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Gastro retentive Drug Delivery System: An Overview

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ABSTRACT

The oral route of drug delivery is most preferred route of drug delivery due to its various advantages like patient compliance, ease of administration. But it has some drawbacks like non site specificity. To overcome this drawback gastroretentive drug delivery system is used. To understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. This review also includes different approaches for Gastroretentive drug delivery system i.e. floating drug dosage systems, swelling or expanding systems, high density system, mucoadhesive systems, Magnetic systems, raft forming system, evaluation tests, advantages, disadvantages, future prospects, different marketed preparations.

Keywords: Gastroretentive drug delivery system, Floating DDS, gastric retention.

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INTRODUCTION

The most promising route of drug delivery is considered as the oral route. The effective oral drug delivery process depends upon the different factors such as gastric emptying process, drug release from the dosage form gastrointestinal transit time of dosage form, and site of absorption of drugs. Many of the oral dosage forms possess various physiological limitations such as variable gastrointestinal transit because of the variable gastric emptying that leads to incomplete drug release, non-uniform absorption profiles and shorter residence time of the dosage form in the stomach. This will lead to incomplete absorption of the drugs having absorption window specially in the small intestines upper part as once the drug passes down the absorption site, the remaining quantity will go unabsorbed. In humans the gastric emptying of dosage forms is affected by different factors due to which wide inter- and intra-subject variations are observed. Various approaches have been proposed to retain the dosage form in the stomach. These methods include floating system, bioadhesive system, swelling system and expanding system and in fact the buoyant dosage unit enhances GRT [gastric residence time] without affecting the intrinsic rate of the emptying. Unfortunately floating devices administered in the single unit form [Hydrodynamically balanced system] HBS are unreliable in prolonging the gastric residence time owing to their 'nothing- or- all' emptying process and, thus they may causes high variability in bioavailibity and local irritation due to the large amount of drug delivered at the particular site of the GIT. Gastroretentive dosage form is the type of the novel drug delivery system which can remain in the stomach for the prolonged period of time and thereby increases the gastric residence time of the drugs. The gastro-retention helps to improve the drugs bioavailability[1-9].

Physiology of the Stomach

The Gastrointestinal tract is essentially the tube about 9 meters long that runs in between the middle of the body to the anus from the mouth and includes the pharynx [throat], stomach, small intestine [which consists of the duodenum, the jejunum and the ileum] oesophagus, and the large intestine [which consists of the cecum, colon and the rectum and appendix]. The gastrointestinal tract walls has the same general structure throughout most of its length from the oesophagus to the anus, with some of the local variations for every region. A stomach is an organ with the capacity for the storage and mixing. The antrum region is mainly responsible for the mixing and the grinding of the gastric contents. The stomach is the collapsed bag with the residual volume of approximately 50ml and contains the small amount of gastric fluid [pH 1–3] and air in fasting conditions. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of

the gastrointestinal tract. The GI tract is in the state of the continuous motility consisting of the 2 modes, inter digestive motility pattern and the digestive motility pattern. The former is dominant in the fasted state with the primary function of cleaning up the residual content of the upper gastrointestinal tract. The interdigestive motility pattern is commonly known as the MMC [migrating motor complex] and is organized in the cycles of activity and quiescence. Each of the cycle lasts for 90–120 minutes and it consists of the 4 phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the fasted state or inter digestive state, a migrating motor complex wave migrates from the stomach down to the gastrointestinal tract every 90–120 minutes. The full cycle consists of the 4 phases, from beginning in to the lower oesophageal sphincter or gastric pacemaker, propagating over the whole of stomach, the duodenum and jejunum and finishing at the ileum. The Phase III is termed the 'housekeeper wave' due to the powerful contractions in this phase tend to empty the Stomach of its fasting contents and the indigestible debris. Administration and subsequent ingestion of the food rapidly interrupts the migrating motor complex cycle and a digestive phase is allowed to take place. The ingested food is initially stored in the upper part of the stomach, where it is compressed gradually by the phasic contractions. The fed state or digestive is observed in the response to ingestion of the meal. It resembles the fasting Phase -II and is not cyclical, but it is continuous, provided that the food remains in the stomach. In the stomach the large objects are retained, during the fed pattern but are allowed to pass during the Phase- III of the inter digestive migrating motor complex. It is thought that the sieving efficiency [that is 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. A fasted-state emptying pattern is independent of the presence of any of the indigestible solids in the stomach. The patterns of contractions in the stomach occur such that the solid food is reduced to the particles of less than the 1mm diameter that are emptied through the pylorus as the suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal. Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to ≤1mm and propel the food through the pylorus. However, it has been shown that ingestible solids ≤7mm can empty from the fed stomach in humans.

Different Features of Stomach

Gastric pH: Fasted healthy subject 1.1 ± 0.15

Fed healthy subject 3.6 ± 0.4

Volume : Resting volume is about 25-50 ml

Gastric secretion: Pepsin, Acid, Gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of the hydrogen ions per hour. Effect of the food on the Gastric secretion: About 3 liters of secretions are added to the food[10-12].

Needs for Gastro Retention

1. The Local or the sustained drug delivery to the stomach and proximal Small intestine to treat certain conditions.
2. The drugs that are absorbed from the proximal part of the GIT [gastrointestinal tract].
3. It is particularly useful for the treatment of the peptic ulcers caused by H. Pylori Infections.
4. The drugs that are absorbed due to the variable gastric emptying time.
5. The drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of the gastrointestinal tract[13].

Drug Candidates Suitable for Gastroretentive Drug Delivery System

Drugs having poor colonic absorption but get rapidly absorbed in the upper parts of the GIT are the suitable candidates to be employed for gastroretention.

- Those drugs that get primarily absorbed in stomach and upper part of stomach e.g. calcium supplements, cinnarizine and chlordiazepoxide.
- The drugs that exhibit low solubility at the high pH values. For e.g. Diazepam and Verapamil HCl.
- The drugs that have the property of degrading in stomach For e.g. Ranitidine HCl and metronidazole.
- The drugs that disturb the normal colonic bacteria. For e.g. Amoxicillin trihydrate
- The drugs with narrow absorption window. For e.g. riboflavin and levodopa .
- The drugs that act locally in the stomach. For e.g .Misoprostol and antacids[14].

Drugs those are Unsuitable for Gastroretentive Drug Delivery Systems

a) The drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

b) The drugs that have very limited acid solubility e.g. phenytoin etc.

c) The drugs that suffer instability in the gastric environment e.g. erythromycin etc[15].

Requirements for the Gastroretentive Formulations

- To serve as a reservoir it should release the contents slowly.
- To facilitate the retention it must form a cohesive gel barrier.
- It must maintain specific gravity which is lower than the gastric contents

- The selection of the excipients is an important strategic decision for the design of the dosage form with consistence and the controlled residence in the stomach.
- The water soluble cellulose derivatives represent the typical class of the polymers best suited for such purposes. It has been suggested that the higher molecular weight polymers and slower rates of the polymer hydration are usually associated with the better behaviour of the floating[16].

Advantages

- The FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the exact pharmacological effect of drugs that are supposed to activate different types of receptors at different concentrations.
- The slow release of the drug into the body reduces the counter activity to minimum level leading to higher drug efficiency.
- The retention of the drug in the gastric formulation at stomach minimizes the amount of drugs that reaches the colon, thereby preventing the degradation of drug that degrades in the colon
- The GRDDS is highly advantageous in case of drugs having local action e.g. Antacids
- The bioavailability of many drugs increases when formulated as Floating dosage form .e.g. Riboflavin Controlled release Gastroretentive Dosage form (CR-GRDF) is highly bioavailable than non GRDF-CR polymeric formulations.
- The drugs like aspirin that cause irritation to gastric mucosa when come in contact with it. Therefore to overcome this formulation of such drugs is prepared for administration[17].

Disadvantages

- This system requires a high level of fluid in the stomach for drug delivery the stomach, so that the drug dosage form float and work efficiently.
- This system is not suitable for drugs that have solubility or stability problem in GIT.
- This system is not suitable for drugs that irritate the gastric mucosa and the drugs that are not stable in the stomach's acidic environment.
- This system do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
- There are certain drugs that get well absorbed along the gastric tract and undergo significant first pass metabolism, may not be suitable for floating systems because of the slow gastric empting that leads to reduced systemic bioavailability. [17-18]

Factors Affecting the Gastroretentive System

Table 1: Different factors affecting the GRDDS

1	Density	9	Patient related factor; a) Gender b) Age c) Posture
2	Size	10	Concomitant drug administration
3	Shape of dosage form	11	Biological factors
4	Single or multiple unit formulation	12	Disease state
5	Fed or Unfed State	13	Volume of GI Fluid
6	Nature of Meal	14	Effect of Buoyancy
7	Caloric content	15	pH

1) The Density of dosage forms

The dosage forms having the density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. The density of < 1.0 gm/ cm3 is required to exhibit floating property. However the floating tendency of the dosage form usually decreases as the function of time, as the dosage form gets immersed into the fluid, as the result of the development of hydrodynamic equilibrium[9, 19, 20].

2) The Size of the dosage form: The mean GRT of non floating dosage forms are highly variable and greatly dependent on their size which may be large, medium and small units. In most of cases, the larger the dosage form the greater will be the GRT due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. The dosage forms having the diameter of more than 7.5 mm show the better gastric residence time compared with one having 9.9 mm. Thus the size of the dosage form appears to be an important factor affecting gastric retention[9,21,22].

3) The Shape of the dosage form

Tetrahedron-shaped and ring-shaped devices have a better gastric residence time as compared to other shapes.

Single or multiple unit formulation: The multiple unit formulations show the more predictable release profile and insignificant impairing of performance due to the failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit the larger margin of safety against dosage form failure compared with single unit dosage forms[23].

4) The Fed or unfed state: under the fasting conditions

The GI motility is characterized by periods of strong motor activity or the MMC [migrating myoelectric complex] that occurs every 1.5 - 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, the MMC is delayed and GRT is considerably longer.

5) The Nature of meal

The feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to the fed state thus decreasing the gastric emptying rate and prolonging drug release[24].

6) The Caloric content

The gastric residence time can be increased by 4 - 10 hours with the meal that is high in proteins and fats.

7) The Frequency of feed

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

8) The Patient related Factors

Gender: For Male- 3.4} 0.6hr For: Female-4.6}1.2hr.

Age: Elderly people, especially for those over 70, have the significantly longer GRT.

Posture: The GRT can vary between supine and upright ambulatory states of a patient.

9) The Concomitant drug administration

The Anticholinergic like atropine, propentheline-increase the GRT. Metoclopramide and cisapride-decrease GRT[25-26].

10) The Biological factors

Crohn's disease. and Diabetes[24]

11) The Disease states

Hypothyroidism, gastric ulcer, diabetes, increase GRT. The Duodenal ulcers, Hyperthyroidism decrease GRT.[27]

12) The Volume

The resting volume of the stomach is 25 - 50 ml. The volume of liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster.

13) The Buoyancy

On comparison between floating and non floating dosage units, it was observed that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence time in the GIT, while the non floating dosage units sank and remained in the lower part of the stomach. The floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus

and were subjected to propelling and retropelling waves of the digestive phase. It was also observed that out of the floating and nonfloating units, the floating units had the longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms.

14) The pH

In the fasting state, the pH of the stomach is approximately 1.5 - 2.0 and in fed state is 2.0 - 6.0. Hence, a large volume of water has to be administered with an oral dosage form due to which the pH rises from 6.0 - 9.0. The stomach does not get time to produce sufficient acid when the liquid empties the stomach therefore generally basic drugs have the better chance of dissolving in fed state than in the fasting state[18].

Approaches for Gastroretentive Drug Delivery System

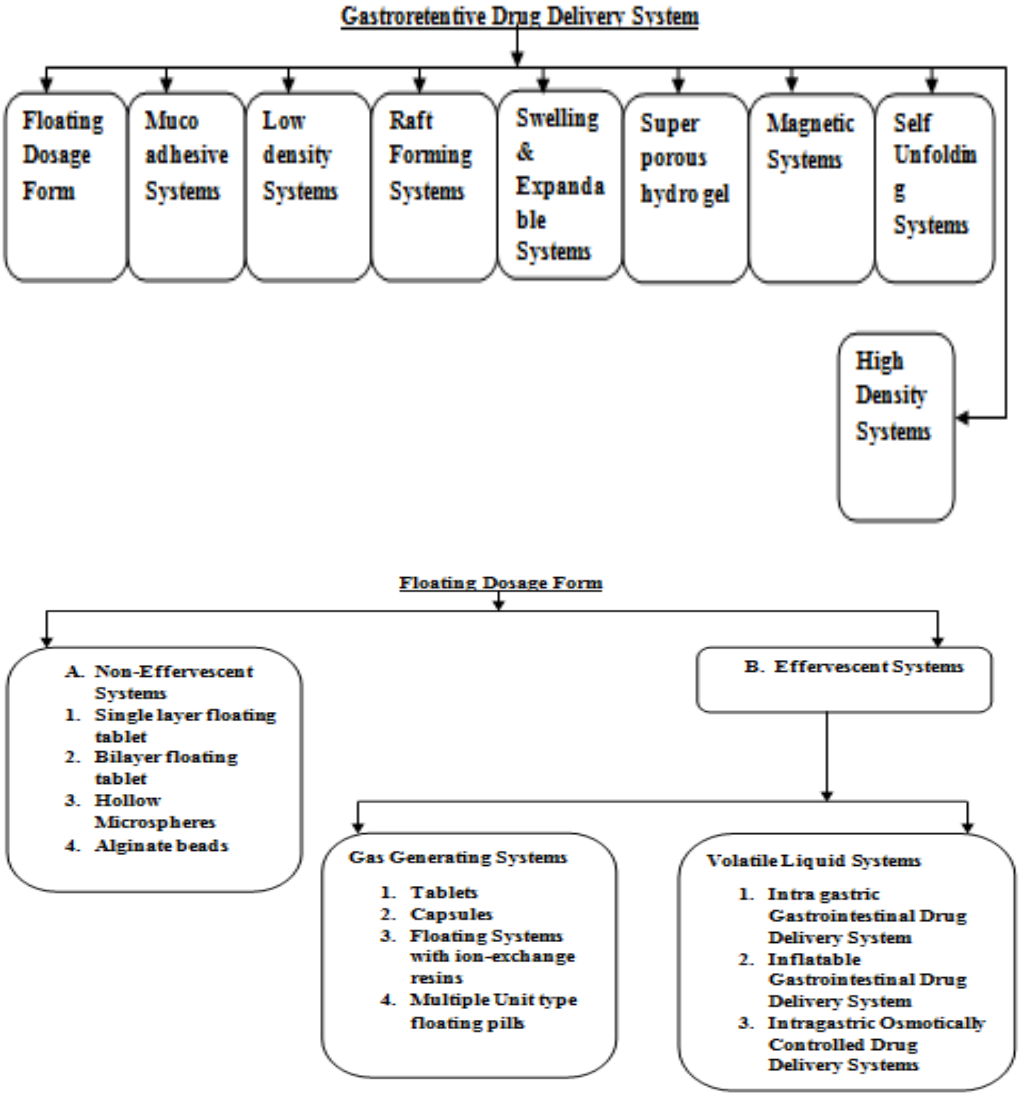

Figure 1: Various approaches for GRDDS

I) Floating Dosage Forms

A) Non Effervescent Systems

The Non-effervescent FDDS is based on the mechanism of swelling of the polymer or bioadhesion to the mucosal layer in the GI tract. The most commonly used excipients in non-effervescent FDDS are polysaccharides, gel forming or highly swellable cellulose type hydrocolloids, and matrix forming material such aspolyacrylate, polycarbonate,polystyrenepolymethacrylate, as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single layer floating tablets

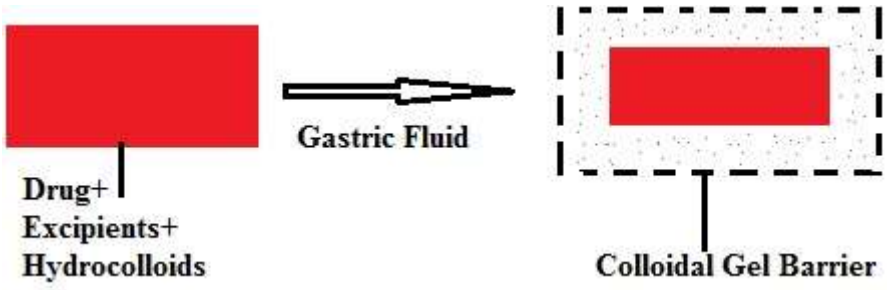

Figure 2: Single layer floating tablet

These are formulated by the intimate mixing of the drug with a gel-forming hydrocolloid, which swells when comes 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

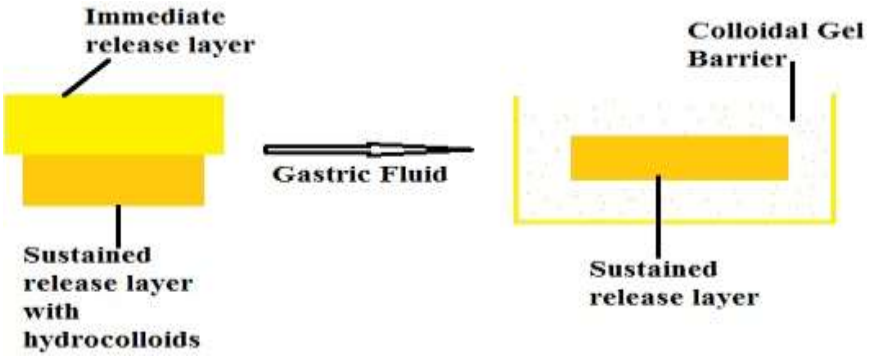

Figure 3: Bilayer Floating Tablet

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

3. Hollow microspheres

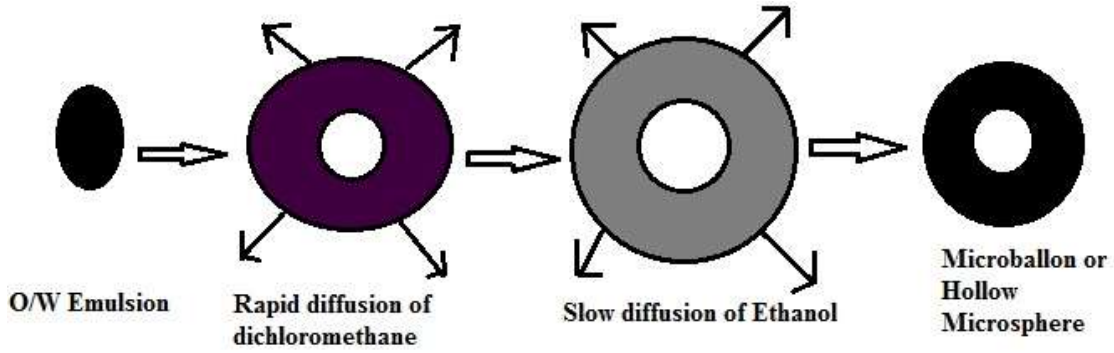

Figure 4: Formulation of Floating hollow microsphere or microballon

The hollow microspheres [microballoons] which are loaded with the drug in their outer polymer shells were prepared by the 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 400C. A gas phase generated in dispersed polymer droplet by the evaporation of the dichloromethane formed an internal cavity in microsphere of the polymer with drug. For more than 12 hours in vitro the microballoons floated continuously over the surface of acidic dissolution media containing surfactant.

4. Alginate beads

The Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Approximately 2.5 mm diameter of spherical beads can be prepared by dropping the sodium alginate solution into the aqueous solution of calcium chloride, which causes precipitation of calcium alginate which leads to formation of the porous system, which can maintain the floating force for over 12 hours. When compared with solid beads, which gave a short residence time of one hour and the prolonged residence time of more than 5.5 hours was given by these floating beads[4,28-30].

B) Effervescent Systems

1. Gas Generating Systems

A. Tablets

The floating bilayer tablets with controlled release for furosemide were developed by Ozdemir et al., 2000. By using the kneading method the low solubility of the drug could be enhanced by preparing the solid dispersion with β cyclodextrin mixed in the 1:1 ratio [Singh and Brahma 2000]. One layer contained the polymers HPMC K4M, HPMC K100M and CMC [for the control of the drug delivery] and a drug. The effervescent mixture of sodium bicarbonate and citric acidis in second layer. The lesser the compression force the shorter is the time of onset of floating is revealed by the *in vitro* floating studies, that is., when the tablets were compressed at 15 MPa,

these could begin to float at the 20 minutes whereas at the force of 32 MPa the time was prolonged to 45 minutes. The radiographic studies on six healthy male volunteers revealed that floating tablets were retained in stomach for six hours and further the blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of the urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

B. Floating capsules

The floating capsules are prepared by filling with the mixture of sodium alginate and sodium bicarbonate. During *in vitro* tests the systems were shown to float as a result of the generation of CO2 that was trapped in the hydrating gel network on the exposure to the acidic environment.

C. Multiple unit type floating pills

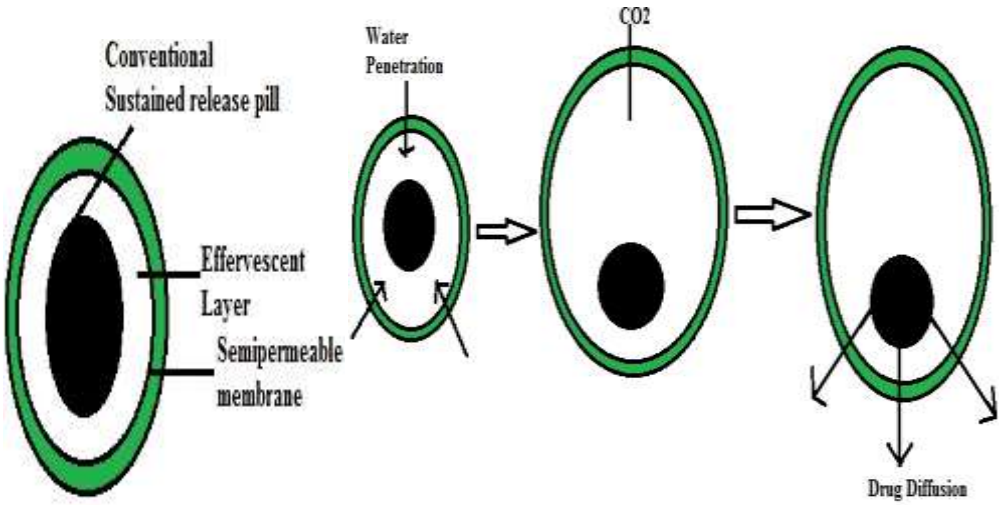

Figure 5: Effervescent gas generating system and drug release

This system consists of sustained release pills as ‘seeds’ surrounded by the double layers. The effervescent agents is present in inner layer while the outer layer is of swellable membrane layer. When the system is immersed in the dissolution medium at the body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the system.

D. Floating system with Ion-Exchange resins

A floating system using ion exchange resin that was loaded with the bicarbonate by mixing the beads with 1M sodium bicarbonate solution [Shweta Arora et al., 2005]. The loaded beads were then surrounded by the semipermeable membrane to avoid the sudden loss of CO2. Upon coming in contact with the gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO2 generation thereby carrying beads the toward the top of gastric contents and

producing the resin beads floating layer. The *in vivo* behavior of the coated and uncoated beads was monitored using the single channel analyzing study in 12 healthy human volunteers by the gamma radio scintigraphy. The studies showed that the gastric residence time was prolonged considerably [24 hours] as compared with the uncoated beads [1 to 3 hours] [31].

II. Volatile Liquid / Vaccum Containing Systems

1. Intragastric floating gastrointestinal drug delivery system

Due of floatation chamber this system can be made to float in the stomach, which may be the vacuum or filled with air or the harmless gas, while drug reservoir is encapsulated inside the microprous compartment.

2. Inflatable gastrointestinal delivery systems

An inflatable chamber is incorporated in this system, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in to the stomach. These systems are fabricated by loading the inflatable chamber with the drug reservoir which can be the drug, impregnated polymeric matrix, then encapsulated in the gelatin capsule. After the 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 to the stomach. The drug is continuously released from the reservoir into the gastric fluid.

3. Intra gastricosmotically controlled drug delivery system

This system is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in the biodegradable capsule. The capsule quickly disintegrates in the stomach, to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms the deformable hollow polymeric bag that contains the liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of 2 components; drug reservoir compartment and the osmotically active compartment. The drug reservoir compartment is enclosed by the pressure responsive collapsible bag, which is impermeable to vapour and liquid and has the drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within the semi permeable housing. The water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt, in the stomach. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after the predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach[32].

II) Bioadhesive or Mucoadhesive Drug Delivery Systems

The bioadhesive drug delivery systems are used as the delivery device within the human to enhance drug absorption in the site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach Hence, they improve the prolongation of gastric retention. The basis of adhesion in that the dosage form can stick to the mucosal surface by the different mechanism. These mechanisms are:

1] The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

2] The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or the interpenetration of mucin strands into a porous structure of the polymer substrate.

3] The absorption theory, suggests that bioadhesion is due to the secondary forces such as Vander Waal forces and hydrogen bonding.

4] The electron theory, which proposes the attractive electrostatic forces between the glycoprotein mucinnet workand the bio adhesive material. The materials commonly used for bioadhesion are cholestyramine, poly acrylic acid, sodium alginate chitosan, hydroxypropyl methylcellulose [HPMC], sucralfate, dextrin, tragacanth, PEG[polyethylene glycol] and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of the mucus in the gastrointestinal tract [GIT] [11, 33-34].

III) Low Density Systems

The gas-generating systems inevitably have the lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems [<1 g/cm3] with immediate buoyancy have been developed therefore. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called as ‘‘microballoons’’ because of the low-density core [Sato and Kawashima, 2004]. Mostly the techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Cellulose acetate, polycarbonate, calcium alginate, low methoxylated pectin, agar and Eudragit S, are commonly used as polymers. The Buoyancy and drug release are dependent on the quantity of polymer, the plasticizer–polymer ratio and the solvent used[31].

IV) Swelling and Expandable Systems

1. Swelling systems

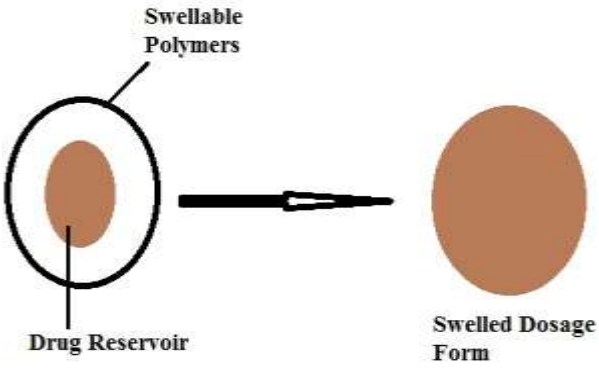

Figure 6: Swelling Systems

These are the type of non-floating gastroretentive drug delivery system which when enters stomach swells [due to presence of swellable polymers] to an extent that cannot pass through the pyloric sphincter leading to its retention in to the stomach[35].

2. Expandable system

When swallowed, these dosage forms swell to the size that prevents their passage through the pylorus. As the result, the dosage form is retained in to the stomach for the long period of time. This system is sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in to the gastric cavity for several hours even in the fed state. The sustained and controlled drug release may be achieved by selecting the polymer with the proper molecular weight and swelling properties. The polymer imbibes water and swells as the dosage form comes in contact with gastric fluid. The extensive swelling of these polymers is the result of the presence of the physical chemical crosslink's in the network of hydrophilic polymer. These cross-links prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. The balance between the extent and the duration of the swelling is maintained by a degree of cross linking between the polymeric chains. The high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for the prolonged period. On the other hand, the low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross-linking is required to maintain the balance between swelling and dissolution. The swollen system eventually will lose its integrity because of the loss of mechanical strength caused by abrasion or erosion or will burst into the small fragments when the membrane ruptures due to continuous expansion. These systems also may erode in the presence of gastric juices so that after the predetermined time the device no longer can attain or retain the expanded configuration.

The expandable GRDFs are usually based on three configurations:

1] The small collapsed configuration which enables sufficient oral intake

2] Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.

3] The smaller form that is achieved in the stomach when the retention is no longer required that is after the GRDF has released its active ingredient, thereby enabling evacuation[36-38].

V) Super Porous Hydrogel Systems

This swellable system differs sufficiently from the conventional types to warrant separate classification. The Super porous hydrogel that expand dramatically [hundreds of times their dehydrated form within a matter of seconds] when immersed into water. With the pore size ranging, 10nm - 10µm the absorption window by conventional hydrogel is the very slow process and several hours may be needed to reach an equilibrium state during which parameter evacuation of the dosage form may occur. In this approach to improve GRT super porous hydrogel of average pore size less than the100µm, swell to equilibrium size within a minute due to rapid water uptake by the capillary wetting through numerous interconnected open pores. They swell to a large size [swelling ratio: 100 or more] and are intended to have sufficient mechanical strength to with stand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material[2,39,40].

VI) Magnetic Systems

To enhance the gastric retention time [GRT] this approach is based on the simple principle that the dosage form contains the small internal magnet and a magnet placed on the abdomen over the position of the stomach. Though the magnetic system seems to work the external magnet must be positioned with the degree of precision that might compromise patient compliance[34].

VII) Self-Unfolding Systems

This system is capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. The drug can be either contained in the polymeric composition of the gastroretentive system or included as the separate component. Different methods were suggested to provide for the self unfolding effect.

(1) The use of hydrogels swelling in contact with the gastric juice.

(2) Osmotic systems, comprising an osmotic medium in a semipermeable membrane.

(3) Systems based on low-boiling liquids converting into a gas at the body temperature[31].

VIII) High Density (Sinking) System or Non- Floating Drug Delivery System

This approach involves the formulation of dosage forms with the density that must exceed density of normal stomach content [~ 1.004 gm/cm3]. These formulations are prepared by coating drug on the heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm3. The density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time. But, effectiveness of this system in human beings was not observed and no system has been marketedv[41, 42].

Evaluation of Gastroretentive Dosage Form

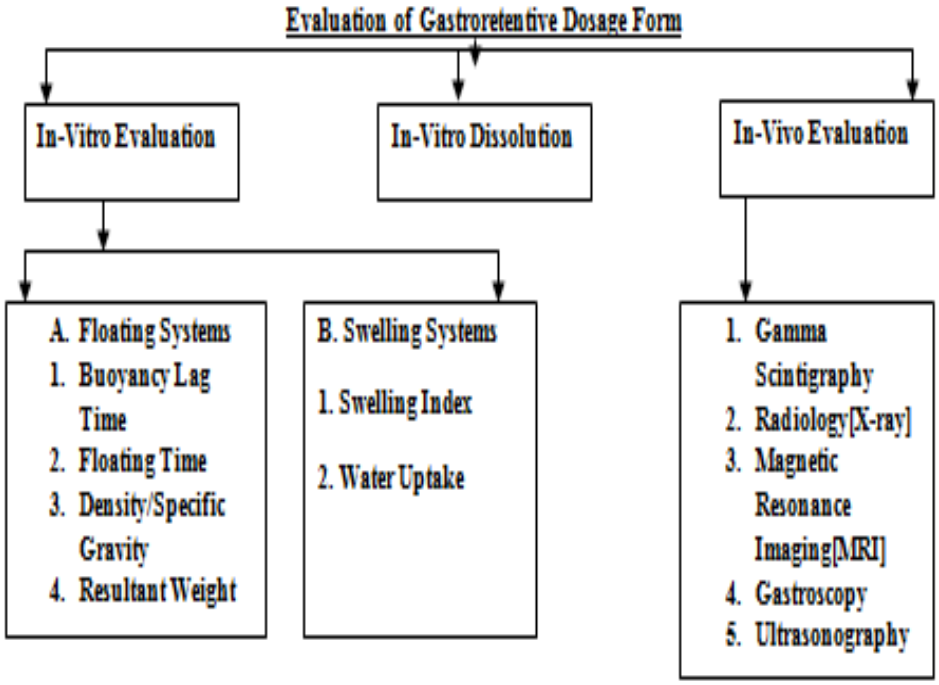

Figure 7: Different evaluation tests for GRDDS

A) *In-Vitro* Evaluation

I) Floating systems

a) Buoyancy Lag Time

It is determined to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time

The test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37^0C.The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

c) Specific Gravity / Density

The density can be determined by the displacement method using Benzeneas displacement medium.

d) Resultant Weight

We know that the bulk density and floating time are the main parameters for describing the buoyancy. But only a single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as the function of time. For eg: A matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some of the drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of the dosage form. The magnitude and direction of force/resultant weight [up or down] is corresponding to its buoyancy force [Fbuoy] and gravity force [Fgrav] acting on dosage form. So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

II) Swelling systems

a)Swelling Index

After immersion of swelling dosage form into SGF at 37^0C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

b) Water Uptake

It is the indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at the regular interval and weight changes are determined with respect to the time.

So it is also termed as Weight Gain.

Water uptake = WU = (Wt – Wo) × 100 / Wo

Where, Wt = weight of dosage form at time t

Wo = initial weight of dosage form

III) *In-vitro* dissolution Behaviour

The release of the medicament was studied by using USP-II type dissolution apparatus {paddle type}. The dissolution study was performed at pre-determined speed and temperature of about 37± 0.5 ^{0}C in an appropriate dissolution medium. The 5ml of sample was withdrawn at predetermined interval and the volume of dissolution medium was maintained by adding the same volume of dissolution medium. The absorption of withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve[25, 27, 43-45].

B) *In-Vivo* Evaluation

a) Gamma Scintigraphy

The Gamma Scintigraphy relies on the administration of a dosage form containing small amount of radioisotope e.g., ^{152}Sm which is a gamma ray with a relatively short half-life. The isotope has to be incorporated into the GRDF in advance. Then, the short time prior to the study the formulation has to be irradiated in the neutron source that causes it to emit gamma rays. The emitted ray can be imaged using "gamma camera" – a form of the scintillation counter, combined with the computer to process the image and thereby the DF can be tracked in the GI tract. This technique is elegant and provides proper assessment of gastroretentivity in humans.

b) Magnetic Resonance Imaging (MRI)

MRI is a noninvasive technique that is not associated with radioactivity and allows observation of the total anatomical structure in relatively high resolution. The visualization of the GI tract by MRI has to be further improved by the administration of contrast media. For the solid dosage forms the incorporation of a super paramagnetic compound such as the ferrous oxide enables their visualization by MRI. The technique allows obtaining many pictures from the same subject and is safe.

c) Radiology (X-Ray)

In this technique, the radio-opaque material has to be incorporated in the dosage form, and its location is tracked by the X-ray pictures. This technique is used to evaluate gastroretentivity of GRDFs and the disintegration rate of dosage forms in vivo and also to determine the oesophageal transit. Although it is consider cheap and a simple method to use its major disadvantage is the safety issue owing to repeated exposure to the x-ray that increase the risk for the volunteers.

d) Gastroscopy

This is commonly used for the diagnosis and monitoring of the GIT. This method utilizes fibre optics or video system and can be easily applied for monitoring and locating GRDFs in to the stomach. Hence, it is too inconvenient to conduct the procedure frequently in the same experiment for one subject. In the human, the procedure can be applied with or without slight anesthesia while it requires the complete anesthesia in dogs.

e) Ultrasonography

It is used sometimes; it is not used generally because it is not traceable at intestine[44,46-49].

Future Prospects

The control of drug release profiles has been the major aim of pharmaceutical research and development in the past two decades, the control of the GI transit profiles could be the focus of the

next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, the so-called 'once-a-day' formulations may be replaced by the novel gastroretentive products with release and absorption phases of approximately 24 hours[50].

Table 2: Commonly used drug in formulation of gastro retentive dosages forms[5,9]

Sr. No	Dosage Forms	Drugs
1	Floating Capsules	Propranolol, Pepstatin, Nicardipine
2	Floating Microspheres	Griseofulvin, Terfenadine, Aspirin
3	Floating Tablets	Atenolol, Captopril, Prednisolone, Verapamil
4	Powders	Several basic drugs
5	Films	Cinnerzine
6	Floating Granules	Prednisolone, Diclofenac sodium, Indomethacin

Table 3: Gastroretentive products available in the market[5,6]

Sr. No	Brand name	Active Ingredient
1	Cytotec®	Misoprostal
2	Madopar ®	L-DOPA and Benserazide
3	Conviron	Ferrous sulfate
4	Cifran OD ®	Ciprofloxacin
5	Valrelease ®	Diazepam

CONCLUSION

This article provides information regarding the gastroretentive drug delivery systems and its evaluation process. The foregoing shows that gastroretentive drug delivery systems have great potentials, for formulating both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer is required. Inspite of number of difficulties to be worked out to achieve prolonged gastric retention, many pharmaceutical companies are focusing towards commercialization of this technique.

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