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A Review on Gastroretentive Floating Drug Delivery System

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ABSTRACT

One of the most feasible approaches for achieving prolonged and predictable drug delivery profiles in gastrointestinal tract is to control the Gastric Residence Time (GRT) using gastro retentive dosage forms (GRDFs) that offer a new and better option for drug therapy. Oral delivery of drugs is by far the most preferable route of drug delivery. Oral-rate controlled drug delivery systems have an important area among novel drug delivery system. But these oral sustained release drug delivery systems suffer greatly due to their short gastric residence time/ gastric emptying time. Whereas prolonged gastric residence increases duration of drug release, reduces drug waste, and improves drug solubility in gastric pH. In order to overcome these drawbacks novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time were discovered and they successfully exists today as gastro retentive dosage forms, in academic and industrial research groups. The objective of our review is to compile the recent advancements and literatures regarding the novel dosage form i.e. the floating drug delivery systems (FDDS) that can be retained in the stomach for a prolonged period of time and gives therapeutic action in a predetermined manner. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail.

Keywords: Floating drug delivery, Buoyancy, Oral drug delivery, Gastro retention, Effervescent, Gastric emptying time etc.

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INTRODUCTION

Davis, in 1968 firstly described the concept of floating drug delivery systems (FDDS) after experiencing gagging or chocking by some persons, while swallowing medicinal pills. The researchers suggested that such difficulty could be overcome by providing pills having a density less than 1.0 gm/ ml, so that pill will float on water surface. The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve and maintain therapeutic concentration within range and to show pharmacological action with minimum incidence of adverse effects. [1, 2] To achieve this goal one should maintain dosing frequency and suitable route of administration. Various routes that are used these days include oral, parenteral, topical, nasal, rectal, vaginal, ocular etc. Out of these routes, oral route of drug delivery is considered as the most favored route of drug delivery, because of ease of administration, more flexibility in designing, ease of production and low cost. Gastro retentive drug delivery system belongs to oral controlled drug delivery system group that are capable to retain in the stomach by passing the gastric transit. These dosage forms are also defined as floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug. The real challenge in the development of a gastro retentive drug delivery system is not just sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper part of the GIT until all the drug is completely released. This can be accomplished by floating drug delivery system which helps to retain dosage form in the stomach and releases the drug in controlled manner for longer period of time. GRDDS is retained for longer periods of time in the stomach e.g. hydrophilic matrix tablets, floating capsules and bio-adhesive tablet. Thus the longer period of gastric retention as compared to other oral controlled drug delivery system can be attributed. The floating results in release of the drug in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drugs by changing the concentrations of polymers. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. [3, 4, 5]

Mechanistic Aspects of Floating Drug Delivery System

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co administration of gastric emptying delaying drugs. Among these, the floating dosage forms have been used most commonly. However, most of these approaches are influenced by a number of factors that affect their efficacy as a gastro retentive system. [6, 7, 8]

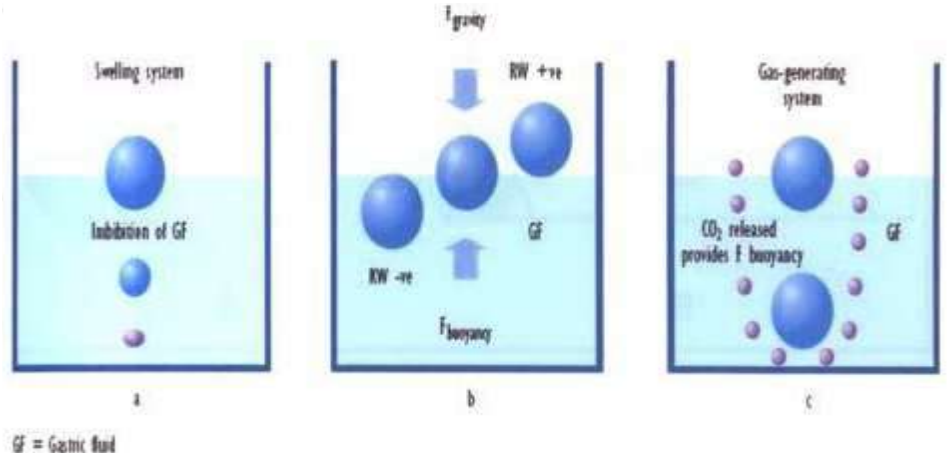

Figure 1: Mechanism of floating system

Anatomy of Stomach:

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing. Anatomically the stomach is divided into 3 regions: fundus, body and antrum (pylorus). [9, 10, 11]

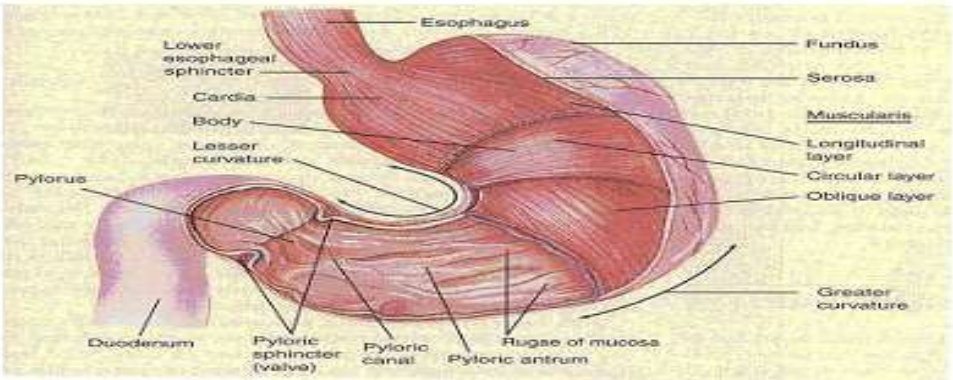

Figure 2: Diagram of human stomach

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. It has been reported that the mean value of pH in fasted healthy subjects is 1.1± 0.15. But when food comes into the stomach, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basal gastric secretion in women is slightly lower than that of men. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases:-

1. Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.

2. Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

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

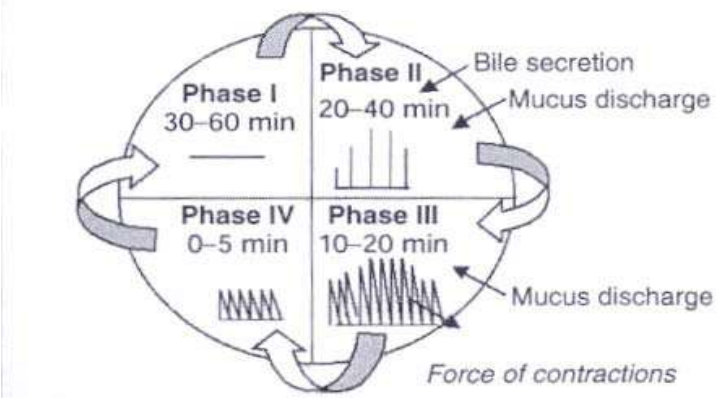

Figure 3: Motility pattern in GIT

Drugs those are suitable for gastro retentive drug delivery systems

1. Drugs acting locally in the stomach. E.g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach. E.g. Amoxicillin
3. Drugs that is poorly soluble at alkaline pH. E.g. Furosemide, Diazepam, Verapamil, etc.
4. Drugs with a narrow window of absorption. E.g. Cyclosporine, Methotrexate, Levodopa, etc.
5. Drugs rapidly absorbed from the GI tract and E.g. Metronidazole, tetracycline
6. Drugs that degrade in the colon. E.g. Ranitidine, Metformin HCl.

7. Drugs that disturb normal colonic microbes. E.g. antibiotics against Helicobacter pylori.

Drugs those are Unsuitable for gastro retentive drug delivery systems

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

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

3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc. [12, 13]

After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. 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. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

FACTORS AFFECTING FLOATING DRUG DELIVERY SYSTEM

Density:

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size and Shape:

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilo pond per square inch (KSI) are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes.

Fed or Unfed State:

Under fasting conditions the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (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 the meal:

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

Caloric Content:

GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed:

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender:

Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age:

Elderly people, especially those over 70 years have a significantly longer GRT.

Posture:

GRT can very between supine and upright ambulatory states of the patients.

Concomitant drug administration:

Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

Biological factors:

Diabetes and Crohn's disease. [14,15]

Requirements for Gastric Retention

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease. [16]

Types of Gastroretentive Dosage Forms

A. Floating drug delivery systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system [17, 18]

(a) Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after

oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier18. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types: [19, 20, 21]

(i) Colloidal gel barrier system

Sheth and Tossounian first designated this 'hydro dynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloid gel barrier around its surface. [22, 23]

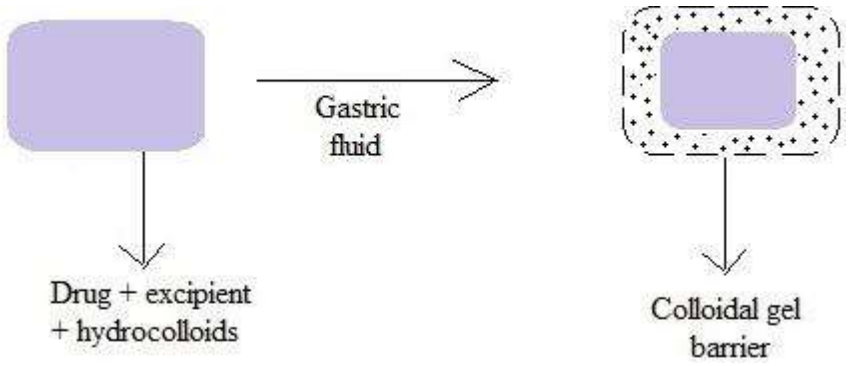

Figure 4: Figure showing formation of colloidal gel barrier

(ii) Micro porous compartment system

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls20. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption. [24, 25]

(iii) Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at 40^{o}C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours. [26]

(iv) Hollow microspheres / Micro balloons

Hollow microspheres loaded with drug in their outer polymer shelf 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 solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h. [27, 28]

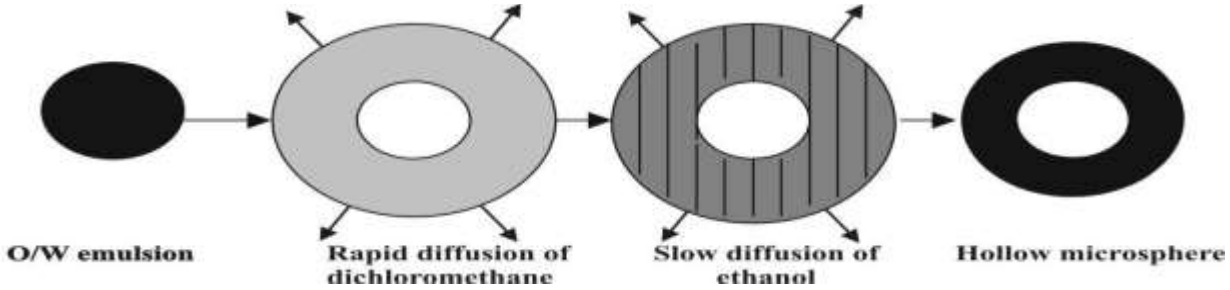

Figure 5: Formulation of floating microspheres

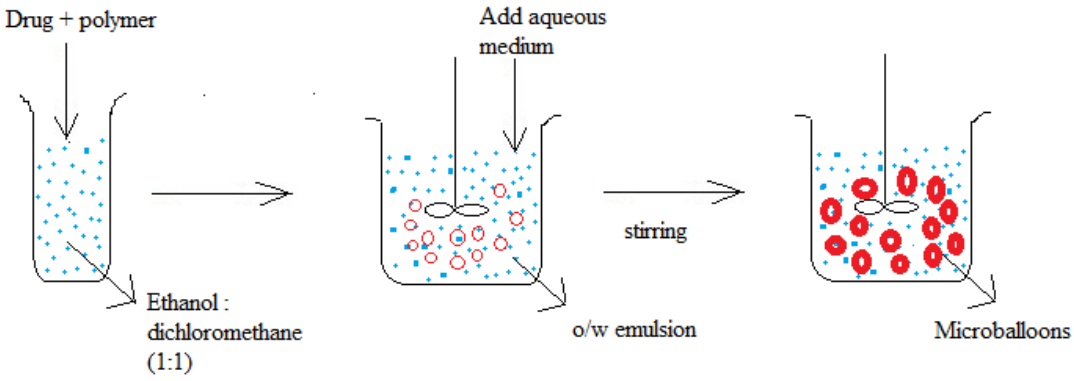

Figure 6: Flowchart showing steps involved in preparation of micro balloons

(b) Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is

released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion exchange resin technology. [29, 30, 31]

Figure 7: Effervescent (gas generating) systems

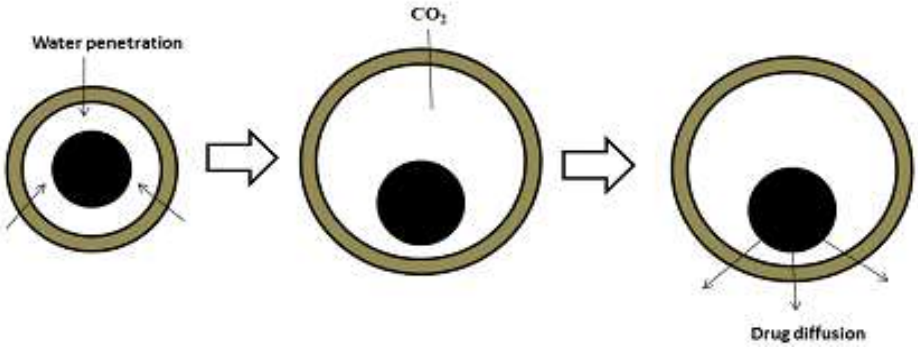

Figure 8: Drug release from effervescent (gas generating) systems.

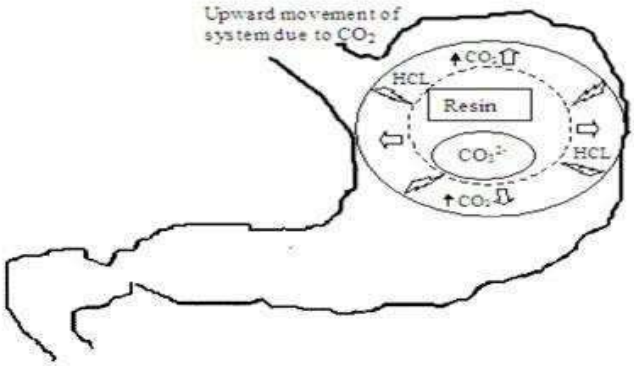

Figure 9: Pictorial presentation of working of effervescent floating drug delivery system

B. **Expandable systems** Expandable gastro retentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that

prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties. [32,33,34,35]

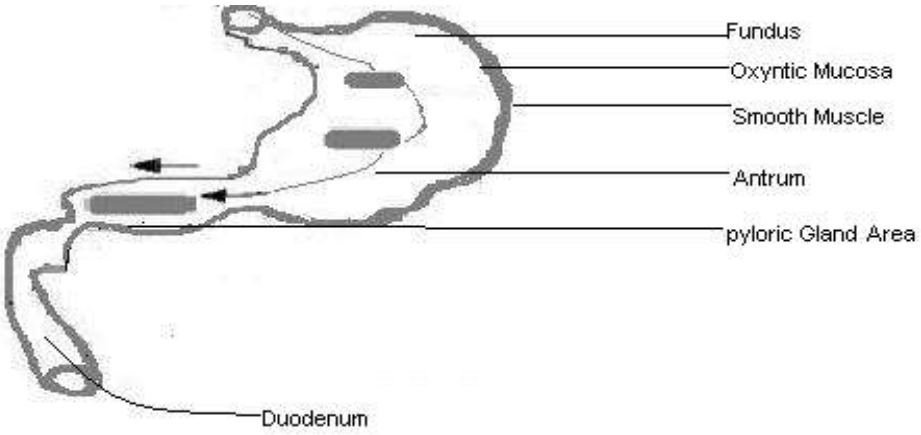

Figure 10: Swelling and Expanding Systems

C. Bio/Muco-adhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric muco adhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of muco adhesion as a gastro retentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan. [36, 37]

D. High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium

dioxide and iron powder. [38] These materials increase density by up to 1.5–2.4g/cm^3. Some FDDS products available in the market are listed in Table 1.

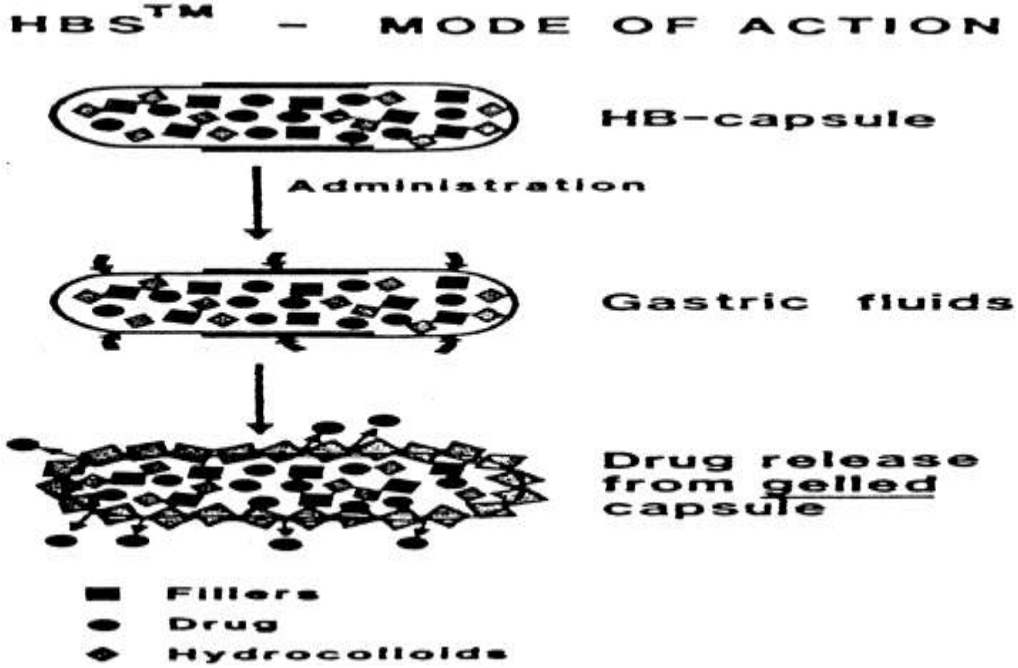

Figure 11: working principle of the hydrodynamically balanced system within the gel structure

Table 1: Marketed Products of FDDS[39]

Dosage Form	Drugs	Brand Name	Company ,Country
Floating Controlled Release Capsule	Levodopa,Benserazide	MODAPAR	Roche Products, USA
Floating Capsule	Diazepam	VALRELEASE	Hoffmann-LaRoche,USA
Effervescent Floating Liquid Alginate Preparation	Aluminium hydroxide, Magnesium carbonate	LIQUID GAVISON	Glaxo Smith Kline, INDIA
Floating Liquid Alginate Preparation	Aluminium- Magnesium antacid	TOPALKAN	Pierrc Fabre Drug, FRANCE
Colloidal gel forming FDDS	Ferrous sulphate	CONVIRON	RANBAXY,INDIA
Gas-generating floating Tablets	Ciprofloxacin	CIFRAN OD	Ranbaxy, INDIA
Bilayer floating Capsule	Misoprostal	CYTOTEC	Pharmacia,USA

Formulation of Floating Dosage Form

The following types of the ingredients can be incorporated in to FDDS.

1. Hydrocolloids,
2. Inert fatty materials,
3. Release rate accelerants,

4. Release rate retardant,
5. Buoyancy increasing agents and
6. Miscellaneous

1. Hydrocolloids

Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. Eg. Acacia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2.Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy. [40]

2. Inert fatty materials

Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Eg. Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used. [41]

3. Release rate accelerant

The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight. [42]

4. Release rate retardant

Insoluble substances such as dicalcium phosphate, talc magnesium strearete decresesd the solubility and hence retard the release of medicaments. [43]

5. Buoyancy increasing agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be adapted up to 80 % by weight.[44]

6. Miscellaneous

Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems. [45]

Approaches to Achieve Gastric Retention: Several techniques are reported in the literature to increase the gastric retention of drugs. [46]

1) **High-density systems: -** These systems, which have a density of ~3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements. The only major drawback with these systems is that it is technically difficult to manufacture them with a large

amount of drug (>50%) and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation. [47]

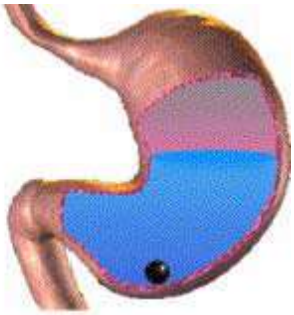

Figure 12: High density systems

2) Swelling and expanding systems

These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state.

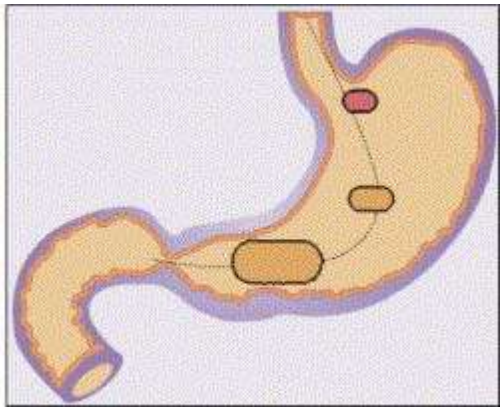

Figure 13: Swellable tablet in stomach

By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer. [48, 49, 50]

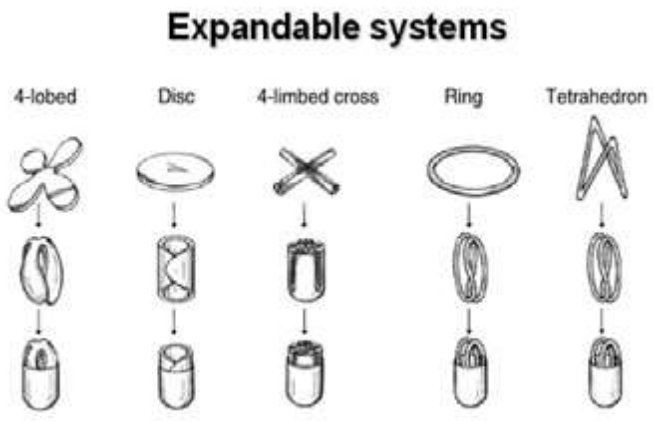

Figure 14: Different geometric forms of unfoldable systems

3) Incorporating delaying excipients

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system. [51]

4) Modified systems

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modules of drug delivery device. [52]

5) Mucoadhesive & bioadhesive systems

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin.

6) Floating systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas. [53]

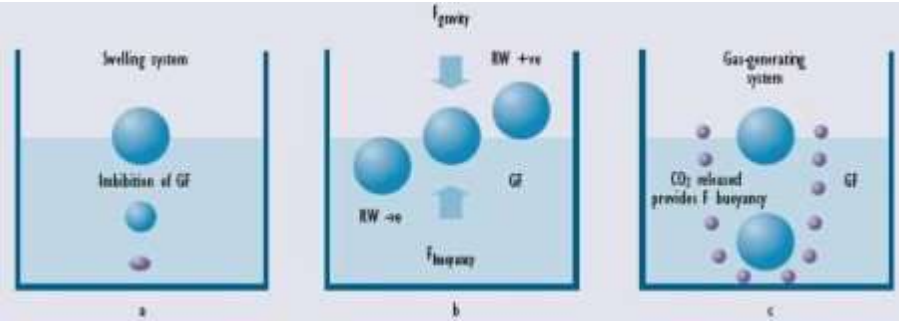

Figure 15: The mechanism of floating systems

Evaluation of Floating Drug Delivery Systems

1. **Angle of Repose**

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. [54]

$$\text{Tan } \theta = \frac{h}{r}$$

Where,

h= height of the powder cone and r= radius of the powder cone.

Table 2: Standard values of angle of repose

Angle of repose	Flow property
$>25^0$	Excellent
25^0-30^0	Good
37^0-40^0	Fair
Beyond 40^0	Poor

2. **Bulk density and Tapped density**

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each batch, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted. LBD (loose bulk density) and TDB (tapped bulk density) were calculated using the following equations.[55]

$$\text{LBD} = \frac{\text{Weight of powder blend}}{\text{Untapped volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of powder blend}}{\text{Tapped Volume of the packing}}$$

3. Hausner's ratio (HR)

This was calculated as the ratio of tapped density to bulk density of the sample

$$HR = \frac{\text{Tapped Density}}{\text{ulk Density}}$$

4. Determination of drug content in tablets

Three tablets from each batch are selected randomly and transferred to a 100 ml volumetric flask filled up with 0.1N HCL. Kept it for 48 hours then took 1ml from each of volumetric flask and transferred to the test tubes. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength. Then finally determine the drug content in tablets. [56]

5. Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a citizen electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. [57]

$$\text{Percentage Deviation (PD)} = \frac{\text{Wavg} - \text{Winitial}}{\text{Wavg}}$$

Where,

Wavg = average weight and

Winitial = initial weight

Table .3: Standards for uniformity of weight as per I.P

Avg. wt. of tablet	% Deviation
80 mg or < 80mg	10
> 80mg to < 250 mg	7.5
> 250mg or more	5

6. Drug release kinetics of floating tablets

To analyze the mechanism of drug release and release rate kinetics from the dosage form, the data obtained were fitted into zero order, first order, Higuchi release and Korsmeyer and Peppas release model using Graph Pad Prism 5.0 software, which is specially meant for curve fitting and statistical data analysis.

a. Zero-Order release kinetics

To studies the zero-order releases kinetics the release rate data are fitted to the fallowing equation.

$$F = k.t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, 'F' is the fraction of drug release, 'k' is the release rate constant and't' is the release time.

b. First – order release kinetics

To study the first-order release kinetics the release rate data are fitted to the fallowing equation.

$$F= 100\times (1-e^{-kt}) \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, 'F' is the fraction of drug release, 'K' is the release rate constant, 'e' is exponent coefficient and't' is the release time.

c. Higuchi release model

To study the Higuchi release model the release rate data are fitted to the fallowing equation.

$$F= K.t^{1/2} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where, F' is the fraction of drug release and 'K' is the release rate constant

d. Korsmeyer and Peppas release model

To study the Korsmeyer and Peppas release model the release rate data are fitted to the fallowing equation.

$$\frac{Mt}{M\infty} = K.\,tn \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where,

Mt/M∞ is the fraction of drug release

'n' is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form. [58, 59]

7. Hardness Test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Precision dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined. [60, 61]

8. Determination of weight variation

Twenty tablets selected at the random are weighed accurately and the average weight of the tablet is calculated. Then the deviation of individual weight from the average weight is calculated. [62, 63]

9. Uniformity of Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N HCl, the drug content was determined measuring the absorbance at lambda max after suitable dilution using a Simadzu UV- Visible double beam spectrophotometer 1800. [64]

10. Determination of *in-vitro* dissolution study

The test for *in- vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37^0 C. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replaced with the same volume

of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms.[65, 66]

11. Stability study

Stability is the essential factor for quality, efficacy and safety of drug product. The drug product with insufficient stability can result in change of their physical (hardness, dissolution rate, phase separation) as well as chemical characteristics (formation of high risk decomposition substances). [67]

12. Friability Test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed and transferred into Friabilator. The Friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by the following formula.

$$\text{Percentage Friability} = \frac{W - W0}{W} \times 100$$

Where,

W0= initially weight

W= weight after friability

Percentages Friability of tablets less than 1% are considered acceptable. [68]

13. X ray/ Gamma scintigraphy

For *in vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. In each experiment, the animals are allowed to fast overnight with free access to water, and a radiograph is made just before the administration of the floating tablet to ensure the absence of radio-opaque material. Visualization of dosage form by X-ray is due to the inclusion of a radio-opaque material. The formulation is administered by natural swallowing followed by 50 ml of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine. Gamma scintigraphy is a technique whereby

the transit of a dosage form through its intended site of delivery can be non-invasively imaged *in vivo* via the judicious introduction of an appropriate short lived gamma emitting radioisotope. The inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scinti scanner. But the main drawback of γ- scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceutical.[69]

14. Compressibility index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below

$$\text{Carr's index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{x} 100$$

15. Evaluation of bioadhesive system

The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g. cellophane) or biological (e.g. rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer.[70]

16. Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most dosage forms do not sharp acoustic mismatches across heir interface with the physiological solution. Therefore, ultra sonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydro gels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

17. Differential scanning calorimetry (DSC)

DSC (Shimadzu, Model - DSC-60/DSC- 50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards are used to calibrate the DSC temperature and enthalpy scale. The Sample preparations are hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25° C – 65°C. Inert atmosphere is maintained by purging nitrogen gas at the f low rate of 50ml/min.

18. *In-vitro* buoyancy studies

The in vitro buoyancy was determined by floating lag time method described by Dave B.S. The tablets were placed in 100ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT). [71]

19. Evaluation of swelling systems

a. Weight gain and water uptake (WU)

Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in simulated gastric fluid at 37^{o}C and determining the dimensional changes like tablet diameter and/ or thickness at regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation

$$WU = (Wt - WO) \times 100 / WO$$

In which Wt and Wo are the weights of the dosage form at time t and initially, respectively.

b. Gastro retention

The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. The use of X-rays involves exposing a patient to an X-ray beam, thus permitting the visualization of the GI transit of the dosage form.

20. Particle size analysis, surface characterization (floating microspheres and beads)

The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM). SEM was performed for morphological characterization of microspheres using scanning electron microscope. They were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness, 200nm) under reduced pressure (0.001mmHg). [72]

CONCLUSION

Drug delivery using various gastro retentive technological approaches have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drug candidates. Based on the literature surveyed, it may be concluded that gastro retentive drug delivery offers various

potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer mediated no effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles appear to be a very much effective approach to the modulation of controlled oral drug delivery. Gastro retentive drug delivery system gives maximum benefit to patient so that maximum patience compliance associated with it.

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