} = K_e \times C_d \times V_d = K_e \times D_L$$

Where K_r^0 is the zero-order rate constant for drug release (amount per time),

K_e is the first-order rate constant of overall drug elimination (per hour),

C_d is the desired drug level in the body (amount per volume),

V_d is the volume in which the drug is distributed.

And D_L is the loading dose

The loading dose is required to give initial rapid burst of dose so as to attain therapeutic range immediately after dosing.

❖ Loading dose (D_L) = $C_{SS\text{Avg}} \times V_d / F$

Where, $C_{SS\text{Avg}}$ is the average steady-state plasma level,

And F is the fraction of dose absorbed.

❖ Maintenance dose (D_M) = $K_r^0 \times H$

Where, H = Total desired time for sustained action in hours,

❖ Total Dose = $D_L + D_M$

Calculation of the Loading and Maintenance Dose (Theoretical Release) Profile of Nizatidine:

Loading dose (D_L) = $C_{SS\text{Avg}} \times V_d / F = 610 \times 60 / 0.7 = 52,285 = 52 \text{ mg.}$

$K_e = 0.693/t_{1/2} = 0.693/1.5 = 0.462 \text{ h}^{-1}$

Drug availability rate (Rate of drug input) = $K_r^0 = K_e \times D_L = 0.462 \times 52 = 24 \text{ mg.}$

Maintenance dose (D_M) = $K_r^0 \times H = 24 \times 12 = 288 \text{ mg.}$

If the maintenance dose begins the release of the drug at the time of dosing, it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case, a correction factor is needed to account for the added drug from the maintenance dose. This correction factor is the amount of drug provided during the period from $t=0$ to the time of the peak drug level. Nizatidine reaches peak drug level in 1 hour.

Thus, corrected loading dose $D_{L(\text{corrected})} = 52 - 24 = 28 \text{ mg.}$

Therefore, the total dose required is = $D_{L(\text{corrected})} + D_M = 28 + 288 = 316 \text{ mg.}$

Table 6.1: Theoretical release profile of Nizatidine

Time (hours)	Release (mg)	Cumulative % release
1	52	19.25
2	76	28.14
3	100	37.03
4	124	45.92

6	172	63.7
8	220	81.48
10	268	100
12	316	

Nizatidine daily dose is 300 mg, so that we should calculate the dose below that i.e. 268 mg up to 10 hours. The total dose of Nizatidine rounded off to 270 mg (with 28 mg loading dose and 242 mg maintenance dose) for 10 hours period and used in the design of the floating tablets of Nizatidine.

7. RESULTS AND DISCUSSION

7.1. CALIBRATION CURVE OF NIZATIDINE

Different concentrations of Nizatidine were prepared in 0.1 N HCl (pH 1.2) and absorbance values at λ_{max} (314 nm) were noted. The calibration curve showed good linearity with R^2 value 0.9994.

**Table 7.1: Absorbance of Nizatidine with different concentrations
at λ_{max} (314 nm) in 0.1 N HCl**

Concentration ($\mu\text{g/ml}$)	Absorbance
0	0
20	0.073
40	0.143
60	0.213
80	0.284
100	0.339
125	0.441
150	0.531
175	0.601
200	0.704
225	0.806
250	0.870
275	0.972

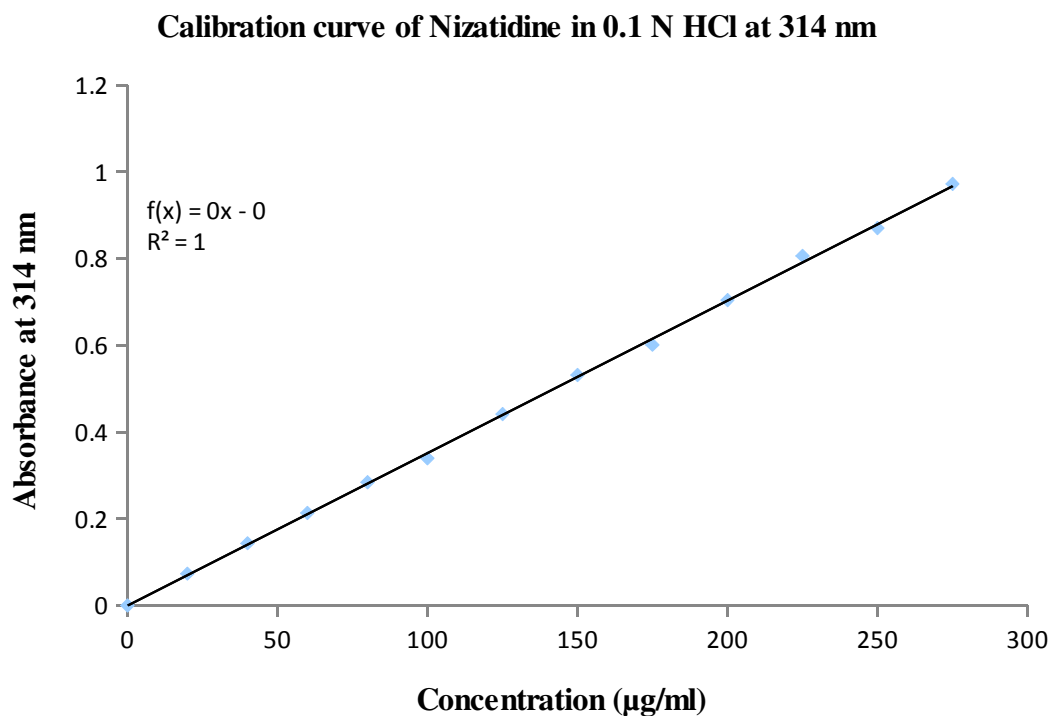


Figure 7.1: Calibration curve of Nizatidine in 0.1N HCl at 314 nm

7.2.1. SOLUBILITY OF NIZATIDINE

Nizatidine is highly soluble in 0.1 N HCl, having quantitative solubility 112.9 mg/mL.

7.2.2.. STABILITY OF NIZATIDINE IN 0.1 HCL

This study was done as per the method described in section 2.2.2.3. Absorbance values at λ_{max} 314 nm at different time points were tabulated.

Table 7.2: Absorbance of Nizatidine at different time points

Time (hours)	Absorbance at λ_{max} 314 nm			Average
	1	2	3	
0	0.992	0.995	0.990	0.992
0.5	0.993	0.994	0.991	0.993
1	0.992	0.993	0.990	0.992
2	0.993	0.994	0.992	0.993
3	0.991	0.992	0.990	0.991
4	0.994	0.993	0.989	0.992
6	0.990	0.991	0.988	0.990
8	0.992	0.992	0.989	0.991
10	0.991	0.990	0.987	0.989
24	0.990	0.991	0.988	0.990

Table 7.2 showed that there was no change in the absorbance of Nizatidine at different time points. This implied that Nizatidine is highly stable in 0.1 N HCl, for 24 hours.

7.2.3. DRUG-EXCIPIENT COMPATIBILITY STUDIES

7.2.3.1. PHYSICAL INCOMPATIBILITY

There is no interaction between drug and excipients except citric acid.

7.2.3.2. CHEMICAL INCOMPATIBILITY

7.2.3.2.1. Fourier Transform Infrared (FTIR) Spectroscopy

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and excipients, samples were analyzed over the range 400–4000 cm^{-1} .

Table 7.3: Infra-Red band assignments for Nizatidine

Wave number (cm ⁻¹)	Groups
3280,3210	NH stretch: 2 groups
3107	CH stretch in NO ₂ -CH-
3094	CH stretch in thiazole ring
2945,2860, 2829,2784	CH stretch in NCH ₃ , CH ₂ CH ₂
1622	C=C, conjugated with NO ₂
1587	Asymmetric NO ₂ stretch, conjugated with C-C; thiazole ring, weak contribution
1521	Thiazole ring
1470,1458, 1435,1422	CH deformation in NCH ₃ , CH ₂ ; CN stretch
1377,1359	Thiazole ring for one frequency is symmetric NO ₂ , H-bonded, conjugated.

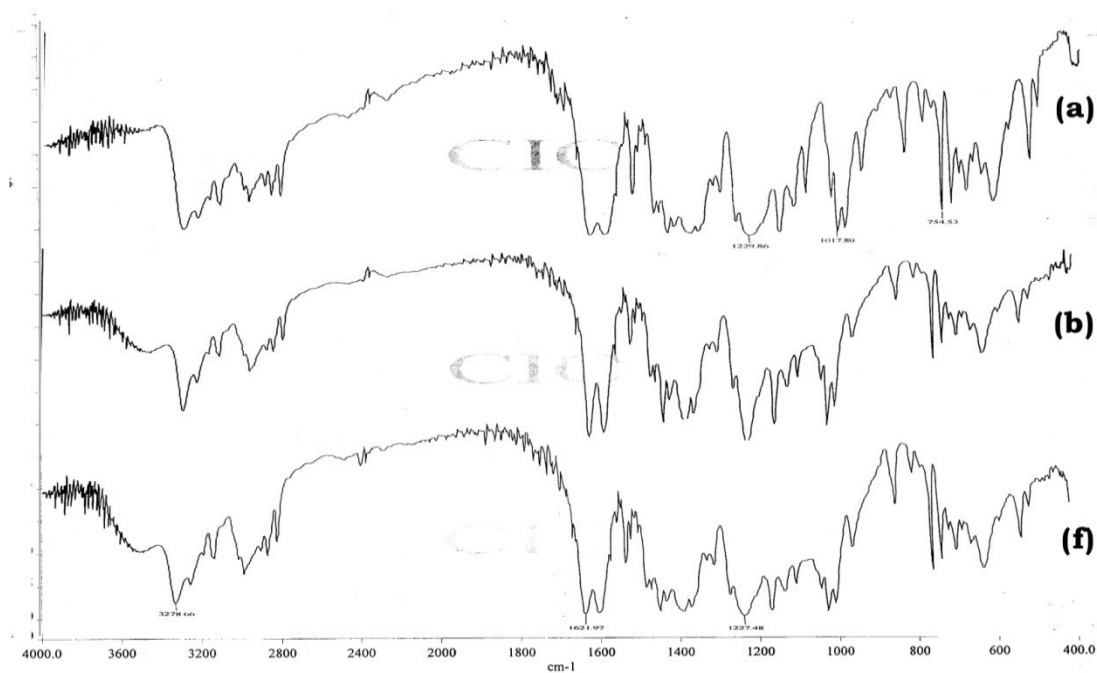


Figure 7.2: Comparison of FT-IR spectra of pure Nizatidine (a), HPMC K4M & Nizatidine mixture (1:1) immediately after preparation (b) and after one month preservation at room temperature (f)

The figure 7.2 suggested that there was compatibility between Nizatidine & HPMC K4M because FTIR spectra of Nizatidine & HPMC K4M mixture (1:1) displayed all the characteristic bands of drug, without any significant spectral shift.

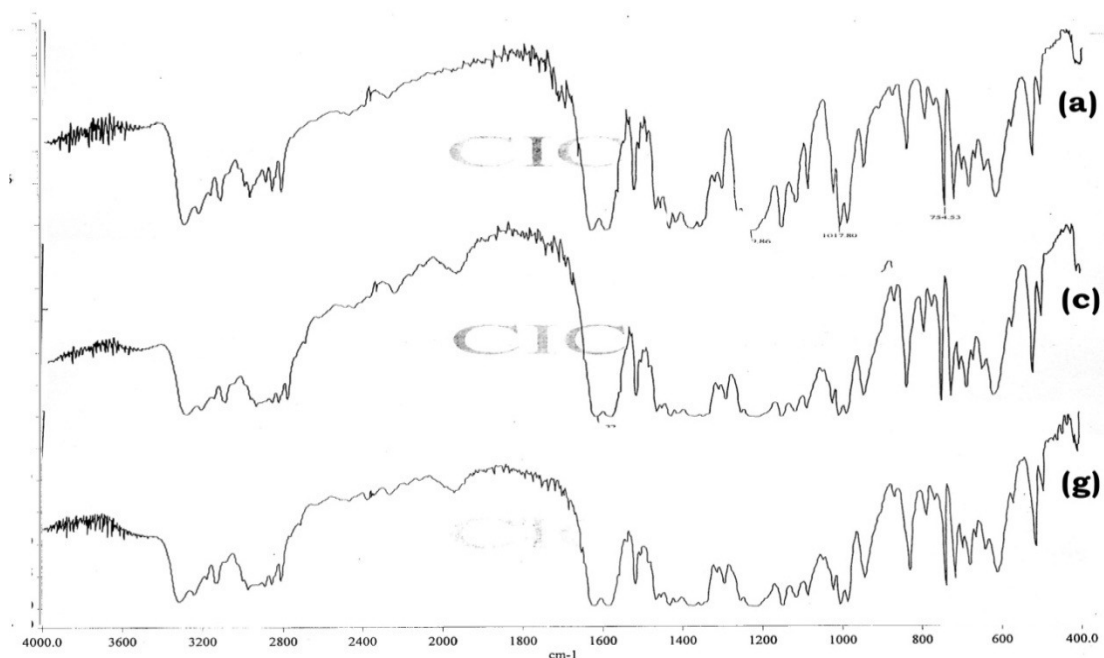


Figure 7.3: Comparison of FT-IR spectra of pure Nizatidine (a), Polyox WSR 1105 & Nizatidine mixture (1:1) immediately after preparation (c) and after one month preservation at room temperature (g)

The figure 7.3 suggested that there was compatibility between Nizatidine & Polyox WSR 1105 because FT-IR spectra of Nizatidine & Polyox WSR 1105 mixture (1:1) displayed all the characteristic bands of drug, without any significant spectral shift.

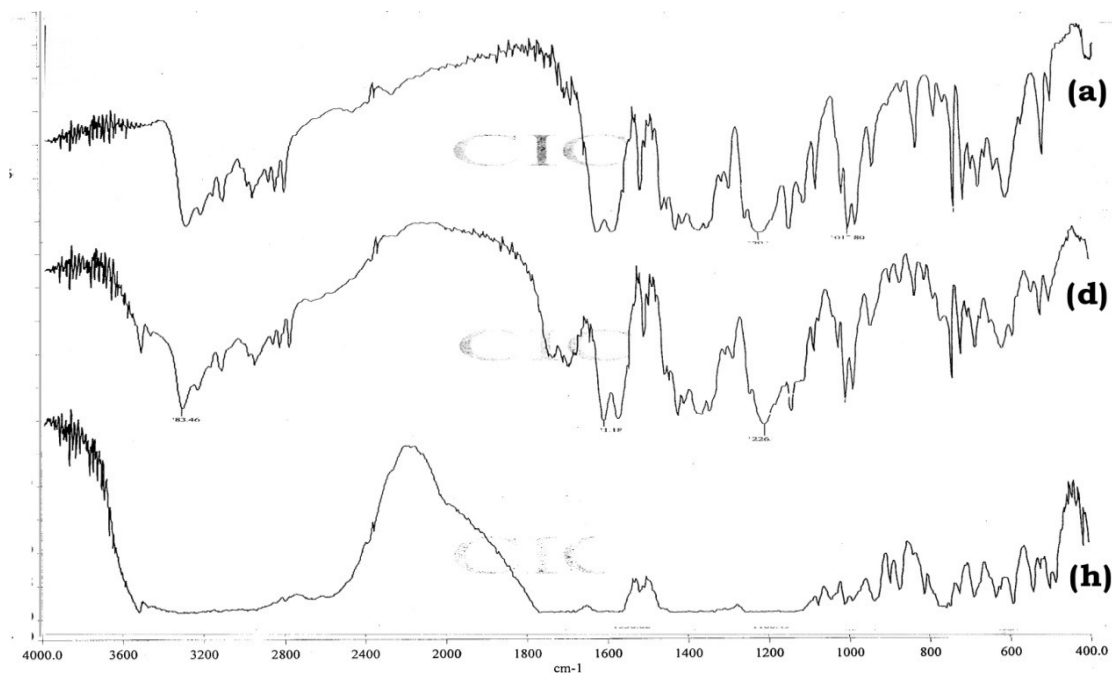


Figure 7.4: Comparison of FT-IR spectra of pure Nizatidine (a), citric acid anhydrous & Nizatidine mixture (1:1) immediately after preparation (d) and after one month preservation at room temperature (h)

The figure 7.4 suggested that there was incompatibility between Nizatidine & citric acid because FTIR spectra of Nizatidine & citric acid mixture (1:1) (figure 4.5 (d)) which was immediately analyzed after preparation showed extra peak at 1700 - 1800 cm^{-1} (shown by arrow) other than characteristic bands of drug. FT-IR spectra of Nizatidine & citric acid mixture (1:1) (figure 7.4 (h)) which was preserved one month and analyzed, showed entirely different peaks which was lacking characteristic bands of drug.

7.2.3.2.2 Differential Scanning Calorimetry (DSC)

The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC curve of pure Nizatidine (NIZ-1) showed a single sharp endothermic peak at 136.32°C (-130.50 J/g) corresponding to its melting point (130–134°C) being started at 132°C and ended at 138°C.

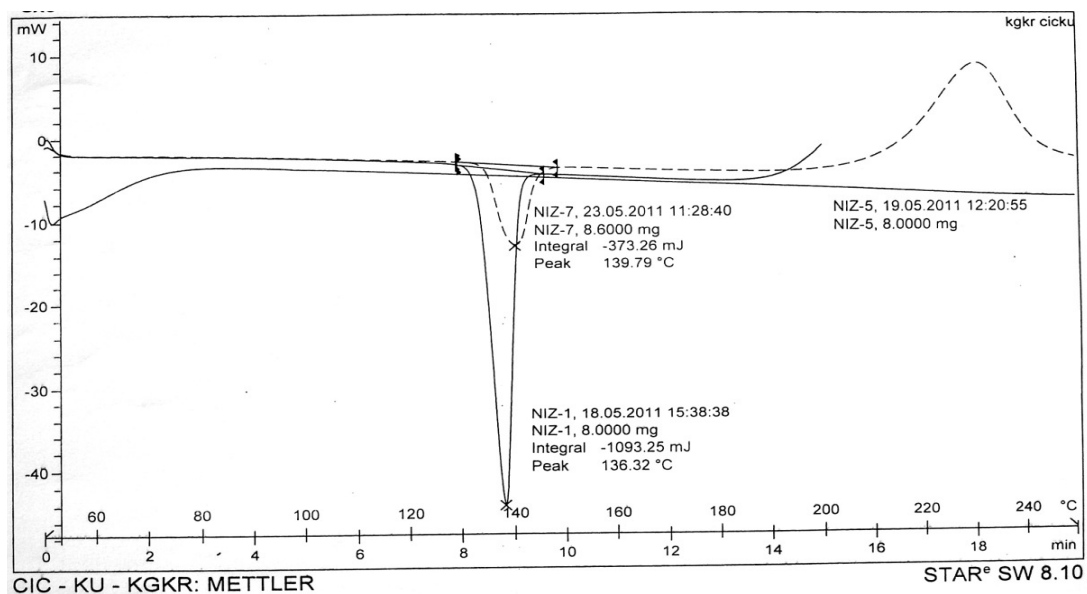


Figure 7.5: DSC curves of pure drug Nizatidine (NIZ-1), pure polymer HPMC K4M (NIZ-5) and 1:1 mixture of Nizatidine & HPMC K4M (NIZ-7)

The figure 7.5 suggested that 1:1 mixture of Nizatidine & HPMC K4M (NIZ-7) is having an endothermic peak of drug at 139.79°C which was well preserved with slight changes in terms of broadening or shifting towards the higher temperature.

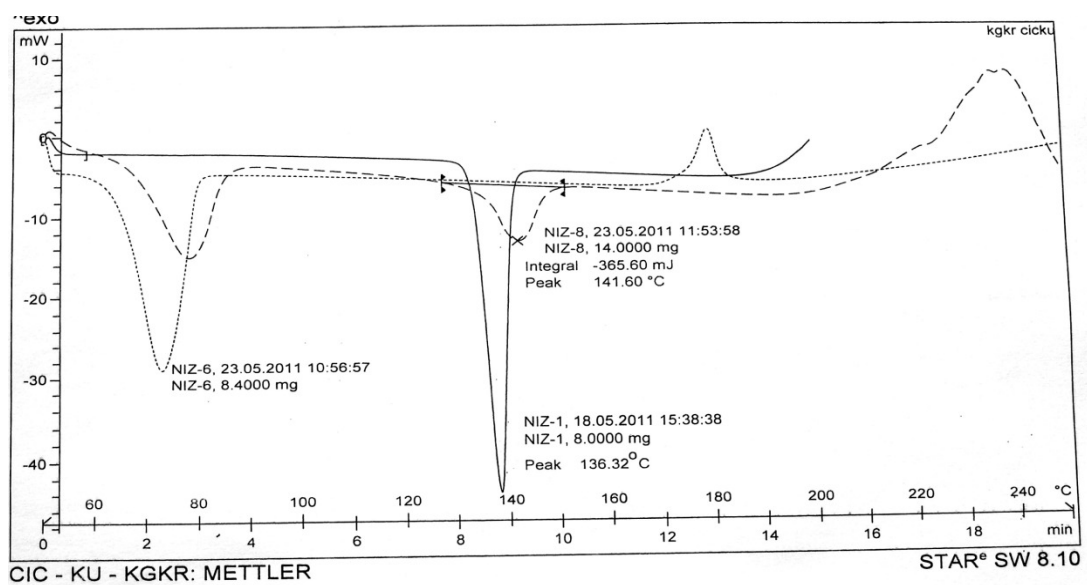


Figure 7.6: DSC curves of Nizatidine pure drug (NIZ-1), pure polymer Polyox WSR 1105 (NIZ-6) and 1:1 mixture of Nizatidine & Polyox WSR 1105 (NIZ-8)

Thus, it was concluded that the drug is compatible with HPMC K4M, Polyox WSR 1105 used in the formulation.

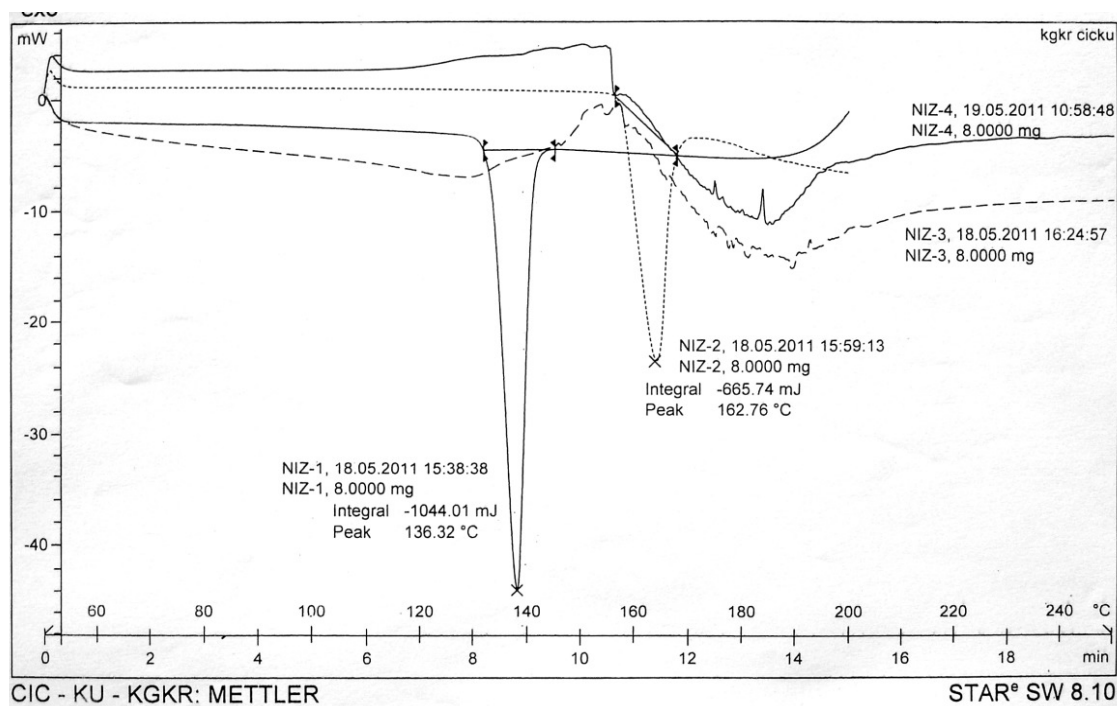


Figure 7.7: DSC curves of Nizatidine pure drug (NIZ-1), pure citric acid anhydrous (NIZ-2), 1:1 mixture of Nizatidine & citric acid immediately after preparation (NIZ-3) and after one month preservation at room temp. (NIZ-4)

The figure 7.7 suggested that citric acid anhydrous (NIZ-2) showed a single sharp endothermic peak at 162.76°C corresponding to its melting point (MP 153°C). Decomposition of the organic acid started immediately after the melting event since the signal did not return to the baseline level, but continued its downward shift. This thermal instability of citric acid anhydrous at temperatures above its melting point was consistent with the TGA findings and was detectable in all the physical blends as a broad peak around 190°C exhibiting concentration-dependent intensity. In NIZ-3 & NIZ-4 endothermic peak of drug disappeared, indicating that there might be potential interaction between Nizatidine & citric acid i.e. Nizatidine is incompatible with citric acid.

From both FT-IR & DSC studies it was concluded that Nizatidine is incompatible with citric acid. Whenever both ingredients are present the scope of brown coloration started. Not clear in immediately after preparation and after one day, but gradually developed. When either of the ingredients citric acid or drug is excluded no coloration was noticed. This clearly proved the interaction between these two ingredients (Nizatidine & citric acid).

7.3. PHYSICAL PROPERTIES OF PREPARED POWDER BLENDS

The physical properties like Compressibility index (CI), Angle of repose and Hausner ratio were calculated and tabulated.

Table 7.4: Physical properties of powder blends of tablet formulations

Formulation	Angle of repose	Compressibility index (%)	Hausner ratio
F2	26.85±0.5	15.71±0.2	1.187
F3	25.09±0.9	14.28±0.1	1.166
F4	24.82±1.2	13.95±0.7	1.162
F5	24.87±0.6	15.00±1.6	1.176
F6	25.64±1.0	14.28±1.2	1.166
F7	26.34±0.6	14.98±0.5	1.171

The above tests are not performed for formulation F1 because of interaction between Nizatidine and citric acid. The results of the physical tests of F2 to F7 of the blend were within the limits and complied with the standards.

7.4. EVALUATION OF POST COMPRESSION PARAMETERS OF FLOATING TABLETS OF NIZATIDINE

All the prepared formulations were tested for physical parameters like weight variation, hardness, thickness, friability and found to be within the Pharmacopoeial limits. The results of the tests are tabulated. The drug content (assay) of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 7.5: post compression parameters of Nizatidine floating tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
F2	501.5 ± 7.83	6.1 ± 0.2	6.13 ± 0.04	0.18	98.3
F3	500.5 ± 7.24	5.9 ± 0.4	6.16 ± 0.04	0.19	98.9
F4	507 ± 8.56	6.1 ± 0.3	6.30 ± 0.03	0.18	99.28
F5	506.5 ± 10.28	6.2 ± 0.2	6.34 ± 0.04	0.20	97.48
F6	504.5 ± 10.91	5.9 ± 0.3	6.32 ± 0.04	0.17	98.96
F7	504.5 ± 8.64	6.1 ± 0.2	6.33 ± 0.04	0.18	98.29

7.5. FLOATING PROPERTIES OF NIZATIDINE FLOATING TABLETS

All the formulations were tested for floating properties like floating lag time and total floating time. All the batches showed good *in vitro* buoyancy.

Table 7.6: Floating properties of Nizatidine floating tablets

Formulation code	Floating Lag time (sec)	Total floating time (hours)
F2	92	10.1
F3	85	10.4
F4	65	6.8
F5	83	8.2
F6	114	10.5
F7	171	10.1

7.6. IN VITRO DRUG RELEASE STUDIES OF PREPARED FORMULATIONS

7.6.1. Release profiles of formulations containing HPMC K4M

Table 7.7: Cumulative percentage drug release from formulations containing HPMC K4M

Time (hours)	Cumulative percentage drug release (%)		Theoretical release
	F2	F3	-
0	0	0	0
0.5	18.36±1.2	17.25±1.1	15. -
1	23.99±0.3	22.26±1.3	19.25
2	31.04±0.9	27.69±0.7	28.14
3	38.10±1.8	35.65±1.8	37.03
4	44.81±2.6	43.19±2.9	45.92
6	63.23±3.0	57.82±1.1	63.7
8	79.03±2.9	74.86±1.6	81.48
10	98.25±1.4	93.13±1.4	100

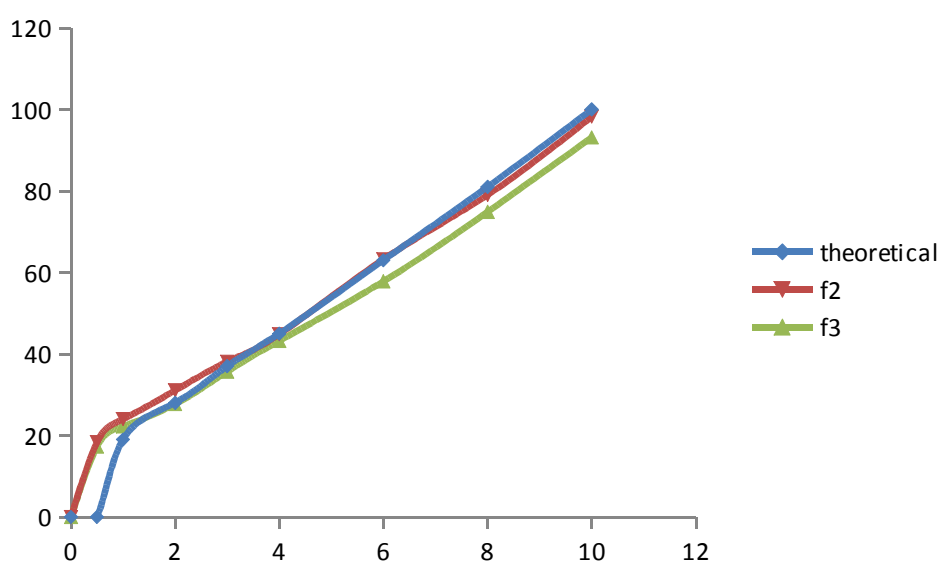


Figure 7.8: Cumulative percentage drug release profiles of F2, F3 formulations containing HPMCK4M

The figure 7.8 suggested the cumulative percentage of drug release from formulations F2 and F3 was 98.25 ± 1.4 and 93.13 ± 1.4 in 10 hours respectively.

These two formulations (F2 & F3) also floated for 10 hrs. Formulations F3 was unable to sustain the drug release as theoretical profile but released the drug within the desired time. Formulations F2 sustained the drug release as theoretical profile and also released the drug within the desired time. So **formulation F2** was considered as **best formulation** among all these. The difference in the drug release profiles of the formulations was due to the presence of different concentrations of polymer.

Time (hours)	Cumulative percentage drug release (%)			
	F4	F5	F6	F7
0	0	0	0	0
0.5	43.94±3.5	28.11±1.5	17.22±2.4	11.66±0.7
1	51.00±2.5	32.83±1.6	19.98±1.9	15.13±0.7
2	62.54±3.4	43.23±2.8	26.61±2.5	21.94±0.7
3	74.63±3.6	53.12±4.0	37.03±1.8	31.41±0.2
4	86.33±4.0	64.50±3.32	45.69±1.4	39.05±0.1
6	99.62±1.7	83.20±3.5	66.57±3.8	61.23±2.8
8		100.85±1.0	83.90±3.7	79.06±0.9
10			98.41±1.4	97.19±0.4

Figure 7.9: Cumulative percentage drug release profiles of formulations containing Polyox WSR 1105

From figure 7.9 it could be observed that the polymer polyox WSR 1105 had sustaining effect on the release of drug from the floating matrix tablet. Cumulative percentage of drug release from formulations F4, F5, F6 and F7 were 99.62 ± 1.7 , 100.85 ± 1.0 , 98.41 ± 1.4 and 97.19 ± 0.4 in 6, 8, 10 and 10 hours respectively.

Formulations F4 & F5 were unable to sustain the drug release as theoretical profile and also didn't release the drug for the desired time (6 hours & 8 hours respectively). Formulations F6 & F7 were able to sustain the drug release as theoretical profile and also released the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. **Formulations F6** was considered as **best formulation** among all the four formulations as it showed good sustained release very near to theoretical release profile.

7.7. STABILITY STUDIES

- ▶ The optimized formulation was subjected to stability studies at $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5$ RH for 3 months .
- ▶ The F6 Formulation was evaluated for the physical characteristics, drug content and *In vitro* drug release profile over a period of 3 months.

7.10. DRUG CONTENT AND PHYSICAL Parameters OF FORMULATION F6

S.No.	Time	Physical Parameters	% Drug Content \pm SD ($40 \pm 2^{\circ}\text{C} / 75 \pm 5\% \text{RH}$)
1.	15 days	No change	98.86 ± 0.82
2.	1 month	No change	98.90 ± 0.30
3.	2 month	No change	98.89 ± 0.51
4.	3 month	No change	98.96 ± 0.40

7.11. In vitro % drug Release of Nizatidine (F6) after 3 months stability studies:

S.No.	Time (hrs)	Cumulative % Drug Released \pm SD at $40\pm 2^\circ\text{C}/75\pm 5\% \text{RH}$	
		1 st Day	90 th Day
1.	0	0	0
2.	0.5	17.14 \pm 1.4	17.19 \pm 2.4
3.	1	19.65 \pm 0.9	19.87 \pm 1.9
4.	2	26.49 \pm 2.5	26.61 \pm 2.5
5.	3	36.75 \pm 1.8	37.00 \pm 1.8
6.	4	45.17 \pm 1.5	45.67 \pm 1.5
7.	6	65.04 \pm 2.8	66.54 \pm 3.8
8	8	82.89 \pm 2.7	83.90 \pm 3.7
9	10	98.43\pm0.4	98.40\pm0.4

8. SUMMARY & CONCLUSION:

- ❖ Nizatidine floating tablets were successfully prepared with hydrophilic polymers like HPMC K4M and Poly Ethylene Oxide WSR 1105
- ❖ 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.
- ❖ From the pre-formulation studies for drug excipient compatibility it was observed that Nizatidine had interaction with citric acid. No physical or chemical incompatibility existed between the drug and other excipients.
- ❖ 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.
- ❖ All formulations were tested for buoyancy properties like floating lag time & total floating time. Almost all the formulations showed satisfactory results.
- ❖ All formulations were tested for *in vitro* drug release. The optimized formulations among HPMC K4M and Poly Ethylene Oxide WSR 1105 are F2 and F6. These were chosen because of their close similarity with predicted theoretical release profile.
- ❖ The F6 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 .

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