Chapter 2

Objective of the study
OBJECTIVES OF THE STUDY

1. To formulate different floating drug delivery systems like effervescent, non-effervescent tablets and hollow microspheres.

2. Preformulation studies of drugs and compatibility studies of drug and excipients by FTIR and DSC.

3. To evaluate the prepared dosage forms for floating capabilities, physicochemical properties, surface morphology, micromeritic properties, *in vitro* and *in vivo* studies.
Chapter 3

Review of Literature
Based on the mechanism of floatation, floating delivery systems can be classified into two types

1. Effervescent floating drug delivery system (EFDDS).

2. Non-effervescent floating drug delivery system (NEFDDS).

3.0 BASIC PHYSIOLOGY OF GASTROINTESTINAL TRACT

The anatomy and physiology of GIT should be understood, while developing floating drug delivery systems. The various factors affecting GI motility like pH, nature and volume of gastric secretion and gastric mucus. Anatomically stomach is mainly divided into 3 parts: fundus, body and antrum (pylorus). The proximal part of the stomach is made up of fundus and body region, which serves as reservoir of the undigested substances. Where as distal region (antrum) is major site for mixing action and act as pump for gastric emptying. Gastric emptying occurs based on fed and fasted state of the stomach. Saliva, mucus and debris are commonly present in the fasted state of the stomach. The fasted state is characterized by intra gastric series of cyclic contractions or electrical events takes place, which is known as interdigestive migrating myoelectric complex or migrating myoelectrical cycle (MMC). This activity occurs both through stomach and intestine every 2-3 h. Apparently MMC is further divided into four consecutive phases as described by Wilson and Washington.
Phase I (basal phase): It is a quiescent period which lasts from 30–60 minutes with rare contractions.

Phase II: It consists of intermittent action potential and gradually increases in intensity and frequency as the phase progress and lasts for about 40-60 mins.

Phase III: This is a shorter period of intense, large regular distal and proximal gastric contractions (4-5 contractions per minutes) lasting for about 4-6 mins. This cycle is also known as “house keeper wave”. Since it sweeps undigested gastric contents from stomach to intestine.

Phase IV: A brief transitional phase about 0-5 mins, which occurs between last part of phase III and beginning of phase I. After feeding, this cycle leads to change in the pattern of contractions, which may last for many minutes. This frequent feeding of mixed meal may increase gastric retention time.\(^\text{30}\)
Figure 3.02: Pictorial representation of the typical GI motility pattern in fasting state

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

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

There are many factors that affect gastric emptying of an oral dosage form, viz.

- **Density:** Gastric resident time (GRT) is a function of dosage form buoyancy that 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:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT ≈ 90% to 100% retention at 24 h compared to 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. It is observed that, multi particulate formulations are more reliable as compared to single unit formulations, which suffers “all or none concept”. The units of multi-particulate systems are freely distributed through out the GI tract.

- **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 drug release is prolonged.

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 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than cold fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

Biological factors such as:

Gender: Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and 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. Men and younger people have faster gastric emptying rate when compared to women and old people.

Stress can increase the gastric emptying rate while it is decreased in case of depression.

Posture: GRT can vary between supine and upright ambulatory states of the patient.
Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; and

Diabetes and Crohn’s disease, etc.\textsuperscript{31,32}

In addition to this, body exercise may also influence gastric emptying.\textsuperscript{33,34,35}

**Figure 3.03: Picturisation of various gastroretentive formulations location in the stomach**

### 3.1.1 Advantages of Gastric floating drug delivery systems (GRFDD)\textsuperscript{36}

- The GRFDD are not restricted to medicaments, which are principally absorbed from the stomach, it has been found that these are equally efficacious with medicaments which are absorbed from the intestine.

  eg. Chlorpheniramine maleate

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

  eg. Antacids
The efficacy of the medicaments administered utilizing the sustained release principle of GRFDD has been found to be independent of the site of absorption of the particular medicaments.

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

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

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine.

Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).

Drugs that are less soluble or are degraded by the alkaline pH at the lower part of GIT.

Drugs that are absorbed due to variable gastric emptying time.
Local or sustained drug delivery to the stomach and proximal part of small intestine to treat certain conditions like duodenal ulcers.


### 3.1.2 Disadvantages of Gastric floating drug delivery systems (GRFDD)

- 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.

- Thus, drugs that may irritate the stomach lining and are unstable in its acidic environment should not be formulated in gastro retentive systems.

- Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed well throughout the GI tract will not benefit from incorporation into a gastric retention system.

- The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

- Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.

- Not suitable for drugs that may cause gastric lesions eg. Non- steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.
The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

In all the above systems, the physical integrity of the system is very important and the primary requirement for the success of these systems.

3.1.3 Mechanism of drug release from GRFDD

Different mass transport processes may occur during drug release from polymer-based matrix tablets, including

1) Imbibition of water into the system,
2) Polymer swelling,
3) Drug dissolution,
4) Drug diffusion out of the tablet and
5) Polymer dissolution.

The importance of above process is dependent on the type of drug, polymer & dissolution medium and on the composition of the dosage form.
3.2 PRACTICAL APPROACHES FOR DESIGNING FLOATING DRUG DELIVERY SYSTEMS (FDDS)

3.2.1 Non-Effervescent FDDS

3.2.1.1 Low density floating systems
3.2.1.2 Swellable and expanding systems
3.2.1.3 Bioadhesion systems
3.2.1.4 Modified shapes systems
3.2.1.5 High density systems
3.2.1.6 Delayed release gastric emptying approaches
3.2.1.7 Microballoon/ Hollow microspheres
3.2.1.8 Magnetic systems

3.2.2 Effervescent FDDS

3.2.2.1 Effervescent systems (tablets, capsules and granules)
3.2.2.2 Raft forming systems
3.2.2.3 Programmable drug delivery systems
3.2.2.4 Beads/pills

The concept of floating drug delivery system was described in the literature as early as 1968, when David disclosed a method of overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pills having a density less than 1.0 g/ml so that pill will float on the surface of water.\textsuperscript{37}

Over last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, which includes the following systems
3.2.1 NON-EFFERVESCENT FDDS

The non-effervescent FDDS works on the mechanism of polymer swelling, bioadhesion of the polymer to mucosal layer of GI tract. The most commonly used excipients for the preparation of non-effervescent FDDS are gel forming or swellable type hydrocolloids, polysaccharides and matrix forming polymers like polymethacrylates, polycarbonates, polyacrylates polystyrenes and bioadhesive polymers like chitosan and carbopols. One of the approaches in the development of such floating dosage forms involves thorough mixing of drug and gel forming hydrocolloids. After oral administration, the dosage form comes in contact with gastric fluids and gets swollen, forms a gelatinous barrier at the surface. The swollen dosage form maintains a relative integrity of shape and bulk density less than 1.0 g/ml. The air entrapped within the swollen polymer matrix imparts buoyancy to the dosage forms. Apart from this, swollen gel structure acts as a reservoir for the dosage forms and provides sustained release effect to the dosage forms. The slow release of drug is controlled by the formation of gelatinous barrier by diffusion mechanism.\(^{38}\)

3.2.1.1 Low density floating systems

These systems are also known as hydro dynamically balanced systems (HBS) or floating drug delivery systems (FDDS). They have a bulk density lower than density of gastric fluid, i.e. their bulk density is less than 1 g/cm\(^3\). The specific gravity of gastric fluid is approximately 1.004-1.01g/cm\(^3\), thus FDDS remains buoyant in stomach without affecting gastric emptying rate for prolonged period of time, releasing the drug slowly at desired rate. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose
(HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems.

Figure 3.04: Schematic localization of an intragastric floating system in the stomach

Sheth and Tossounian\textsuperscript{39} have developed hydrodynamically balanced capsules containing mixture of drug and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolved in gastric fluid followed by swelling of mixtures, formation of a gelatinous barrier and maintains bulk density less than 1.0 g/cm\textsuperscript{3}, which remained buoyant on the gastric fluid for an extended period of time.
Bolton and Desai\textsuperscript{30,40} have developed controlled release floating tablets of theophylline using agar and mineral oil. Tablets were made by dispersing a drug/mineral oil mixture in warm agar gel solution and pouring the resultant mixture into tablet moulds, which on cooling and air drying formed floatable tablets. The amount of agar required to form the floatable tablet was remarkably low (2% tablet). The light mineral oil prevents escape of entrapped air in the gel matrix when placed in gastric fluid due to its inherent hydrophobic property.

Figure 3.05: Hydrodynamically balanced system (HBS) showing gelatinous polymer barrier formation and drug release

Figure 3.06: Improvement in HBS
3.2.1.2 Swelling and expanding systems

These systems are such that after administration they swell to that extent which prevents their exit from stomach through pyloric sphincter. As a result, the dosage form is retained in stomach for long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter.

![Swellable drug delivery systems](image)

**Figure 3.07: Swellable drug delivery systems**

3.2.1.3 Bioadhesive Systems

These systems are used to localize a delivery device within the lumen and cavity of body to enhance the drug absorption process in site specific manner. Various bioadhesive polymers are used to achieve the effective bioadhesion. These polymers tend to form hydrogen and electrostatic bonds at the mucus membrane polymer boundary. Rapid hydration when in contact with the muco-epithelial surface appears to favor adhesion.
3.2.1.4 Modified shape systems

These are non-disintegrating geometric shapes molded from plastic elastomer or extruded from polyethylene blends which extend the gastric residence time (GRT) depending on the size, shape and flexural modulus of drug delivery system.

Klausner et al.\textsuperscript{41} have described a novel levodopa gastroretentive dosage form, based on unfolding polymeric membranes, that combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. \textit{In vitro} studies showed that unfolded form reached within 15 min after administration and it was confirmed \textit{in vivo} in beagle dogs. The unfolded form was maintained for a minimum period of 2 hours. It was concluded that this dosage form could improve therapy of drugs with narrow absorption window. However, there are possibilities of the polymeric films get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.

![Different geometric forms of unfoldable systems](image)

\textbf{Figure 3.08: Different geometric forms of unfoldable systems}
3.2.1.5 High density formulations

High density formulations have a density greater than that of stomach contents. This can be achieved by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide and iron powder.

Figure 3.10: Schematic localization of a high density system in the stomach
3.2.1.6 Delayed release gastric emptying approaches

This approach includes feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach and decrease the gastric emptying rate.

3.2.1.7 Microballoon / Hollow microspheres and Microparticles

Microballoons / hollow microspheres loaded with drugs were prepared by simple solvent evaporation or solvent diffusion evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low methoxylated pectin etc.

The various buoyant preparations include hollow microspheres (microballoons), granules, powders, capsules, tablets, pills and laminated films. Most of the floating systems reported in literature are single unit systems, such as hydrodynamically balanced systems and floating tablets. But these systems are unreliable and nonreproducible in prolonging gastric residence time in the stomach when orally administered, owing to their fortuitous (‘all or nothing’) emptying process.\(^{42}\)

Figure 3.11: SEM photographs of microballoon and microparticle
Figure 3.12: Schematic presentation of the structure of low-density floating matrix tablets

3.2.1.8 Magnetic systems

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach.

On the other hand, Rouge and coworkers showed that multiple unit dosage forms decreases the inter-subject variability in absorption and minimizes probabilities of dose dumping by uniform distribution within the gastric content and provides longer duration of action.43

The rationale for designing of FDDS is as follows

I) Retention in the stomach as per the clinical demand or need

II) Convenience for patient

III) Ability to load substantial amount of drug with different physicochemical properties and release them in a controlled manner

IV) Complex matrix integrity of sustained release (SR) formulation in the stomach, inexpensive optimization between floatation time and release rate, lag time (time taken by the system to float) must be less. The FDDS are classified based on the mechanism of buoyancy into effervescent and non
effervescent systems and these technologies are utilized in their development.\textsuperscript{44}

Harrign\textsuperscript{15} has developed intragastric floating drug delivery device. The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3.png}
\caption{Intragastric floating drug delivery device}
\end{figure}

Mitra\textsuperscript{46} has prepared “multilayered, flexible sheet like medicament device. It was buoyant in the gastric juice and had sustained release characteristics. The device composed of at least one dry, self-supporting carrier film made up of a water insoluble polymer. The drug was dispersed or dissolved in the polymer layer and the barrier film overlaid the carrier film. The barrier film composed of one water insoluble, a water and drug permeable polymer or copolymer. The peripheral walls were sealed to prevent direct contact of the drug reservoir with stomach walls. The buoyancy of laminated film is due to presence of small air pockets.

\textbf{Patents}

Alza Corporation was granted patents for the development of drug delivery devices for the controlled and continuous administration of drugs. The osmotically activated device comprised of a hollow deformable unit that was convertible from
collapsed to expandable form and return to original form. The deformable unit is supported by housing that is internally divided into first and second chambers separated by pressure sensitive permeable bladder. The first chamber has medicinal agent and second chamber has volatile liquid, like cyclopentene or ether vaporizes at body temperature and provides floating ability to the system. The device contained a bioerodible plug that allowed the vapor to escape from the system.\textsuperscript{47,48}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3_14}
\caption{Intragastric floating tablet\textsuperscript{49}}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3_15}
\caption{Intragastric floating bilayer tablet\textsuperscript{50}}
\end{figure}
Table 3.01: List of US Patents for FDDS

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>US Patent No.</th>
<th>Ref No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra gastric floating device</td>
<td>4055178</td>
<td>45</td>
</tr>
<tr>
<td>Multilayer flexible sheet device</td>
<td>4451260</td>
<td>46</td>
</tr>
<tr>
<td>Gastric inflatable device</td>
<td>3901232</td>
<td>47</td>
</tr>
<tr>
<td>Osmotically controlled DDS</td>
<td>3786813</td>
<td>48</td>
</tr>
<tr>
<td>Tablet/Capsule</td>
<td>3574820</td>
<td>49</td>
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<tr>
<td>Tablet</td>
<td>4814179, 4140755, 4167558</td>
<td>40,50, 51</td>
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<td>Minicapsule</td>
<td>4101650</td>
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<td>Capsule</td>
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<td>Capsule</td>
<td>3976764</td>
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<td>Granules</td>
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<td>55</td>
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<tr>
<td>Powder(capsule/compressed into tab)</td>
<td>5169638</td>
<td>56</td>
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<tr>
<td>Multilayered floating dosage form</td>
<td>2003232081</td>
<td>57</td>
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</table>

3.2.2 EFFERVESCENT FDDS
3.2.2.1 Effervescent systems (tablets, capsules and granules)

These are matrix type systems prepared with the help of swellable polymers such as hydroxypropyl methylcellulose, polysaccharides or chitosan\textsuperscript{58} and various effervescent components like sodium bicarbonate, calcium carbonate, citric acid or tartaric acid. These dosage forms are developed in such a way that, when they come in contact with gastric juice in the stomach, CO$_2$ is liberated and is trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet.\textsuperscript{59} The multiparticulate floating reservoir types of delivery systems may contain double or triple layers. The triple layered tablets may be prepared, which contains swellable gas generating layer, sustainable approach was utilized in the development of floating or pulsatile drug delivery system based on the coated effervescent core. The dosage form had two layers, first layer consisted of drug, cellulose acetate or HPMC as a sustained release core and second layer consisted of effervescent agents, PEG 4000 (4\% based on the weight of the second layer), lactose or microcrystalline cellulose were used as fillers. Sodium bicarbonate and citric acid were used as an effervescent agent in a ratio of 1:0.76 in the concentration of 30-50 \% of the w/w of the core. The CO$_2$ is generated upon contact with the medium and gets entrapped in the polymeric matrix, which provides buoyancy to the dosage form. They observed that addition of 10-20 \% w/w of HPMC significantly retarded drug release compared to the dosage form without HPMC. The pulsatile release from the ethyl cellulose coated tablets were highly reproducible. Krogel \textit{et al}\textsuperscript{60} concluded that floating or pulsatile drug delivery systems based on the effervescent cores can be obtained depending on the choice of the polymeric coating and core components.
Figure 3.16: Schematic representation of gas-generating systems as monolayer drug delivery system

3.2.2.2 Raft forming system

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO\(_2\). Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO\(_2\) to make the system less dense and float on the gastric fluids. The system contains a gel forming agent (eg. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus.
Chapter 3

Review of literature

3.2.2.3 Programmable drug delivery systems

Farouk sakr has developed programmable drug delivery systems for oral administration. It was a new prototype model device (3 cm long and 0.9 cm internal diameter) made to comprise of a cylindrical shell in the form of oral capsule. Drug was placed in a cylindrical disc made up of slowly eroding polymer and compressed to zero porosity, a flexible rubber disc, compressible acid resistant spring and a special acid impervious non-permeable rubber balooning system containing bicarbonate granules. The device in the form of non-digestible oral capsule containing drug in a slowly eroding matrix was designed to utilize on automatically operated geometric obstruction that keeps the device floating in the stomach and prevents the system from passing through remainder of GIT. The different grades of HPMC were used to develop the eroding matrix. He concluded that duration of action was
dependent on erosion rate of the incorporated polymer and the *in vitro* release of drug from developed device could be maintained up to 20 days.

![Diagrammatic sketch of the device representing its operation mechanism.](image)

Figure 3.18: Diagrammatic sketch of the device representing its operation mechanism. (A,B,C,D.)

(A) Intact device;

(B) Device at the beginning of drug release;

(C) Device with half drug-polymer compact eroded;

(D) Device after complete drug–polymer erosion and evacuation of entrapped carbon dioxide (inflated balloon)

### 3.2.2.4 Beads/pills

Choi *et al.*\(^{63}\) have prepared alginate beads consisting of gas forming agent. The beads were made up of HPMC and sodium alginate (9:1w/w) with gas generating agent in the concentration 0:1 to 1:1(gas forming agent/alginate w/w). The resultant solution was dropped in to 1% (w/v) calcium chloride solution containing 10% (v/v) acetic acid. The suspended beads in solution were stirred on a magnetic stirrer for 10 mins. The prepared beads were separately evaluated for the effect of CO\(_2\) producing agent on size, floating properties, porosity, morphology and mechanical strength of
beads. It was observed that amount of gas forming agent had a significant effect on size, floating ability, porosity, morphology, release rate and mechanical strength. Calcium carbonate formed smaller but stronger beads as compared to sodium bicarbonate. Calcium carbonate was found to be less effective gas generating agent than sodium bicarbonate. But it forms superior quality floating beads with significantly extended drug release.

![Figure 3.19: Gas-generating systems](image)

Atyabi et al.\textsuperscript{64} have developed a floating system using ion exchange resin. The system composed of resin beads, which were loaded with gas generating agent and negatively charged drug. The drug-loaded beads were encapsulated by semipermeable membrane to overcome sudden loss of CO\textsubscript{2} upon arrival in contact with gastric environment of stomach. An exchange of chlorides and bicarbonate ions took place. As a result of this reaction, CO\textsubscript{2} was released and trapped in the membrane, thereby carrying beads towards the top of gastric contents. The \textit{in vivo} behavior of the coated
and uncoated beads was monitored using a single channel analyzing study in twelve healthy human volunteers by $\gamma$-radioscintigraphy. They showed that a coated bead remained in the upper stomach for over 3 h, which was superior to the non-coated beads.

Ichikawa et al.$^{55}$ developed floating capsules composed a plurality of granules having different residence time in the stomach and granules were comprised of a core containing the drug coated by double layer. Inner layer was further divided into 2 sub layers, inner tartaric acid and outer sodium bicarbonate. This layer was coated with expansive polymeric membrane (PVA and shellac), which allowed gastric juice to pass through it and expanded by foam produced by the reaction between gastric juice and foamable layer.

Chen and Hao WH$^{65}$ have studied the effect of formulation variable on in vitro performance of floating sustained release capsules of verapamil. The formulations were comprised of variables like polymer excipients, polymer content, weight of the filled powder mixture (density of the capsule), and amount of effervescent agent.

Ichikawa et al.$^{20}$ developed multiple unit type of floating pills, composed of inner effervescent layer containing sodium bicarbonate and tartaric acid and outer swellable polymeric membrane made up of polyvinyl acetate and purified shellac. The inner layer was further divided into two sub layers to avoid physical contact between sodium bicarbonate and tartaric acid. When the pill was immersed in buffer solution at 37 °C, it settled down at the bottom, buffer solution entered in to the effervescent layer through the outer swellable membrane. CO$_2$ was generated due to reaction between sodium bicarbonate and tartaric acid and formed swollen pills (like balloons) with a density much lesser than 1.0 g/ml. The system was found to float completely
within 10 minutes and had a good floating ability independent of pH, viscosity of the medium and drug release in a sustained manner.

Figure 3.20: Floating pills a) The penetration of water into effervescent layer leads to a CO₂ generation and makes the system to float

(b) Mechanism of floatation
The dosage forms were prepared by using different drugs, polymer(s) and techniques as given in the table 3.02.

Table 3.02: List of drugs explored for various floating dosage forms.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Drug(s)</th>
<th>Dosage form</th>
<th>Polymer(s) used</th>
<th>Method of Preparation</th>
<th>Ref. No.</th>
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<tr>
<td>1</td>
<td>Melatonin</td>
<td>Microspheres</td>
<td>Chitosan</td>
<td>Ionic interaction</td>
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<td>Repaglinide</td>
<td>Microspheres</td>
<td>Eudragit S</td>
<td>Solvent emulsion</td>
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<td>3</td>
<td>Fluorescein Sodium</td>
<td>Beads</td>
<td>Casein-gelatin</td>
<td>Emulsification extraction</td>
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<td>4</td>
<td>Acetohydroximic Acid</td>
<td>Microspheres</td>
<td>Eudragit E Carbopol®</td>
<td>Novel quasi-emulsion</td>
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<td>5</td>
<td>Verapamil</td>
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<td>Polypropylene foam powder, Eudragit RS, Ethylcellulose, Methylacrylate</td>
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<td>6</td>
<td>Nifedipine Nicardipine</td>
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### Table 3.03: Gastroretentive products available in the market

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<th>BRAND NAME</th>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>Liquid Gaviscon</td>
<td>Acid and sodium bicarbonate</td>
</tr>
</tbody>
</table>
3.3. DRUG PROFILES

3.3.1 VERAPAMIL HYDROCHLORIDE

Category: Antihypertensive (Calcium channel blocker)

Structure:

![Chemical Structure of Verapamil Hydrochloride]

**Molecular formula:** \( \text{C}_{27}\text{H}_{38}\text{N}_{2}\text{O}_{4}\cdot\text{HCl} \)

**Molecular weight:** 491.07

**IUPAC name:** \( \alpha\text{-}[3\text{-}[(2\text{-}(3,4\text{-Dimethoxyphenyl})\text{ethyl}]\text{-methylamino}] \)

proply]-3,4-dimethoxy-(1-methyl)benzene-acetonitril hydrochloride.

**Description:** White crystalline powder with no discernible odour.

**Solubility:** Soluble in water, methylene chloride, dimethyl formamide and methanol.

**Mechanism of action:** Verapamil HCl acts by blocking the cellular entry of \( \text{Ca}^{2+} \) through calcium channel rather than its inter cellular actions.

**Half-life:** \( 4 \pm 1.5 \) h.

**Storage:** Store in well-closed containers.

**Usual dose range:** Hypertension: The usual initial dosage is 120 mg Verapamil HCl given twice daily, the usual maintenance dosage is 120 mg to 240 mg per day.
**Therapeutic uses:** It is used in the treatment of angina pectoris, arrhythmias, myocardial infarction, hypertension, and prophylaxis migraine headaches.

**Pharmacokinetics:**

**Absorption**
Oral absorption of labeled 14C-verapamil in man averaged over 90%. The absolute BA is 10–20%, indicating extensive first-pass metabolism. Peak plasma concentrations are reached within 1–2 h after administration of a single dose.

**Distribution**
The apparent volume of distribution of verapamil is about 2.5 L/kg.

**Metabolism and Excretion**
Verapamil is extensively metabolized in the liver, primarily by N-dealkylation and O-demethylation. Nor-verapamil is the only active metabolite formed. Further metabolism results in the forming of several metabolites that are excreted as inactive conjugates.
3.3.2 ROSIGLITAZONE MALEATE

Category: Anti-diabetic

Structure:

Molecular formula: $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$

Molecular weight: 473.52

IUPAC name: 5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl] methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate

Description: A white to off-white powder.

Solubility: It is readily soluble in ethanol and a buffered aqueous solution with pH of 2.3; solubility decreases with increasing pH in the physiological range.

Mechanism of action: Rosiglitazone improves glycemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPARγ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPARγ-responsive
genes also participate in the regulation of fatty acid metabolism.

**Half-life:** 3-4 h

**Storage:** Stored in an airtight container, protected from light.

**Usual dose range:** 2 to 8 mg per day in divided doses.

**Therapeutic uses:** For the treatment of Type II diabetes mellitus.

**Pharmacokinetics:** The absolute bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about 1 hour after dosing. Administration of rosiglitazone with food resulted in no change in overall exposure (AUC), but there was an approximately 28% decrease in $C_{\text{max}}$ and a delay in $T_{\text{max}}$ (1.5 hours). These changes are not likely to be clinically significant; therefore, rosiglitazone may be administered with or without food. It is 99.8% bound to plasma proteins, primarily albumin. Rosiglitazone is extensively metabolized in the liver to inactive metabolites via N-demethylation, hydroxylation, and conjugation with sulfate and glucuronic acid.
3.3.3 LOSARTAN POTASSIUM

Category: Antihypertensive {Angiotensin II receptor (type AT1) antagonist}

Structure:

[Chemical structure image]

Molecular formula: C_{22}H_{22}ClKN_{6}O

Molecular weight: 461.01

IUPAC Name: 2-butyl-4-chloro-1-[p-(o-1Htetrazol-5ylphenyl) benzyl] imidazole-5-methanol mono potassium salt

Description: White to off-white free-flowing crystalline powder

Solubility: It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone

Mechanism of action: Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (eg. vascular smooth muscle, adrenal gland)

Half Life: 1.5 to 2.5 h

Storage: Store in a well closed container
Usual dose range: 25-100 mg in daily divided doses

Therapeutic uses: Losartan Potassium used in treatment of hypertension.

Pharmacokinetic Profile:

Absorption: Losartan Potassium is absorbed from the gastrointestinal tract

Bioavailability: 25-35%

Distribution: Both Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively

Metabolism: Undergoes substantial first-pass metabolism by cytochrome P450 enzymes

Elimination: Plasma half life of Losartan Potassium is about 1.5 to 2 h.
Chapter 3  
Review of literature

3.4 EXCIPIENT PROFILES

3.4.1 CHITOSAN

Structure:

Chemical name: Poly-\(\beta-(1, 4)\)-2-Amino-2-deoxy-D-glucose.

Synonym: Poly (D-glucosamine) Deacetylated chitin

Molecular weight: 1, 10,000 - 1, 50,000

Description: Chitosan occur as odorless, solid light yellow powder

Functional category: Used in cosmetics, controlled drug delivery, mucoadhesive dosage forms, microspheres, liposomes preparation

pH: 4 to 6 (1% w/v aqueous solution)

Glass transition temperature: 203 °C

Physical form: 75-85 % deacetylated

Solubility: Soluble in acetic acid solution, sparingly soluble in water, practically insoluble in ethanol (95 %) and other organic solvents

Chemical stability: Stable

Materials to avoid: Strong oxidizing agents

Toxicological information: LD\(_{50}\): Oral - rat > 10,000 mg/kg, oral - mouse >16 g/kg

Storage: Store at room temperature.
3.4.2 POLYVINYL PYRROLIDONE (PVP)

Structure:

\[
\text{Synonyms: } \text{Povidone, Polyvidone, Polyvinyl pyrrolidone}
\]

Chemical name: Poly-[1-(2-oxo-1-pyrrolidinyl)- ethylene]

Chemical formula: \((\text{C}_6\text{H}_9\text{NO})_n\)

Description: White to creamy- white colored powder

Solubility: Soluble in water, in ethanol, in chloroform, insoluble in ether.

pH: 3.0 – 7.0 (5 % aq. Soln.)

Melting point: Softens at 150 °C

Molecular weight: 40000

Applications: Clarifying agent, stabilizer, dispersing agent, dissolution enhancer, viscosity-increasing agent, suspending agent and tablet binder

Toxicological information: \(\text{LD}_{50}\): Oral - rat - 100.000 mg/kg

Storage: Stored in an airtight container in a cool, dry place.
3.4.3 ETHYLCELLULOSE (7CPS)

Structure:

\[
\begin{array}{c}
\text{CH}_3\text{O}\text{C}_2\text{H}_5 \\
\text{OC}_2\text{H}_5 \\
\text{OC}_2\text{H}_5 \\
\end{array}
\]

Synonyms: Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name: Ethylcellulose with complete ethoxyl substitution (DS=3) is \( \text{CH}_2\text{O}_6(\text{C}_{12}\text{H}_{22}\text{O}_5)n\text{C}_{12}\text{H}_{23}\text{O}_5 \) where \( n \) can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of \( \beta \)-anhydroglucose units joined together by acetal linkages.

Description: Ethyl cellulose is a kind of white grains or powder, having no smell or tastes.

Specific gravity: 1.12–1.15 g/cm\(^3\)

Viscosity: The viscosity of ethylcellulose is measured typically at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene:20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available; they may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPas (7–100 cps). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and...
durable films. The viscosity of an ethylcellulose solution increases with an increase in ethylcellulose concentration; e.g. the viscosity of a 5% w/v solution of Ethocel Standard 4 Premium is 4 mPas (4 cps) and of a 25% w/v solution of the same ethylcellulose grade.

**Density (bulk):** 0.4 g/cm$^3$

**Moisture content:** Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

**Solubility:** Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl group is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).
3.4.4 EUDRAGIT L 100

Structure:

Chemical Name: Poly(methacrylic acid, methyl methacrylate) 1 : 1

Molecular weight: 250,000.

Description: It is a solid substance in form of a white powder with a faint characteristic odour.

Solubility/permeability: Soluble in intestinal fluid from pH 6

Viscosity (dynamic): 50–200 mPas.

Storage: Store at controlled room temperatures (USP, General Notices). Protect against moisture. Any storage between 8 °C and 25 °C fulfils this requirement.

Acid Value: 315mgKOH/g polymer

Stability: Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage Stability data are available upon request.

Glass Transition

Temperature (Tg): >150°C

Toxicological information:

LD_{50}: 2 - 20 mg/kg body weight
3.4.5 POLYETHYLENE OXIDE

Structure:

![Polyethylene Oxide Structure](image)

**Synonyms:** Polyox; polyoxiane; polyoxirane; polyoxyethylene.

**Structural Formula:** Polyethylene oxide as a non-ionic homopolymer of ethylene oxide, represented by the formula $(\text{CH}_2\text{CH}_2\text{O})_n$, where $n$ represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide or suitable antioxidant.

**Molecular weight:** 100,000

**Melting point:** 65–70°C

**Moisture content:** <1%

**Description:** White to off-white, free-flowing powder & slight ammoniacal odor.

**Solubility/permeability:** 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.
3.4.6 HYDROXY PROPYL METHYL CELLULOSE

Structure:

Chemical Name: Cellulose, 2 Hydroxy Propyl methyl ether

Functional category: Coating agent, film former, stabilizing agent, tablet binder, viscosity increasing agent.

Description: Hydroxy propyl methylcellulose is an odorless and tasteless, white or creamy-white colored fibrous or granular powder.

Acidity / alkalinity: pH 5.5–8.0 for 1% w/w aqueous solution.

Melting point: Browns at 190° – 200°C, chars at 225° - 230°C

Moisture content: HPMC absorbs moisture from atmosphere. The amount of water absorbed depends upon the initial moisture content, temperature and relative humidity of the surrounding air.

Solubility: Soluble in cold water, forming a viscous colloidal solution. Practically insoluble in chloroform, ethanol and ether.

Stability: It is very stable in dry condition from pH 3.0- 11.0. Aqueous solutions are liable to be affected by microorganism. It has attracted significant recent attention for drug delivery application. It remains
glassy in dehydrated state and swollen in presence of water to form an elastic gel. It is categorized under the class ‘hydrogels’. It is soluble in cold water; insoluble in alcohol, ether and chloroform but soluble in mixture methylene chloride and methanol. It is very stable in dry condition from pH 3.0 – 11.0. Aqueous solutions are liable to be affected by microorganism.

**Viscosity:** HPMC K15M-15000cps (2% aqueous solution).
3.4.7 ACCUREL® MP 1000 (Low density polypropylene foam powder)

Structure:

\[
\text{CH}_3
\]

Synonym: Microporous polypropylene homopolymer powder

Appearance: White to off-white powder

Application: Microporous carrier for the production of additive concentrate at temperature up to 80 °C via physical absorption of the additive. This product is most effective for the incorporation of thermally sensitive additive and for those which cannot be processed by conventional extrusion compounding techniques.

Solubility: Practically insoluble in water

Particle size: < 1.5 mm

Melting point: 156 °C

Void content: 73 ± 2 %

Bulk density: 125 ± 20 kg/m³

Toxicological information: LD₅₀: Oral > 2000 mg/kg, Dermal > 2000 mg/kg.
3.4.8 KARAYA GUM\textsuperscript{85}

**Structure:**

\[
\text{Structure Image}
\]

**Synonyms:**

Tragacanth Indian, Gum karaya from sterculia tree

**Definition:**

A dried exudation from the stems and branches of Sterculia urens Roxburgh and other species of Sterculia (Fam. Sterculiaceae) or from Cochlospermum gossypium A.P. De Candolle or other species of Cochlospermum (Fam. Bixaceae); consists mainly of high molecular-weight acetylated polysaccharides, which on hydrolysis yield galactose, rhamnose, and galacturonic acid, together with minor amounts of glucuronic acid

**Description:**

Unground product: occurs in tears of variable size and in broken irregular pieces having a characteristic semi-crystalline appearance; pale yellow to pinkish brown; translucent. Powdered product: pale grey to pinkish brown; a distinctive odour of acetic acid. Items of commerce may contain extraneous materials such as pieces of bark which must be removed

**Functional uses:**

Emulsifier, stabilizer, thickening agent

**Solubility:**

2 g added to 50 ml of water swells to form a granular,
stiff, slightly opalescent gel which is acid to litmus; insoluble in ethanol

**Loss on drying:** Not more than 20% (105 °C, 5 h)

**Microbiological criteria:** Salmonella spp.: Negative in 1 g; E. coli: Negative in 1 g

**Toxicological information:** LD₅₀: Oral - rat - 9.100 mg/kg.
3.5 Review of research papers

Timmermans J and Moes AJ\textsuperscript{86} have carried out a comparative evaluation of gastric transit floating (F) and non-floating (NF) matrix dosage forms and results were found that GRT of the non-floating forms were variable and greatly dependent on their size which are in the order small<medium<large units. Floating strength may vary with time and usually decrease after immersion into the fluid as a result of hydrodynamic equilibrium development.

Fahmy RH \textit{et al.}\textsuperscript{87} have prepared calcium silicate (CaSi)/calcium alginate (Ca-Alg)/hydroxypropyl methylcellulose (HPMC) mucoadhesive-floating beads that provide time and site-specific drug release of alfuzosin hydrochloride (Alf). Beads were prepared by simultaneous internal and external gelation method utilizing $3^2$ factorial design as an experimental design; with two main factors evaluated for their influence on the prepared beads; the concentration of CaSi as floating aid ($X (1)$) and the percentage of HPMC as viscosity enhancer and mucoadhesive polymer ($X (2)$), each of them was tested in three levels. Developed formulations were evaluated for their yield, entrapment efficiency, particle size, surface topography, and buoyancy. Differential scanning calorimetry, Fourier transform infrared spectroscopy, \textit{in vitro} drug release, as well as \textit{in vitro} mucoadhesion using rat stomach mucosal membrane were also conducted. Percentage yield and entrapment efficiency ranged from 57.03 \% to 78.51 \% and from 49.78 \% to 83.26 \%, respectively. Statistical analysis using ANOVA proved that increasing the concentration of either CaSi or HPMC significantly increased the beads yield. Both CaSi and HPMC concentrations were found to significantly affect Alf release from the beads. Additionally, higher CaSi concentration significantly increased the beads diameter while HPMC concentration showed significant positive effect on the mucoadhesive properties of beads. CaSi/Ca-
Alg/HPMC beads represent simple floating-mucoadhesive gastroretentive system that could be useful in chronopharmacotherapy of benign prostatic hyperplasia. 

Pahwa R et al.\textsuperscript{88} have reviewed gastroretentive floating drug delivery systems as efficient approaches for enhancing the bioavailability and controlled delivery of various therapeutic agents. Significant advancements exploiting chitosan have been made worldwide, in order to investigate these systems according to patient requirements, both in terms of therapeutic efficacy as well as patient compliance. Such systems precisely control the release rate of the target drug to a specific site, which facilitates an enormous impact on health care. The authors reviewed different novel strategies for the development of various gastric floating dosage forms utilizing chitosan as a promising excipient. In the review, authors attempted to provide new insights on various physicochemical and biological characteristics of chitosan, along with its potential applications in a wide array of biomedical approaches. Numerous and significant research findings in the vistas of chitosan-based gastroretentive floating drug delivery technology are also discussed. They have considered chitosan has as a unique and efficacious agent possessing a myriad spectrum of desired characteristics. It is emphasized that recent scientific advancements in the use of this excipient as a carrier will yield new generation gastroretentive drug delivery systems, with better pharmacotherapeutic interventions. 

Wasnik S et al.\textsuperscript{89} have developed stomach drug delivery system of azithromycin (AZH) as a model drug for eradication of Helicobacter pylori (H. pylori). Floating microspheres of AZH were prepared by the solvent evaporation method. The prepared microspheres were evaluated for particle size, incorporation efficiency, \textit{in vitro} buoyancy and \textit{in vitro} drug release characteristics. The formulations were prepared at a variable stirring rate (300 to 500 rpm) and
temperature (30-50 °C). Surface morphology characteristics were studied using scanning electron microscopy (SEM). They found mean particle size of the microspheres significantly increased with increasing polymer concentration and was in the range 252.26 ± 6.50 to 380.91 ± 4.59 micron. Angle of repose was between 26.42° to 35.83°. Tapped density ranged between 0.493 to 0.612 g/cm³. The compressibility index of all formulations was found in the range of 12.41 to 17.16%, which was < 20 indicating good flow characteristics. The encapsulation efficiency of the prepared microspheres was in the range of 27.8 ± 4.30 to 66.23 ± 2.08%. The physical state of the drug, before and after formulation was determined by differential scanning calorimetry (DSC). Percentage buoyancy of the microspheres was in the range 45.52 ± 0.69 to 68.71 ± 0.61% for 8 h. In vitro drug release studies were performed in simulated gastrointestinal fluid (SGF), pH 2.0 as dissolution medium (900 mL) for 8 h. Effects of stirring rate during preparation, polymer concentration and temperature on the size of microspheres and drug release were also observed. The results of the present studies indicated that the floating microspheres of AZH were formulated to provide site specific delivery of drug with a view to provide an effective and safe therapy for eradication of H. pylori with a reduced dose and reduced duration of therapy.

Singh B et al. have prepared Lamivudine effervescent floating-bioadhesive hydrophilic matrices using the floating-bioadhesive potential of carbomers and cellulosic polymers. The prepared tablets were evaluated for in vitro drug release, floatation and ex vivo bioadhesive strength. The optimal composition of polymer blends was systematically chosen using central composite design and overlay plots. Pharmacokinetic studies were carried out in rabbits, and various levels of in vitro / in vivo correlation (IVIVC) were established. In vivo gamma scintigraphic studies
were performed in human volunteers using (99m) Tc to evaluate formulation retention in the gastric milieu. From the results, they found that optimized formulation exhibited excellent bioadhesive and floating characteristics besides possessing adequate drug-release control and pharmacokinetic extension of plasma levels. The successful establishment of various levels of IVIVC substantiated the judicious choice of in-vitro dissolution media for simulating the in vivo conditions. In vivo gamma scintigraphic studies ratified the gastroretentive characteristics of the optimized formulation with a retention time of 5h or more.

Thitinan S et al. 91 have developed a novel gastroretentive pulsatile drug delivery platform by combining the advantages of floating dosage forms for the stomach and pulsatile drug delivery systems. A gastric fluid impermeable capsule body was used as a vessel to contain one or more drug layer(s) as well as one or more lag-time controlling layer(s). A controlled amount of air was sealed in the innermost portion of the capsule body to reduce the overall density of the drug delivery platform, enabling gastric floatation. An optimal mass fill inside the gastric fluid impermeable capsule body enabled buoyancy in a vertical orientation to provide a constant surface area for controlled erosion of the lag-time controlling layer. The lag-time controlling layer consisted of a swellable polymer, which rapidly formed a gel to seal the mouth of capsule body and act as a barrier to gastric fluid ingress. By varying the composition of the lag-time controlling layer, it was possible to selectively program the onset of the pulsatile delivery of a drug. They found that the new delivery platform offers a new method of delivery for a variety of suitable drugs targeted in chronopharmaceutical therapy. This strategy could ultimately improve drug efficacy and patient compliance, and reduce harmful side effects by scaling back doses of drug administered.
Guguloth M et al.\textsuperscript{92} have prepared floating tablets by inclusion of citric acid as an acidifier. The prepared tablets were characterized and found to exhibit satisfactory physicochemical characteristics. The effects of citric acid at different concentrations on drug release and floating properties were studied. All the prepared batches showed good \textit{in vitro} buoyancy. From the results, they observed that the tablets remained buoyant for 24 h. The best formulation (F4c), consisting of 1.5\% citric acid and 18\% HPMC K4M, was selected based on \textit{in vitro} characteristics and used \textit{in vivo} radiographic studies by incorporating barium sulphate. From study, they revealed that the tablets remained in the stomach for 205 ± 8.4 min in fasting human volunteers. \textit{In vivo} studies were carried out for the best formulation in eight healthy male human volunteers, and the pharmacokinetic parameters of the developed formulation were compared with marketed conventional (Norbid) tablets. Based on the \textit{in vivo} performance in a two-way, crossover study design in healthy subjects, the developed floating tablets showed superior bioavailability than the Norbid tablets. The increased bioavailability of developed formulation was found to be 16.27\%. The conventional norfloxacin tablets show incomplete drug absorption resulting in lower bioavailability. Norfloxacin is better absorbed in the stomach. The dosage forms that remain in the stomach are referred to as gastroretentive drug delivery systems. Gastroretentive floating tablets of norfloxacin were developed by employing three different polymers, which prolonged the drug release from the dosage forms. Tablet floatation was achieved by an effervescent mechanism. Citric acid at different concentrations was used in formulations to provide an acidic microenvironment. The prepared tablets were characterized for hardness, weight variation, thickness, friability, floating lag time, and dissolution. Around 12 tablet formulations were prepared. The best
For formulation (F4c) was selected based on in vitro characteristics and used in vivo radiographic studies by incorporating barium sulphate as a radio-opaque agent.

Chen YC et al.\textsuperscript{93} have developed a gastroretentive drug delivery systems (DDSs) to prolong the gastric residence time and to increase the overall bioavailability, effervescent multiple-unit floating DDSs (muFDDSs). These systems consist of drug (losartan) and effervescent (sodium bicarbonate) containing pellets coated with a blended polymeric membrane, which was a mixture of gastrointestinal tract (GIT)-soluble and GIT-insoluble polymers. The addition of GIT-soluble polymers, such as hydroxypropyl methylcellulose, polyethylene glycol (PEG) 6000, PEG 600, and Kollicoat\textsuperscript{®} IR, greatly increased the water uptake ability of the GIT-insoluble polymers (Eudragit\textsuperscript{®} NE, RS, and RL; Surelease\textsuperscript{®}; and Kollicoat\textsuperscript{®} SR) and caused them to immediately initiate the effervescent reaction and float, but the hydrated films should also be impermeable to the generated CO\textsubscript{2} to maintain floatation and sufficiently flexible to withstand the pressure of carbon dioxide to avoid rupturing. The study demonstrated that the water uptake ability and mechanical properties could be applied as screening tools during the development of effervescent muFDDSs. The optimized system of SRT(5)P600(5) (i.e., a mixture of 5% Kollicoat\textsuperscript{®} SR and 5% PEG 600) with a 20% coating level began to completely float within 15 mins and maintained its buoyancy over a period of 12 h with a sustained-release effect.

Alabazi MY and Elzein H.\textsuperscript{94} have formulated and evaluated a floating tablet formulation of dexchlorpheniramine maleate (DCPM) using full factorial design. A 32 factorial design (nine runs) was utilized to optimize the formulation, the contents of hydroxypropyl methyl cellulose (HPMC) (X1) and Carbopol 934P (X2) being taken as independent variables and t50\% (Y1), % drug release after 6 h (Y2), % drug...
release after 12 h (Y3), and floating lag time (FLT) (Y4) as the dependent variables. The tablets showed 99.26 to 102.47 % of the labeled amount of dexchlorpheniramine maleate indicating uniformity of content. The tablets containing DCPM released 72.28 to 99.46% of drug at the end of 12 h by an in vitro release study. They also examined hardness, friability, floating capacity, weight variation and content uniformity. In addition, the tablets were evaluated for in vitro release characteristics for 24 h. The optimal batch (F9) was selected by regression analysis and followed Higuchi kinetics. The drug release mechanism was found to be a complex mixture of diffusion, swelling and erosion. The floating tablets of DCPM developed may be used clinically for prolonged drug release for at least 16 hrs, thereby improving bioavailability and patient compliance.

Ming-TS et al. have investigated the effect of different types of swellable polymers and addition of an ionic complex of polyelectrolytes with regard to the swelling behavior. In this study four different grades of HEC 250 examined (H, HX, HHX and M), HEC 250HHX exhibited the greatest swelling index. Lower molecular weight PEO, varying from Mw 100K to Mw 900K, exhibited a low swelling index and dissolved almost completely after immersion for 2 to 4 h in the medium. However, the swelling ability of PEO (Mw 8,000K) was found to be sustainable to an extent greater than that for HEC 250HHX. Combination of a lower molecular weight PEO (Mw 900K) with HEC 250HHX resulted in a lower swelling index than that for HEC 250HHX alone, whereas a high molecular weight PEO (Mw 8,000K) incorporated with HEC 250HHX resulted in a higher swelling rate. However, the addition of an ionic complex of polyelectrolytes produced only a slight improvement in swelling index. HEC exhibited a suitable swelling index apart from the higher molecular weight PEO (Mw 8,000K). The addition of 50 % carbopol in HEC would
be preferable to increase the swelling of the tablet. The swelling index obtained from
the formulation with 10% to 50% of chitosan showed a good swelling index in the
pH 1.2 media, but the degree of swelling size was not high enough as required.

Sreenivasa RN et al.\textsuperscript{96} have prepared captopril matrix tablets by direct
compression technique using different polymers and natural gums. Formulations were
designed by varying the concentrations of karaya gum, gellan gum, pullulan gum &
HPMC. The formulations containing pullulan gum and gum karaya (3:1) as polymer
matrix exhibited better release of drug. The formulation with gum karaya and pullulan
gum in the ratio (1:1) took 3 mins to become buoyant and showed better floating
property along with controlled drug release in comparison to all other formulations.

Elmowafy EM et al.\textsuperscript{97} have formulated the single-unit matrix tablets using
polysaccharides (k- carrageenan, gellan gum, xyloglucan and pectin) and blends of
polysaccharides (k- carrageenan and gellan gum) and cellulose ethers
(hydroxylpropylmethyl cellulose, hydroxylpropyl cellulose, sodium carboxy methyl
cellulose) by direct compression technique. The floating approach was achieved by
the use of the low density polypropylene foam powder.

Zhang ZH et al.\textsuperscript{98} have prepared floating calcium alginate beads of berberine
for targeting the gastric mucosa and prolonging their gastric residence time. The
floating beads were prepared by suspending octodecanol and berberine in sodium
alginate (SA) solution. The suspension was then dripped into a solution of calcium
chloride. The hydrophobic and low-density octodecanol enhanced the sustained-
release properties and floating ability of the beads. The bead formulation was
optimized for different weight ratios of octodecanol and SA and evaluated in terms of
diameter, floating ability and drug loading, entrapment and release. \textit{In vitro} release
studies showed that the floating and sustained release time was effectively increased
in gastric media by addition of octodecanol. *In vivo* studies with rats showed that a significant increase in gastric residence time of beads had been achieved.

Singh V *et al.* have developed hollow microspheres as a new dosage form of floating drug delivery system with prolonged stomach retention time. Hollow microspheres containing ranitidine hydrochloride were prepared by solvent evaporation method using Eudragit RLPO dissolved in a mixture of dichloromethane and ethanol. The maximum yield and drug loading amount of hollow microspheres were 88.45 % and 80 ± 4.0 %, respectively. The *in vitro* release profiles showed that the drug release rate decreased with increasing viscosity of Eudragit RLPO, while diameter of hollow microspheres increased with the increase of drug polymer weight ratio. Hollow microspheres could prolong drug release time (approximately 24 h) and float over stimulate gastric fluid for more than 12 h. These results demonstrated that ranitidine HCl hollow microspheres were capable of sustained delivery of the drug for longer period with increased bioavailability.

Shukla D *et al.* have designed a multilayered dosage form of doxofylline, using pastillation technology, for the chronotherapeutic management of nocturnal asthma. Pastilles consisting of the drug, polyethylene glycol and colloidal silicon dioxide were generated using an in-house laboratory-scale pastillation device. The pastilles were further coated with enteric polymers and a floating layer, using conventional coater. The pastilles were subjected to physicochemical analysis, morphological characterization, *in vitro* drug release studies and *in vivo* pharmacokinetic studies in rats. It was observed that colloidal silicon dioxide was instrumental in improving the contact angle of the pastilles. The uncoated pastilles released the drug immediately, while the enteric-coated (10 % w/w) pastilles were found to have sufficient acid resistance when the coat is applied with 5 % (v/v)
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triethyl citrate as plasticizer. The in vivo blood serum profile indicated that the pastilles coated with the enteric coat and the additional floating coat were effective in significantly delaying the in vivo drug release required for the chronotherapeutic treatment of nocturnal asthma. The present work opens a new alternative to the conventional tablet or capsule dosage form for the development of both immediate-release and modified-release drug delivery systems.

Amrutkar PP et al.\textsuperscript{101} have developed multiparticulate floating drug delivery system based on gas generation technique to prolong the gastric residence time and to increase the overall bioavailability. Zolpidem tartarate is a non-benzodiazepine, sedative-hypnotic, which finds its major use in various types of insomnia. Modified release dosage form of zolpidem tartarate adapted to release over a predetermined time period, according to biphasic profile of dissolution, where the first phase is immediate release phase for inducing the sleep and the second phase is modified release phase for maintaining the sleep up to 10 h. The system consists of zolpidem tartarate layered pellets coated with effervescent layer and polymeric membrane. The floating ability and in vitro drug release of the system were dependent on amount of the effervescent agent (sodium bicarbonate) layered onto the drug layered pellets, and coating level of the polymeric membrane (Eudragit\textregistered NE 30D). The system could float completely within 5 min and maintain the floating over a period of 10 h. The multiparticulate floating delivery system of zolpidem tartarate with rapid floating and modified drug release was obtained.

Khan ZA et al.\textsuperscript{102} have investigated the feasibility of the design of a novel floating elementary osmotic pump tablet (FEOPT) to prolong the gastric residence of a highly water-soluble drug. Diethylcarbamazine citrate (DEC) was chosen as a model drug. The FEOPT consisted of an osmotic core (DEC, mannitol, and hydrophilic
polymers) coated with a semipermeable layer (cellulose acetate) and a gas-generating gelling layer (sodium bicarbonate, hydrophilic polymers) followed by a polymeric film (Eudragit RL 30D). The effect of formulation variables such as concentration of polymers, types of diluent, and coat thickness of semipermeable membrane was evaluated in terms of physical parameters, floating lag time, duration of floatation, and *in vitro* drug release. The Fourier transform infrared and X-ray diffraction analysis were carried out to study the physicochemical changes in the drug excipients powder blend. The integrity of the orifice and polymeric film layer was confirmed from scanning electron microscopy image. All the developed FEOPT showed floating lag time of less than 8 mins and floating duration of 24 h. A zero-order drug release could be attained for DEC. The formulations were found to be stable up to 3 months of stability testing at 40 °C/75 % relative humidity.

Khan FN and Dehghan MH have prepared stabilized gastro-retentive floating tablets of atorvastatin calcium to enhance bioavailability. Oral bioavailability of atorvastatin calcium (ATC) is very low (only 14%) due to instability and incomplete intestinal absorption and/or extensive gut wall extraction. When ATC is packed in the form of tablets, powders, etc., it gets destabilized as it is exposed to the oxidative environment, which is usually present during the production process, the storage of the substance, and the pharmaceutical formulation. Water sorption and viscosity measurement studies are performed to get the best polymer matrix for gastro-retention. A $3^2$ factorial design used to prepare optimized formulation of ATC. The selected excipients such as docusate sodium enhanced the stability and solubility of ATC in gastric media and tablet dosage form. The best formulation (F4) consisting of hypromellose, sodium bicarbonate, polyethylene oxide, docusate sodium, mannitol, crosscarmellose sodium, and magnesium stearate, gave floating lag time of 56±4.16 s.
and good matrix integrity with \textit{in vitro} dissolution of 98.2\% in 12 h. After stability studies, no significant change was observed in solubility, floating lag time, total floating duration, matrix integrity and sustained drug release rates, as confirmed by DSC and powder X-ray diffraction studies. \textit{In vivo} pharmacokinetic study performed in rabbits revealed enhanced bioavailability of F4 floating tablets, about 1.6 times compared with that of the conventional tablet (Storvas\textsuperscript{®} 80 mg tablet). These results suggest that the gastric resident formulation is a promising approach for the oral delivery of ATC for improving bioavailability.

The following chapter gives the materials and methods used to obtain inferences.