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A Comprehensive Discussion about Gastro Retentive Drug Delivery System

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ABSTRACT

There are numerous routes for administration of drug in the body but compliance to patient always remained the major concern for researchers. Although oral administration is often used for the drugs with poor oral bioavailability due to limited absorption or degradation in the GIT but still it is considered as the most convenient one. The basic aim of development of oral modified release dosage form is to accomplishment more anticipated and amplified bioavailability of drugs. One of the promising systems is gastro retentive drug delivery system. Numerous techniques have been tried to retain the drug in the gastric media.

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INTRODUCTION

The drugs having small therapeutic window show extensive absorption at proximal part of the small intestine. In spite of enhanced absorption of small intestine, the rate of drug absorption at these sites is reduced because drug rapidly passes through these regions. Thus by increasing the gastric residence time of such formulations may profoundly improve the extent of absorption.

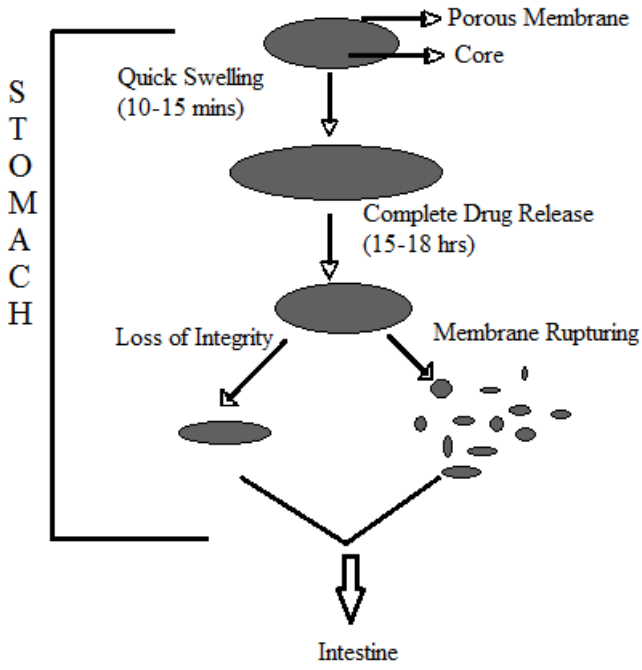

Figure 1: Schematic representation of novel gastro retentive drug delivery system

Drugs having tendency to float in gastric fluids are ideal candidates for elevated bioavailability and show good absorption in the upper part of small intestine.

The floating systems normally possess the density up to the value of 1.004 g/cm^3 that is usually greater than that of the gastric fluid. So, system with this kind of properties inclines to settle at the bottom of the stomach. This can be achieved by incorporating an inert powder such as ZnO, TiO_2 etc.[1, 4]

The benefits of easy administration, increased patient compliance and flexibility in formulation make oral drug route, the most preferred method of drug delivery.[2] There are numerous physiological factors such as incapability to detain and limited drug delivery inside the desired areas of the gastrointestinal tract and the extremely capricious nature of gastric

emptying manner that retard the progress.[3] The floating systems can reduce the dosing rate and minimize oscillations in plasma drug concentration. Gastro retentive floating drug delivery mechanism is thought to be the most encouraging practice for future of refining and exactitude of pharmaceutics. The results of this kind of drug delivery systems have exhibited positive ability for the regulation of the release promptness with position explicit absorption.[5]

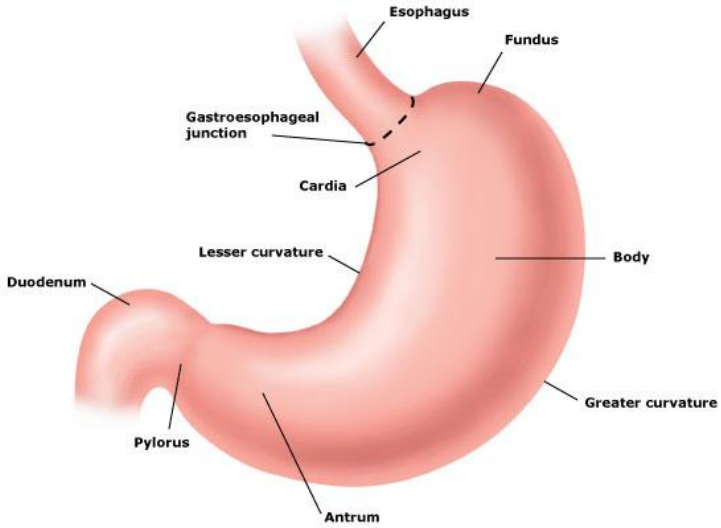

Figure 2: Anatomy and physiology of stomach

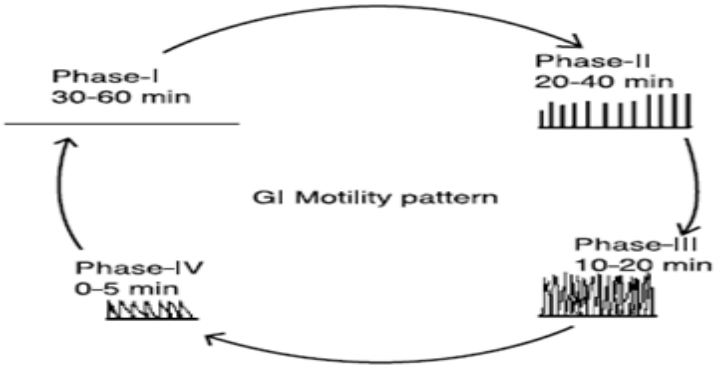

Figure 3: Phases of gastric motility

Factors Affecting Gastric Retention

A gastro-retentive system is sensitive to various aspects which govern the competence of gastric retention time of dosage form.

Density

The dependency of gastric retention time is related by direct relation with the density. The density is basically a function of dosage form buoyancy.

Size

The intensified GRT has size specific trends of diameter. For example dosage, form with value up to 7.5 mm have more existence than of 9.9 mm diameter.

Shape of dosage form

The improved gastric retention time of 90% to 100% is displayed by the Tetrahedron ring-shaped devices with a flexural modulus. The values of modulus range from 48–22.5 kilopounds / square inch (KSI) at 24 hours in comparison with other shapes.

Single or multiple unit formulations

There are numerous unit formulations which present highly anticipated release profile and minor negative aspects. The fiasco of units roots this performance and permitco-administration of units with various release profiles or containing incompatible substances. Further, it allows a greater edge of security against dosage form failure in comparison to single unit dosage forms.

Fed or unfed state

The pattern of the gastric motility is different for the fasting and fed state. The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases, such as Phase I (basal phase), Phase II (pre-burst phase), Phase III (burst phase) and Phase IV (transition period between phase III and phase I) as mentioned in Figure 3. The Gastrointestinal motility in fasting circumstances is described with help of periods of strong motor activity or the migrating myoelectric complex (MMC). The GRT of the unit has trend to be quite less while overlapping of the timings if administration of formulation with MMC. However, in the fed state, MMC is normally migrating myoelectric complex is deferred in situation of feeding. The Gastro retention time will be significantly lengthier.

Nature of meal

During the fed state, the motility pattern of the stomach can be affected by various factors. These factors can be indigestible polymers or fatty acid salts. So the ultimate consequence can be expected in the drop of gastric emptying speed and prolong drug release.

Caloric content

A meal with high proteins and fats can cause the strengthening in gastric retention time up to 4 – 10 hours.

Frequency of feed

The low frequency of MMC results when consecutive meals are given. It can cause ultimately the amplification of gastric retention time up to 400 minutes and above. Single meal results in better frequency of MMC and lower gastric retention time.

Gender

The mean ambulatory GRT in both males and females is independent of the weight, height and body surface. It is normally smaller in males like 3.4±0.6 hours in contrast to the females considering their age and race. It is found to be more in females (4.6±1.2 hours).

Age

The gastric retention time is prolonged in people of age 70 and above.

Posture

Gastric retention time is said to differ between horizontal and upright ambulatory status of the patient.

Biological factors

These factors include the Diabetes and the syndrome called Crohns disease, etc**.** [6, 4]

Advantages of Gastro- retentive drug delivery system:

- Gastro retentive drug delivery system offers enhanced absorption for those drugs which predominantly exhibit the trend of absorbance in the stomach. e.g., ferrous salts, antacids, etc.
- It is advantageous for drugs which have domain of action in the stomach. e.g., antacids, etc.
- It gives comfort of production with simple apparatus.
- A deprived absorption is projected as the result of vigorous intestinal movement and a short transit in gastro retentive drug delivery system. e.g., in certain sort of diarrhea, this kind of behavior is predictable.
- It has tendency to slow down the dosing speed and ultimately improves the patient compliance.
- The inconsistent trend in plasma drug concentration confines the deviances of bioavailability. The continuous drug release sustains a desired plasma drug concentration through this system.
- The gastro-retentive drug delivery systems can significantly increase the healing influence of the drugs with short half-life.
- These systems can help for the formulation of drugs which are not stable in intestinal pH.
- The absorption of drugs with solubility in stomach is boosted by this system.
- No hazard of dose dumping is expected in such a system.
- Gastric irritation is also prevented with help of delayed release effect and unfluctuating release of drug in these systems. [7,22]

Disadvantages of Gastro Retentive Drug Delivery System:

- Gastro retentive drug delivery system is incompatible for drugs with limited acid solubility. e.g., Phenytoin, etc.

- GRDDS is not appropriate for drugs with unstable behavior in acidic environment. e.g., Erythromycin.
- This system is not suitable for drugs irritating nature or which produces gastric lesions on slow release. e.g., Aspirin, NSAID, etc.
- These systems are not favorable for the drugs with selective absorbance in colon. e.g. Corticosteroid, etc.
- These systems do not coordinate well with drugs that have capability to undergo absorption in GI tract. e.g., Isosorbide, Dinitrate, Nifedipine, etc.
- Floating drug delivery systems need high fluid level in stomach to float and work efficiently.
- The high turnover proportion of gastric mucus is one of the most difficult problems for bioadhesive system.
- The prolonged presence in stomach is one of the very main negative aspects of these systems. Normally size-increasing GRDDS with this problem can be severally dangerous after many administrations. [8, 33]

Approaches for Gastro Retention

The improvement of the preservation of an oral dosage form in the stomach is achieved by various methods. It has two types; floating systems and non-floating systems. The floating systems comprise of effervescent systems and non-effervescent systems. Normally these systems contain lower bulk density in comparison to the gastric fluid. This property gives the rise to the floating nature and then ultimately these systems release the drug slowly in a predictable ratio. The non-floating systems consist of basically six systems. These systems are bioadhesive swellable high density and inflatable systems.[6]

Floating System:

The lesser bulk density of these prepared systems made them float and they remain resistant in the stomach without disquieting gastric emptying rate for a persistent time period. The drug is released progressively at the expected rate from the system at the time when the

system is floating in gastric substances. The remaining system is squashed from the stomach as with the after the release of drug the remaining system is squashed out. An enhanced gastric retention time and well-controlled variations in plasma drug concentration are end products. These systems have two forms, non-effervescent and effervescent system**.** [9, 34]

Mechanism of floating systems:

Numerous investigators have worked for holding the dosage form in the stomach as approach of aggregating the remaining time. For this purpose, the floating dosage forms have been most commonly used. Floating drug delivery systems have lesser density than gastric fluids and so remains floating in the stomach without disturbing the gastric emptying rate for an extended time span. When the dosage form is floating on the gastric contents (given in Figure 4 (a), the drug is released gradually at the desired rate. After release of drug, the residual system is squashed from the stomach. This results in an increased GRT and a good control of the deviations in plasma drug concentration. Floating force is also obligatory to retain the dosage form reliably buoyant on the surface of the meal in addition to a nominal gastric content required to permit the appropriate attainment of the buoyancy retention principle. A newly reported apparatus for measurement of resultant weight is used to calculate the floating force kinetics. For the preservation of the submerged object, force corresponding to F (as a function of time) is required and it is measured by this apparatus endlessly. Force equivalent F with higher positive side tends to keep object floating more simply Figure 4(b). It also supports in optimization of floating drug delivery systems with respect to stability and durability of floating forces. These forces are formed to avoid the difficulties of sudden intragastric buoyancy capability abnormalities.

$$F = F\,(\text{buoyancy}) - F\,\text{gravity} = (Df - Ds)\,gv \rightarrow (1)$$

(Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and

g = acceleration due to gravity)**.** [3]

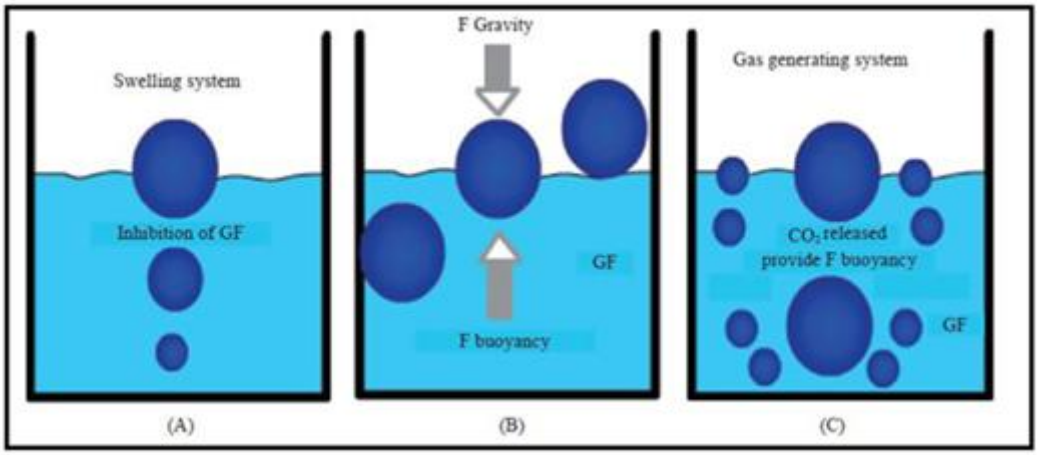

Figure 4: Schematic representation of mechanism of floating drug delivery system

A) Effervescent Systems

Effervescent methods employ matrices fabricated with swellable polymers and effervescent constituents (e.g., sodium bicarbonate, citric acid or tartaric acid). Carbon dioxide is released producing the initiation to float in the stomach as the system is prepared while entering it. [10]

Volatile liquid containing systems

The further types are given below.

1. Intra-gastric Floating Gastrointestinal Drug Delivery System:

In this type of system floatation in the stomach because of floatation chamber. Air or a harmless gas, filled or there will be space however drug material is confined inside a microporous barrier. **[**11**]**

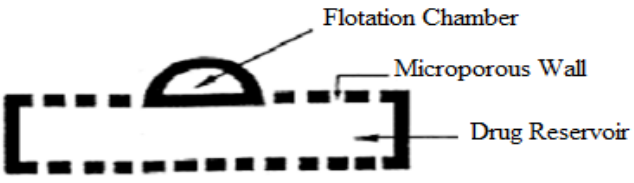

Figure 5: Intra-gastric Floating Gastrointestinal Drug Delivery System

2. Inflatable Gastrointestinal Delivery Systems:

Inflatable systems comprise of an inflatable chamber. The system has liquid ether that gasifies at body temperature to cause the chamber to swell in the stomach. The inflatable chamber filled with drug. The dissolution of the capsule for the release of drug reservoir takes place along with the inflatable chamber advanced oral administration. The active drug component pool conserves into the gastric fluid when the involuntary inflation of inflatable chamber take place**. [**12**]**

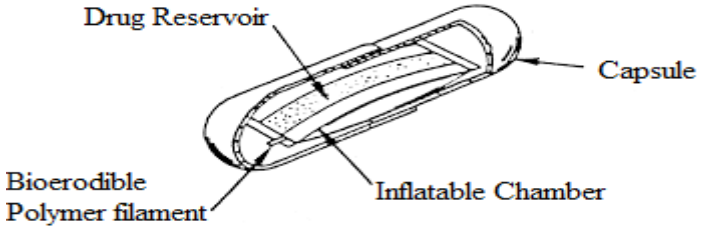

Figure 6: Inflatable Gastrointestinal Delivery Systems

3. Intra-gastric osmotically controlled drug delivery system:

These systems comprise an osmotic pressure controlled drug delivery device and an inflatable floating backing in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. A deformable resonating polymeric bag is made inside by the inflatable support. It involves liquid that gasifies at body temperature to fill the bag. There are two parts of osmotic pressure controlled drug delivery device, Drug reservoir compartment and an osmotically active compartment. The pressure responsive collapsible bag is resistant to vapor and liquid and it contains drug delivery orifice. The osmotically active compartment comprises an osmotically active salt and is enclosed within a semi-permeable membrane. The water in the gastrointestinal fluid is nonstop absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt in the stomach. Subsequently, the formation of an osmotic pressure takes place which acts on the portable bag and in turn compels the drug reservoir compartment to decline its volume. It further generates the drug reservoir compartment to decrease its volume and start the drug release of a drug solution formulation over the delivery orifice. The floating support is also forced to comprise of a bio-erodible plug. This bio-erodible plug corrodes after projected time to deflate the maintenance.

The emptying of deflated drug delivery system from the stomach takes place consequently.[10,13,36]

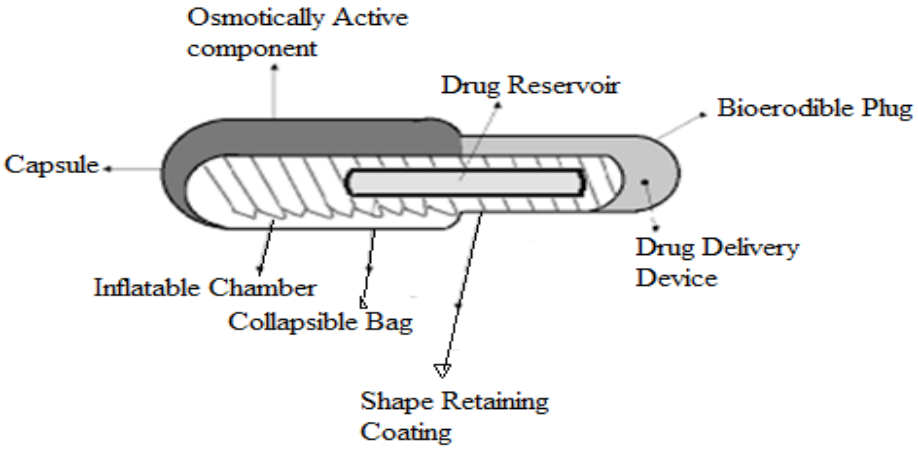

Figure 7: Intra-gastric osmotically controlled drug delivery system

Gas – generating systems:

Carbon dioxide is released by the reaction of carbonate/bicarbonate salts and citric/tartaric acid while the gas generating buoyant delivery systems employ this effervescent reaction. The carbon dioxide gets captured in the jellified hydrocolloid layer of the systems. It ultimately lowers specific gravity and compels it to float over chime. [14]

Floating capsules:

The key constituents of floating capsules are sodium alginate and sodium bicarbonate and a mixture of both is filled in it. The production of carbon dioxide results and shows the floating of systems during *in-vitro* tests. Carbon dioxide was confined in the hydrating gel network on exposé to an acidic atmosphere. [33]

Floating pills:

A variety of sustained release formulations with several unit kind of dosage forms and encircled by two layers are Floating pills. The two layers are dived in such way that the exterior layer is swellable membrane and the interior layer comprise of effervescent agents. The outer swellable membrane is the reason of system swelling. Then it is followed by the sinking of system. The release of CO_2 (Carbon Dioxide) is result of effervescent agents which causes the floating of system. [15]

Ion-Exchange Resins:

The display of gastric retentive properties by a coated ion exchange resin bead formulation with bicarbonates is experienced. A negatively charged drug is attached to the resin with bicarbonates loaded. The encapsulation of subsequent beads takes place in a semipermeable membrane to overcome the quick loss of CO_2. An interchange process of chloride and bicarbonate ions occur after the entry into acidic atmosphere of stomach and the outcome of process is release of CO_2. It later gets confined in a membrane in that way that it transports beads in the direction of the top of gastric content. It makes a floating layer of resin beads while on the other hand, uncoated beads drop swiftly**.** [16]

Matrix Tablets:

These tablets have capacity to be articulated in a single layer matrix table. It can done by employing bicarbonates in the matrix making hydrocolloid gel agent or in a double layer matrix together with gas generating matrix as a discrete first layer while the drug behaves as the second layer. There is a possibility of triple layer matrix tablet but in these days the gas generating matrix consists of one layer and rest two comprise drug layers.[12]

B) Non-effervescent system:

This type of dosage forms apply a gel forming or swellable and matrix-forming polymers. The one of processes of formulation comprise of gentle mixing of the drug and the gel forming hydrocolloid. The interface of dosage form and gastric fluids results in swelling of dosage form after oral management. These swollen gel-like structures work as a pool and permit sustained release of drug through the gelatinous mass. The enclosed CO_2 in the system slurry can be beneficial to produce microspheres with air pockets by which it becomes buoyant. [17]

1) Colloidal gel barrier system:

In this type of system, the gel-forming hydrocolloids permit these systems to remain as buoyant on the stomach content and it eventually prolongs gastric retention time. This extension further increases the quantity of drug at its absorption locations in the solution form. The hydration of hydrocolloids takes place and in consequence forms a colloidal gel

barrier around its surface as contact with gastric fluid occurs. It further coordinates in sustained release of drug. [18,19]

2) Micro-porous compartment system:

Microporous compartment system is the kind of technology that works by the encapsulation of a drug reservoir inside a microporous compartment and has outlets alongside its upper and lowest walls. The drug reservoir section has its peripheral walls absolutely vacuum-packed to avoid any direct contact with gastric surface and the undissolved drug. The floatation of delivery system over the gastric content is caused by the trapped air in the floatation chamber. The gastric fluid dissolves the drug as it arrives by the aperture. It has further benefit that it transfers the dissolved drug for continual transportation across the intestine for absorption**.** **[**20, 21**]**

3) Alginate Beads:

The multi-unit floating dosage forms, Alginate Beads, are formed with freeze-dried calcium-alginate. The formation these spherically shaped beads with an estimated diameter of 2.5mm can take place by falling sodium alginate solution into aqueous solution of calcium chloride. The precipitation of calcium alginate takes place and it further forms a porous system. These systems in comparison with solid beads give a better extended residence time of more than 5.5 hours while solid beads give a short residence time of 1 hour. [22, 23]

Micro-balloons or Hollow Microspheres:

This type of system loaded with drugs is prepared by simple solvent evaporation or solvent diffusion technique to encompass the gastric retention time of the dosage form. The drugs are loaded in their polymer shelf. The polymers used and the plasticizer polymer ratio and the solvent used for formulation very important for buoyancy and drug release. The consistent floatation of these hollow microspheres takes place over the surface of an acidic dissolution media containing surfactant for more than 12 hours. The study results have shown the fact that micro balloons have shown the ability to sustain for 3 hours against peristaltic movements in human after dispersion in the upper part of stomach as administrated orally. [24, 25]

Non-floating system

High Density Systems:

The High density systems with density of about 3gram/cm^3 are confined in the stomach. These systems have capacity to endure its peristaltic movements. There is a huge disadvantage of such systems that the manufacture process of such formulations with high quantity of drug (>50) with attainment of density 2.8gram/cm^3 is very difficult.[7, 22]

Bioadhesive or Mucoadhesive drug delivery systems:

These systems are employed for the detection of dosage form to increase the drug absorption in a site-specific method. Many bioadhesive polymers are utilized as they have ability to stick to the epithelial surface in the stomach. So the gastric retentive time of the dosage forms is increased. Gastric mucoadhesion is said to be incapable of making dosage forms proficient enough to repel the solid population forces of the stomach wall. The ability of mucoadhesion as a gastro-retentive force is also declining by the nonstop production of mucous by the gastric mucosa to replace that is lost through peristaltic contractions and the dilution of the stomach content. The bioadhesive drug delivery systems face a major problem of the high turnover rate of the gastric mucus in the gastrointestinal tract and ultimately resulting in limited retention time [17, 24]

Swelling system:

These swelling system after oral administration swell to an extent that inhibits their passage through the pylorus. So the dosage form remains persistent in the stomach for an extended duration. The swelling systems are occasionally denoted as plug type systems due their capability of remain lodged at the pyloric sphincter. The resulting polymeric matrices halt in the gastric cavity for numerous hours. A continual and precise drug release can be anticipated by choosing a polymer with the suitable molecular weight and swelling characteristics. The polymer swallows water and swelling takes place as the interaction of polymer with gastric fluid occurs. [31]

Raft forming systems:

These systems are very renowned these days because of antacids and drug delivery for gastrointestinal infections and disorders. The cohesive gel formed because of interaction with gastric fluids is main part of mechanism of these systems and portion of the liquid swells developing a continuous layer called a raft. The floatation of raft on gastric fluids takes place due to low bulk density formed by the production of carbon dioxide (CO_2). These raft forming systems are generally used for gastroesophageal reflux treatment with Liquid Gaviscon. [32, 19]

Magnetic system:

Magnetic systems are another effort to improve the gastric retention time (GRT). They are constituted in simple method. This dosage form consists of a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Normally magnetic system are considered to be working normally but the position of the external magnet is key point in this method. The wrong degree of precision of its position can compromise patient compliance**.** [33, 16]

Super porous Hydrogels:

These hydrogels are formed by numerous approaches like phase separation, cross-linking method, gas-blowing method, etc. The concepts of gastric intestinal physiology, these kinds of hydrogels have to comprise following characteristics to behave as gastric retention device.

1. Initial small size sufficient for easy swallowing.
2. Fast swelling sufficient to overcome gastric emptying by IMMC.
3. Large size of swollen hydrogels adequates enough to be retained in the stomach.
4. Strong swollen hydrogel to persist contraction pressure, abrasion and shear forces in stomach.

The most common employed method for formation of Super porous Hydrogels is Gas blowing method. This process works by crosslinking polymerization of monomers in the presence of gas bubbles. The well-ordered addition of various constituents like monomer, cross-linker, foam stabilizer, polymerization initiator, initiation catalyst (if any) and foaming agent in a test tube of specific size. A favorable low pH of monomer solution is sustained at 5

to 6 in the start before adding foaming agent and later its addition leads to creation of bubbles. Then it subsequently increases the pH of solution which speeds up the polymerization process. The formation of homogenous porous hydrogels (super porous hydrogels) takes place ultimately by synchronized foaming and gelation processes. Afterward, the washing and drying are performed with various techniques and in result, it impacts the swelling and mechanical performance of resultant hydrogels**.** [8, 13, 34]

Table 1: Various natural and synthetic polymers used in Floating Drug Delivery System

Natural polymers [27, 28]	**Synthetic polymers** [29, 30]
Chitosan	HPMC K4M
Pectin	HPMC K15M
Xanthan gum	HPMC K100M
Guar gum	Carbopol 934 P
Alginates	Ethyl cellulose
Gellan gum	Methylcellulose
Starch	Sodium carboxy methyl cellulose
Karaya Gum	Polyvinyl alcohol
Honey locust gum	Polyamides
Tamarind Gum	Polycarbonates
Aloe Mucilage	Polyalkylene glycols
Psyllium Husk	Polyvinyl ethers
Tara gum	Hydroxypropyl cellulose
Okra gum	Hydroxyethylcellulose
Carrageenan	Eudragit (RL100, L100, RS PO, RS EPO,S100)
Arabinogalactose	Polyvinylpyrrolidone (PVP)

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