ABSTRACT
The oral route of drug administration is the most convenient and commonly used method of drug delivery. Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric contents the drug is released slowly at a desired rate from the system. After the release of drug, residual system is emptied from the stomach. This result in increase in the gastric residence time and a better control of fluctuation in plasma drug concentration. Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug- delivery systems for more than 12 hours. Several approaches are utilized in prolongation of the gastro retention time. In this review, the current technological developments of FDDS and Pharmaceutical basis of their design, advantages and future potential are discussed. In addition marketed products have been discussed.

KEY WORDS: Floating drug delivery systems, its classification and application, Gastric residence time (GRT), Absorption window.

INTRODUCTION
A drug delivery system is a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of
the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The oral route of drug administration has been the one used most for both conventional as well as novel drug delivery. The reasons for this preference are obvious because of ease of administration and widespread acceptance by patient. [1] The basic goal of drug therapy is to provide a therapeutic amount of drug to proper site in the body to promptly achieve and then maintain desired drug concentration. Conventional drug therapy results in see-saw fluctuation of drug concentration in systemic circulation causing either lethal effect or no therapeutic action. [2] Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. The de novo design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability (BA) of drugs. [3]

Controlled release systems provide a release profile independent of external environment and predominantly controlled by the design of the system. Moreover, the conventional dosage forms in place of delivering minimal effective concentration of drug at required site or organ tends to get into general circulation at higher concentration leading to untoward side effects. Therefore many pharmaceutical industries and research institutes oriented their effects to develop programmed unattended delivery of drug at a rate and for a period to meet and achieve the therapeutic need.

A major constraint in oral Controlled Release Drug Delivery System is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed in a particular portion of gastrointestinal tract only or are absorbed to a different extent in various segments of gastrointestinal tract. Such drugs are said to have an “absorption window”. Thus, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically decreases the time available for drug absorption after it and limits the success of delivery system. [4, 5]

Gastro Retentive Dosage Forms (GRDF) can remain in gastric region for several hours and hence significantly prolong the gastric residence time of drug what are less soluble in high pH environment. It has application also for local drug delivery to the stomach and proximal
small intestine. Gastro retentive drug delivery system helps to provide better availability of new products with therapeutics possibilities and substantial benefits for patients. [6]

1.1 Stomach
The stomach is J- shaped enlargement of the GI tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondriac regions of the abdomen.

1.1.1 Physiology of Stomach

![Figure no. 1: Anatomy of Stomach](image)

The stomach is ‘a gland with cavity’, extending from its junction with lower end of the oesophagus (cardia) to its junction with the duodenum (pylorus). The lesser curvature is inner concavity on the right, while the greater curvature is the outer convexity on the left side of the stomach. [7] The stomach has 5 anatomical regions

1. Cardia - the oesophago-gastric junction.
2. Fundus - the portion above the horizontal line drawn across the oesophago gastric junction.
3. Body - the middle portion of the stomach between the fundus and the pyloric antrum.
4. Pyloric antrum - the distal third of the stomach.
5. Pylorus - the junction of distal end of the stomach with the duodenum, which has powerful spincture muscle.

The mucosal folds in the region of the body and the fundus are loose (rugae), while the antral mucosa is somewhat flattened. Gastric canal is the relatively fixed portion of the pyloric antrum and the adjoining lesser curvature; it is the site for numerous pathological changes such as gastritis, peptic ulcer and gastric carcinoma. [7, 8]
1.1.2 HISTOLOGY OF STOMACH

Figure no. 2: Cells of the gastric mucous membrane and their secretions

The stomach consists of four layers

1. **Serosa** - It is divided from the peritoneum which is deficient in the region of lesser and greater curvatures.

2. **Muscularis** - Consist of three layers of smooth muscle fibers – the outer longitudinal, the middle circular and inner oblique. The pyloric spincture is the thickened circular muscle layer at the gastroduodenal junction.

3. **Submucosa** - It is a layer of loose fibroconnective tissue binding the mucosa to the muscularis loosely.

4. **Mucosa** - It consists of two layers- superficial and deep. Between the two layers is the lamina propria.

The secretory products of the gastric mucosa are the gastric juice. Gastric juice consists of hydrochloric acid, pepsin, mucin and electrolytes like Na⁺, K⁺, HCO₃⁻ and Cl⁻. Hydrochloric acid is produced by the parietal (Oxyntic) cells by the interaction of Cl⁻ ions of the arterial blood with water and carbon dioxide in the presence of the enzyme, carbonic anhydrase. Physiologically, the gastric secretions are stimulated by the food itself. [⁹] The distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states. The GI tract is always in a state of continuous motility. There are two modes of motility pattern, digestive mode and interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is further divided into four phases. [¹⁰, ¹¹]
1. Phase 1-(Basic phase) - lasts from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase) - lasts for 20-40 minutes with intermittent action potential and contractions, which gradually increases in intensity and frequency as the phase progresses.
3. Phase 3-(Burst phase) - lasts for 10-20 minutes which includes intense contractions and peristaltic waves involving both the proximal and distal gastric regions (housekeeper waves). In this phase, indigestible solids are removed from the fasted stomach.
4. Phase 4 - lasts for 0-5 minutes is a transition period of decreasing activity until the next cycle begins.\[12\]

The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive Migration Myoelectric Complex (MMC). It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food.\[13\]

1.2 FACTORS AFFECTING GASTRIC RETENTION

1. Density- Density determines the location of the system in the stomach. Systems with density lower than gastric contents can float on the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus.\[14\]

2. Size- The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the
smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine \[15,16\]

3. **Shape of dosage form** - Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 KSI are reported to have better GRT ≈ 90% to 100% retention at 24 hours compared with other shapes. \[17\]

4. **Fed or unfed state, under fasting conditions** - 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. \[18-20\]

5. **Nature, Caloric Content and Frequency of Feed** - 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. GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats. 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. \[21-23\]

6. **Effect of Gender, Age and Posture** - 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. Elderly people, especially those over 70, have a significantly longer GRT. \[24\]

1.3 **MECHANISM OF FLOATING SYSTEM**

The system is floating on the gastric contents [given in the Figure 4 (a)], the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight
has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side [Figure 4(b)]. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. [25]

\[
F = F_{\text{buoyancy}} - F_{\text{gravity}} = (D_f - D_s) \cdot g \cdot v
\]

\[\text{Where,}\]
\[F = \text{total vertical force}, \quad D_f = \text{fluid density},\]
\[D_s = \text{object density}, \quad v = \text{volume},\]
\[g = \text{acceleration due to gravity} \quad \text{GF= gastric fluid.}\]

\[\text{Figure no.4: Mechanism of floating system}\]

**Approaches to Design Floating Dosage Forms**

Different approaches designed to developed gastroretentive drug delivery system as shown in figure no. 5. The concept of FDDS was first described in 1968, a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medicinal pills. Such a difficulty could be overcome by providing pill having density of less than 1.0 g/cm\(^3\). So that pill will float on water surface. Since several approaches have been used to developed an ideal floating drug delivery system. [26]
1.4.1 Floating Drug Delivery Systems (FDDS)

Floating drug delivery systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, effervescent systems and non-effervescent as shown.\textsuperscript{[27]}

\textbf{A. Effervescent Systems (Gas-generating Systems)}

Effervescent systems include use of gas generating agents, carbonates or any other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO\textsubscript{2}) gas, are usually incorporated in the dosage form, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature. The most commonly used excipients utilized in development of effervescent FDDS are swellable polymer such as Hydroxypropyl methylcellulose (HPMC),\textsuperscript{[28]} Polysaccharides, e.g. Chitosan, Sodium alginates. The matrices are so prepared that upon arrival in the stomach CO\textsubscript{2} is liberated by the acidity of the gastric contents and is trapped in the gellified hydrocolloid, which create an upward motion of the dosage form and maintains its buoyancy. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable,
allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.\textsuperscript{[29]} These effervescent systems further classified into two types.\textsuperscript{[30]}

I. Gas–generating systems
II. Volatile Liquid/Vacuum Containing Systems.

I. Gas – Generating Systems:

1. Intra Gastric Single and double Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration. Intra Gastric Bilayer Floating Tablets are also compressed tablet containing two layer i.e. i. Immediate release layer and ii. Sustained release layer.

2. Multiple Unit Floating Dosage Systems

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. The main drawback of such system is “all or none” phenomenon. In such cases there is a danger of passing of the dosage form to intestinal part.\textsuperscript{[31]}

A floating system made of multiple unit forms has relative merits compared to single unit forms.

1. The gastric emptying of a multiparticulate floating system would occur in a consistent manner with small individual variations.
2. Each dose consists of many subunits; the risk of dose dumping is reduced.
3. Single unit dosage forms have the disadvantage of being an all-or-none emptying form. The whole dose is lost if the dosage form is not able to retain itself in the desired place. This problem is not seen with multiparticulate dosage forms.
4. Multiparticulate systems distribute in the whole of gastrointestinal tract fluids. This avoids localized action that can be harmful, as in case of single-unit dosage forms.\textsuperscript{[32]}
A new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills shown in figure no.6. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub layers to avoid direct contact between the 2 agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml. [33]

Figure No. 6: Floating Pill (a) Penetration of water into effervescent layer leads to CO2 generation, and makes the system float (b).

II. Volatile Liquid / Vacuum Containing Systems
1. Intragastric Floating Gastrointestinal Drug Delivery System:
These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment, as shown in Figure no. 7

Figure no. 7: Intra Gastric Floating Gastrointestinal Drug Delivery Device
2. 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, then encapsulated in a gelatin capsule as shown in figure no.8. 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 continuously released from the reservoir into the gastric fluid.

![Figure no. 8: Inflatable Gastrointestinal Delivery Systems](image)

3. Osmotic Regulated System

It is comprised of an osmotic pressure controlled drug delivery device and inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric somatically 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 Osmotically controlled drug delivery device consists of two components drug reservoir compartment and osmotically active compartment as shown in figure no. 9.

![Figure no.9: The Osmotically controlled drug delivery device](image)
B. NON EFFERVESCENT SYSTEM

The non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate polystyrene as well as bioadhesive polymer such as chitosan and Carbopol. One of the approaches to the formulation of such floating dosage form involves intimate mixing of drug with a gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure act as reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. When such dosage form comes in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated, as a result, the drug dissolve in and diffuse out with the diffusing solvent, creating a ‘receding boundary’ within the gel structure. [34]

1. Single Layer Floating Tablets

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

2. Bilayer Floating Tablets

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

3. Alginate Beads

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over
12 hours. When compared with solid beads, which gave a short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 hours.

4. Hollow Microspheres
Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

1.4.2. Mucoadhesive or bioadhesive system
The potential of the drug delivery system to localize a drug at the site of absorption for an extended period of time and to promote intimate contact between the formulation and the underlying absorbing tissue has great appeal to both local and systemic effects. Good defined Bioadhesion as the state in which two materials, at least one of which being of a biological nature, are held together for an extended period of time by interfacial forces. The adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion. [35]

The component of the mucus involved in interactions is the mucin molecules. These are glycoproteins of high molecular weight present in the concentration of 0.5-5 %, which are also responsible for the viscoelastic properties of the mucus. The mucin is negatively charged at physiological pH because of sialic acid residues in the oligosaccharide units. [36] On a molecular level, mucoadhesion can be explained based on molecular interactions. Hydrogen bonds are often considered to be the most important types of the secondary chemical bonds that can be formed in the mucoadhesion process. For adhesion to occur, molecules must bond across the interface of mucus.

1.4.3. High-Density Systems [37]
These systems with a density of about 3 g/cm³ are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm³ acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material
such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Figure no. 10.

Figure No.10: Schematic localization of an intragastric floating system and a high density system in the stomach.

1.4.4. Swelling and Expanding 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 gastroretentive form and a final small form enabling evacuation following drug release.[38] Unfoldable and swellable systems have been investigated. Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends in the stomach. Different geometric forms can be proposed by scientist in the form of tetrahedron,[39] ring, [40] or planar membrane [4-lobed, disc or 4-limbed cross form] of bioerodible polymer compressed within a capsule as shown in figure no. 11

Figure no. 11: Different geometric forms of unfoldable systems
These dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.

1.4.5. Raft forming system

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 (as shown in Figure no.12) on contact with gastric fluid. [41] 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 gastroesophageal reflux treatment. [42, 43] E.g. Liquid Gaviscon® (GlaxoSmithKline).

![Figure No. 12: Schematic illustration of the barrier formed by a raft-forming system](image)

1.4.6. Ion Exchange Resin

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of CO₂. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate takes place. [44]

![Figure no.13: working of effervescent floating drug delivery system based on ion exchange resin](image)
As a result of this reaction CO₂ was released and trapped in the membrane thereby carrying beads toward the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads, which will sink quickly. Working of effervescent floating drug delivery system based on ion exchange resin shown in figure no.13

1.5 NEED FOR GASTRO RETENTION [45]

1. Drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of GIT.
2. Drugs that are absorbed due to variable gastric emptying time.
3. Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
4. Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections. [46,47]
5. Prolonging the gastric residence time by retaining dosage form in stomach and upper part of GI tract
6. Give sufficient time for drug to be release from dosage form
7. Give sufficient time for drug to be absorbed through GI tract
8. Protecting the degradation of normal GI flora by restricting the dosage form in stomach and upper part of GI tract

1.6 ADVANTAGES OF GASTRORETENTIVE DELIVERY SYSTEMS [48]

1. Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide
2. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. β-lactam antibiotics (penicillins and cephalosporins)
3. Retention of drug delivery systems in the stomach prolongs overall.
4. Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacinc. [56]

1.7 LIMITATIONS OF THE TECHNIQUES OF GASTRORETENTION [49]

More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.

1. 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.
2. Bioadhesion in the acidic environment and high turnover. More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.
3. Not suitable for drugs that may cause gastric lesions e.g. 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.
4. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably easy and logical approaches in development of gastroretentive dosage forms. Hence for the present study, formulation of GRDFs is prepared by floating drug delivery system. In all the above systems the physical integrity of the system is very important and is primary requirement for the success of these systems.

1.8. PREPARATION TECHNIQUES OF MICROCARRIERS \(^{[50]}\)
Preparation of microcarriers should satisfy certain criteria:
1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

1.8.1. Single emulsion technique
The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, di acid chloride etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation.
1.8.2. Double emulsion technique
Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers.

1.8.3. Polymerization techniques
The polymerization techniques conventionally used for the preparation of the microspheres are mainly classified as:
I. Normal polymerization
II. Interfacial polymerization. Both are carried out in liquid phase.

1. Normal polymerization
It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres.

2. Interfacial polymerization
It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

1.8.4. Phase separation coacervation technique
This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervates. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. [51]

1.8.5. Spray drying and spray congealing
These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively.
1.8.6. Solvent extraction
Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer. \[^{52}\]

1.8.7. Ionic gelation \[^{53}\]
An emulsification/internal gelation method is proposed for producing small diameter alginate beads in large quantity. The difficulty in using dispersion/external gelation techniques with ionic polysaccharide is that the calcium source (CaCl\(_2\)) is insoluble in the oil phase. As an alternative, internal gelation of the dispersed alginate droplets may be initiated by releasing Ca\(^{2+}\) from an insoluble complex (calcium salt) through pH reduction. By controlling the conditions under which the water-in oil dispersion is produced, the bead size can be controlled from a few microns to millimeters in diameter in some cases gas forming agents were also used. Generally natural polymers which are easily biodegradable are act as carriers for drug molecules at the targeted site. For that reason we also called beads as microcarriers if their size is in micron. Sodium alginate is widely used natural polymer because it is stable in acidic medium and freely soluble in alkaline medium. \[^{54}\] Hence sodium alginate widely used in gastroretentive dosage forms.

![Figure no.14: Schematic diagram of preparation beads.](image-url)
Table No. 2. Marketed Products of FDDS [55]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>BRAND NAME</th>
<th>DRUG (DOSE)</th>
<th>COMPANY, COUNTRY</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Modapar®</td>
<td>Levodopa (100 mg), Benserazide (25 mg)</td>
<td>Roche Products, USA</td>
<td>Floating CR capsule</td>
</tr>
<tr>
<td>2.</td>
<td>Valrelease®</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann-LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>3.</td>
<td>Liquid Gavison®</td>
<td>Al hydroxide (95 mg), Mg carbonate (358 mg)</td>
<td>Glaxo Smith Kline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>4.</td>
<td>Topalkan®</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid alginate preparation</td>
</tr>
<tr>
<td>5.</td>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>6.</td>
<td>Cifran OD®</td>
<td>Ciprofloxacin (1 gm)</td>
<td>Ranbaxy, India</td>
<td>Gas-generating floating form</td>
</tr>
<tr>
<td>7.</td>
<td>Cytotec®</td>
<td>Misoprostal (100 mcg/200 mcg)</td>
<td>Pharmacia, USA</td>
<td>Bilayer floating capsule</td>
</tr>
</tbody>
</table>

Table No. 3. Various Types of Floating Drug Delivery Systems [56]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>DOSAGE FORM</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Microspheres</td>
<td>Aspirin, Grisiofulvin, p-nitroaniline, Ibuprofen, Terfinadine, Tranilast.</td>
</tr>
<tr>
<td>2</td>
<td>Granules</td>
<td>Diclofenac sodium, Indomethacin, Prednisolone</td>
</tr>
<tr>
<td>3</td>
<td>Films</td>
<td>Cinnarizine</td>
</tr>
<tr>
<td>4</td>
<td>Powders</td>
<td>Several basic drugs</td>
</tr>
<tr>
<td>5</td>
<td>Capsules</td>
<td>Chlordiazepoxide HCl, Diazepam, Furosemide, 1-Dopa, Benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid</td>
</tr>
<tr>
<td>6</td>
<td>Tablets/pills</td>
<td>Acetaminophen, Acetylsalisylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnazirine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, p-aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5′-phosphate, Sotalol, Theophylline, Verapamil HCl</td>
</tr>
</tbody>
</table>

REFERENCES
2. Rawlines EA. Bentley’s textbook of pharmaceutics, Bailey Tindal publication; 1992,8.
42. Caldwell LJ, Gardner CR, Cargill RC, Higuchi T. Drug delivery device which can be retained in the stomach for a controlled period of time, US patent 4758436, July 19, 1988.(expandable system)