GASTRO RETENTIVE DRUG DELIVERY SYSTEM: A NOVEL APPROACH TO ENHANCE GASTRIC RETENTION FOR CONTROL DRUG RELEASE

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ABSTRACT

Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT). Prolonged gastric residence increases duration of drug release, reduces drug waste, and improves drug solubility in gastric pH. We have reviewed various gastro retentive approaches designed and developed until now i.e. floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, high density system, Raft forming system, magnetic systems, super porous hydrogel system. Finally, advantages, disadvantages, potential drug candidates, mechanism, marketed preparation of gastro retentive drug delivery systems were discuss.

KEYWORDS: Gastro retentive drug delivery systems, Gastro retentive approaches, Marketed products

INTRODUCTION

The oral route of drug administration is most commonly used due to its cost efficiency and good care of the patient due to easy administration. Floating drug delivery system is also popularly known by the name of hydro dynamically controlled system. Basically the floating

dosage form is of very low density, which enable drug to float in gastric media in stomach. This results in increasing the residence time of drug in stomach without affecting gastric emptying rate in whole. The dosage form keep floating on gastric content and release drug in slow manner at desired rate, resulting in increased gastric retentive time in the stomach. It also helps in reducing the drug concentration variation in plasma.

These dosage forms are swallowed so that the pharmaceutically active substance can be absorbed via the Gastro-intestinal tract (GIT). The traditional oral delivery system has certain disadvantages that needed to be overcome such as the short retention time in GIT (Jassal, Nautiyal and Kundlas, 2015).

In spite of having many advantages, this dosage form suffers number of disadvantages such as unpredictable gastric emptying time, variation of gastric emptying time from person to person, small gastro-intestinal transit time (8-12 h), and number of drugs have absorption windows in upper part of small intestine. The formulation scientific has to take care of these many number of challenges while designing a gastro retentive drug delivery systems. Apart from this the main challenge that one face is of shorter gastric residence time (GIT), which is unpredictable and changes depending on number of factors.

To be able to design GRDDS in a better way, a thorough knowledge and understanding of anatomy and physiology of GIT is necessary (Shah, Prajapati and Patel, 2017). Gastric emptying states were fed along with fasting. Various literature and reports shows that orally administered controlled drug delivery systems are subjected to two complications are reduced GRT and unpredictable GRT (Bhowmik and Gautam, 2018). Drugs solubility's high alkaline PH of intestine, can be delivered using gastro retentive drug delivery systems.

Gastro retentive drug delivery system is reported to have increased the solubility of such drugs. GRDDS is also used for drugs that degrade is colonic region. It is also beneficial for:

- Improving bioavailability of drug increasing therapeutic efficiency of drug.
- Reducing dose of drug.
- Maintaining uniform concentration of blood.

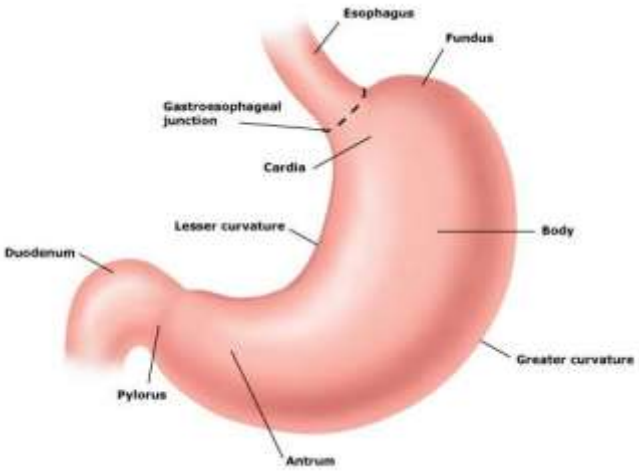

Figure 1: Human stomach structure

Advantages of gastroretentive drug delivery systems

a) Increase in bioavailability and curative efficiency of drugs.
b) It improved drug delivery and drug absorption.
c) By this method controlled amount of drug can be delivered.
d) It has a local action on stomach.
e) It minimizes the mucosal irritation.
f) Increased first pass biotransformation.
g) Ease of administration and improved patient compliance.
h) Low frequency of dosing.
i) Improved therapeutic efficacy.
j) Gastric irritation can be avoided by designing sustained release.
k) This system provides higher efficiency due to reduced counter activity by body

Disadvantages of gastroretentive drug delivery systems

a) FDDS require high fluid level in stomach to float and work effectively.
b) Rugs that absorb selectively in colon E.g. Corticosteroid.
c) Drugs that have very limited acid solubility (eg. phenytoin).
d) The drug that undergoes a significant first pass metabolism (eg. nifedipine).
e) Need high levels of abdominal fluids for the delivery system to float and function efficiently.
f) The presence of food is required to delay gastric emptying.
g) Hydrogel based swelling system takes longer time to swell.
h) Drugs intended for selective release in the colon.

Potential drug candidates for GRDDS

a) Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
b) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, furosemide, riboflavin etc.
c) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
d) Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
e) Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Drugs those are unsuitable for GRDDS

a) Drugs that have very limited acid solubility e.g. phenytoin etc.
b) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
c) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Table 1: Commonly used drugs in formulations of GRDDS

Dosage forms	**Name of drugs**
Tablets	Cephalexin, Ziduvudine, Losartan, Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Amoxycillin trihydrate, Dilitiazem, Florouracil, Metformin Hydrochloride, Atenolol, Diltiazem, Verapamil HCI, Ampicillin.
Capsules	Nicardipine, chlordizepoxide HCI, Furosemide, Misoprostal, Diazepam, Propranlol, Pepstatin, Celiprolol HCl.
Microspheres	Verapamil, Aspirin, Griseofulvin and p-nitroanilline, Ketoprofen, Tranilast, Iboprufen, Terfenadine, Piroxicam, Cholestyramine, Theophylline, Nifedipine, Flurbiprofen, Orlistat.
Film	Albendazole, P-aminobenzoic Acid, Piretanide, Prednisolone, Quinidine gluconate, Cinnarizine.
Bilayer tablets	Misoprostal, Trimetazidine hydrochloride and Metoprolol succinate, Diltiazem HCI and Lovastatin, Atenolol.
Beads	Ranitidine HCl, Loratadine, Curcumin β-cyclodextrin complex, Diltiazem HCl.

Needs of GRDDS

Conventional oral delivery is widely used in pharmaceutical field to treat diseases. Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site. Pharmaceutical field is now focusing towards such drugs which require site specificity.

APPROACHES FOR GRDDS

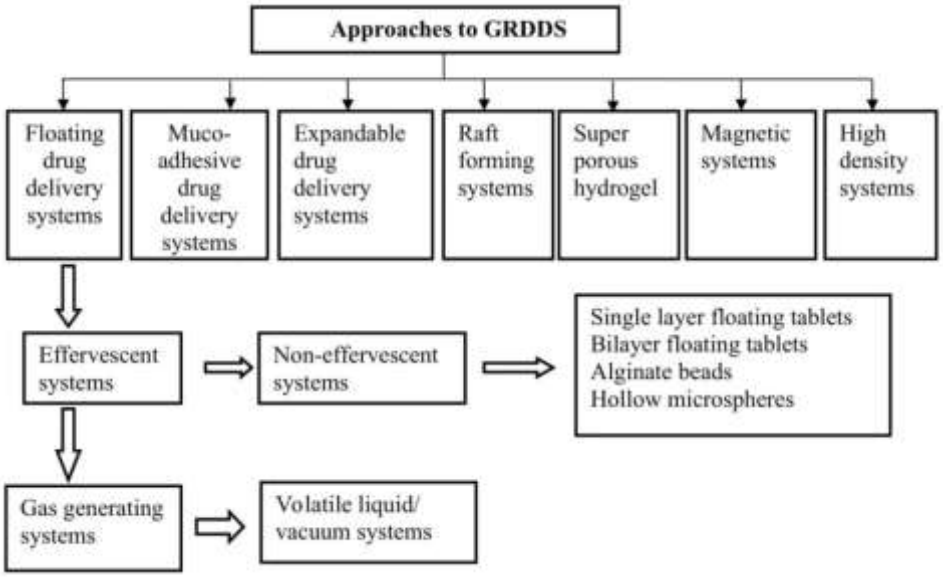

Figure 2: Flow chart of GRDDS

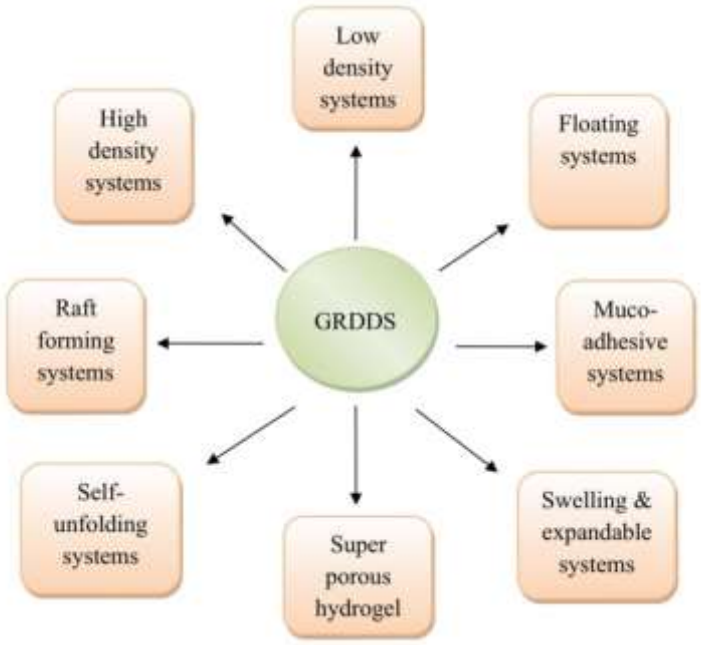

Figure 3: Approaches for GRDDS

Gastro retentive dosage form

The dosage forms that can be maintained in the stomach are called GRDF. Over the last two decades, numerous of GRDF have been designed to the prolong gastric residence time as shown in table 2 (Wagh, Ahirrao and Kshirsagar, 2018).

Table 2: Transit time of dosage form across the GIT

Dosage form	Small intestine	Stomach	Total {transit time h}
Tablet	3.1±0.4	2.7± 1.5	5.8
Capsule	3.2±0.8	0.8±1.2	4.0
Pellets	3.4±0.1	1.2±1.3	4.6
Solution	4.1±0.5	0.3 ± 0.07	4.4

1. Floating drug delivery systems

Floating drug delivery systems are known as low density system because their density is lower than gastric contents, they float in the stomach. Floating drug delivery systems is classified by:

1.1 Effervescent system

1.2 Non effervescent system

Floating drug delivery system

The floating drug delivery system is based on the mechanism system of float, these systems are mainly two different technologies have been utilized in development of FDDS which are: effervescent system and non-effervescent system Intragastric floating drug delivery devices are shown in figure 4 (Satinderkakar, Singh and Shallusandhan, 2015) .

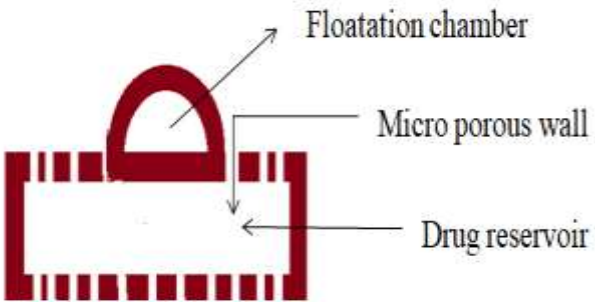

Figure 4: Intragastric Floating Gastrointestinal Drug Delivery System

Intragastric Floating Gastrointestinal Drug Delivery System

*T*hese systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a

micro porous compartment (Jassal, Nautiyal and Kundlas, 2015), (Shah, Patel and Patel, 2009).

1.1 Effervescent Floating system

These systems are matrix type, arranged with the help of swellable polymers, for example, methylcellulose and chitosan and various effervescent compounds, example Sodium bicarbonate, tartaric acid and citric acid. They are planned so that when in contact with the acidic gastric substance, CO_2 is freed and gets entangled in swollen hydrocolloids, which gives lightness to the measurement dosage forms (Bahadur *et al.*, 2008).

Floatation of drug delivery system in the stomach loaded up with vacuum, air, or an inert gas. Gas can be brought into the floating chamber by the volatilization of a natural dissolvable (organic solvent) (e.g., ether or cyclopentane) or by the CO_2 delivered because of a floating responses between organic acids and carbonate–bicarbonate salts (Neumann, Schneider and Koziolek, 2017), (Yadav *et al.*, 2016).

These devices contain an hollow deformable unit that changes over from a fallen to an extended position and comes back to the crumbled position after a pre decided measure of time to allow the unconstrained discharge of thin floatable system from the stomach (Sheikh *et al.*, 2020), (Aoki *et al.*, 2015).

The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas production is reported to be 0.76: 1 (Thakare and Patil, 2014), (Nila *et al.*, 2013). The system is classified as single unit matrix tablets or multiple unit pills. The Single unit matrix tablet may be single or multiple unit are multilayer type (Pahwa *et al.*, 2012).

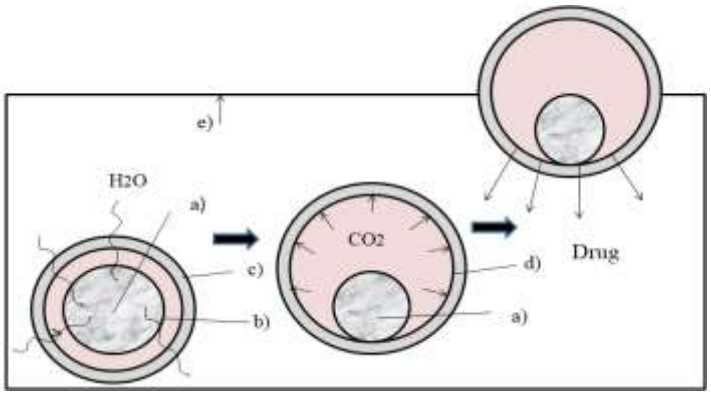

Figure 5: Effervescent floating drug delivery systems

These systems is further classified as below

1.1.1 Volatile Liquid Containing System

The volatile liquid containing system comprises of double chambers having an impermeable, movable bladder separation (Sharma and Khan, 2014), (Rapolu *et al.*, 2012). In volatile liquid

systems, volatile liquids such as ether and cyclopentane are introduced into an inflatable chamber, which volatilize at body temperature allowing inflation of the chamber in the stomach (Tripathi *et al.*, 2019),(Guguloth *et al.*, 2011). The drug continuous to release as the device inflates.

These systems are further classified as below:

a. Intragastric floating gastrointestinal drug system.

b. Inflatable gastrointestinal delivery system.

c. Intragastric-osmotically controlled drug delivery system (Sharma and Khan, 2014)

1.1.2 Matrix tablet

The matrix tablets are types of effervescent systems, matrix tablet developed to prolong gastric residence time, leading to an increase in drug bioavailability (Jaimini, Tanwar and Srivastava, 2012). It can be formulized in a single layer matrix tablet by implementing bicarbonates in the matrix forming hydrocolloid gel agent or in a dual layer matrix along with gas generating matrix together as an individual layer. The drug acts as the second layer. There is a possibility of triple layer matrix tablet.

1.1.3 Gas generating systems

The gas generating system is one layer and rest two is drug layers (Sharma and Khan, 2014). Gas-generating systems achieve their buoyant properties by the generation of gas bubbles. For example, CO_2 can be generated from sodium bicarbonate at an acidic pH (Zhao *et al.*, 2014).

a. Floating capsules

b. Floating pills

c. Floating system with ion exchange resins

1.2 Non Effervescent Floating system

Non effervescent systems is floating system include in a high level of one or more gels (20–75% w/w), highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethyl cellulose), polysaccharides, or matrix forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules (Neumann, Schneider and Koziolek, 2017), (Yadav *et al.*, 2016)

Upon exposure gastric fluid, these gel hydrate formers, polysaccharides and polymers and form a colloidal gel barrier that controls the rate of fluid penetration into the device and result in drug release (Abdelbary, Elsayed and Elshafeey, 2013), (Boldhane and Kuchekar, 2009). As the outer surface of the dosage form dissolves, the gel layer is retained by the hydration of

the adjacent hydrocolloid layer. The effect of air by the swollen polymer reduces the density and floats in the dosage form. The following approaches used to design in the intra-gastric floating systems (Bhadange, Darekar and Saudagar, 2015).

1.2.1 Hydrodynamically balanced intragastric delivery system (HBS)

Hydrodynamically adjusted gastrointestinal drug delivery system, either in the form of capsules or tablets, they are intended to prolonged gastrointestinal time in a zone of the GI tract to maximize the drug, increasing the absorption site in arrangement state and subsequently, prepared for ingestion. These system are contains to drug with gel-forming hydrocolloids intended to stay light on the stomach content (Satinderkakar, Singh and Shallusandhan, 2015)

These are single-unit dosage form, in which hydrophilic polymer have one or more gel-forming in Hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylates, polystyrene, agar, carrageenan or alginic acid are commonly used for excipients to development of in this systems (Wagh, Ahirrao and Kshirsagar, 2018), (T.Ramdas, Dolas, Hosmani Avinash, 2015).

1.2.2 Microballoons or hollow microspheres

Micro balloons or hollow microspheres are filled with drugs in their other polymer layer. When prepared by the simple solvent evaporation method or solvent diffusion method to prolong the gastric retention time (GRT) of the dosage form polymer is used to develop this method. These system are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. (Prajapati *et al.*, 2013), (Bansal *et al.*, 2014).

The float and drug release polymer for dosage are dependent on the plasticizer polymers, ratio and volume used for solvent formulation (Kumar *et al.*, 2016). These micro balloons are float continuously on the surface of an acidic dissolution media containing surfactant for >12 hours. Hollow microspheres are considered to be one of the most promising floating systems as they are combined with the advantages of multi-unit and float much (Yadav *et al.*, 2016)

1.2.3 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 -40ºC 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 (Jassal, Nautiyal and Kundlas, 2015), (Llabot, Manzo and Allemandi, 2004).

1.2.4 Microporous compartment

Microporous compartment is technology based on a drug reservoir inside a micro-compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric surface with the non-dissolved drug. In the stomach, there is air trapped in floatation chamber, causing the delivery system to float above the gastric content. Gastric fluid enters through the pours and dissolves drug for continuous transport into the intestine for absorption (Neumann, Schneider and Koziolek, 2017), (Yadav *et al.*, 2016)

2. Non-floating system

The non-floating systems are a type of gastro retentive drug delivery system (GRDDS).These systems are maintained in the stomach by many mechanisms but not by floating. Non-floating system are further subdivided:-

a) Bioadhesive / mucoadhesive system

b) Super porous hydrogel

c) Swelling system

d) Expandable system

e) Raft forming system

f) Magnetic system

g) Sinking (High density) drug delivery system

h) Alginate bead

2.1 Mucoadhesive drug delivery systems

The mucoadhesive drug delivery systems consist of a mucoadhesive polymers, which adheres to the gastric mucosal surface and prolong its gastric retention in the GIT. The mucus creates the ability to adhere to the gel layer. These polymers can be natural such as sodium alginate, gelatin, guar gum etc. semi-synthetic polymers such as HPMC, carbopol, sodium carboxy methyl cellulose (Satinderkakar, Singh and Shallusandhan, 2015), (More *et al.*, 2018)

The binding polymers are- the surface of the mucus and epithelial can be divided into three broad categories are- Hydration-mediated adhesion, bonding -mediated adhesion and receptor-mediated adhesion (Sharma and Sharma, 2014), (Arifin, Lee and Wang, 2006).

Bioadhesive or mucoadhesive 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 of the

stomach (Potekar, Mulla and Doijad, 2017), (Darbasizadeh *et al.*, 2018). Some of the most promising excipients that have been used commonly in these systems include polycarbophil, Carbopol, lectin, chitosan, CMC etc. (Shah, Prajapati and Patel, 2017), (Ugwoke *et al.*, 1999).

There are various types of mucoadhesion are:

a) ***Hydration-Mediated Adhesion*** This achieved by using hydrophilic polymers which imbibe large amount of water and become sticky, thereby acquiring mucoadhesive properties. The prolonged gastro retention of the bio/mucoadhesive drug delivery system is further controlled by the dissolution rate of the polymer.

b) ***Bonding-Mediated Adhesion*** The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical– mechanical bonding and chemical bonding. Physical–mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature.

c) ***Receptor-Mediated Adhesion*** Polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant like such as tomato lectin interact specifically with the sugar groups present in mucus or on the glycocalyx.

Polymers used in gastroretentive mucoadhesive drug delivery system.

(1) Synthetic polymers

(a) Various grades Poly ethylene oxide like WSR 301, 301, N10, Coagulants.

(b) Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxy-ethyl cellulose, hydroxyl propyl cellulose, hydroxy propyl methylcellulose, sodium carboxy methylcellulose.

(c) Poly (acrylic acid) polymers (carbomer, polycarbophil).

(d) Poly (hydroxyl ethyl methyl acrylate).

(e) Poly (vinyl pyrrolidone).

(f) Poly (vinyl alcohol).

(2) Natural polymers

Tara gum; Sodium alginate; Karaya gum; Guar gum; Xanthan gum

2.2 Super porous hydrogel

Super-porous hydrogel are swellable systems, these are differ adequately from the conventional types to justify separate and classification. With pore sizes between 10 nm to 10 μm, the absorption of water by conventional hydrogels to reach equilibrium state during which early withdrawal can occur in h dosage form. Super-porous hydrogels, average orifice

size > 100 μm, and due to rapid watering by capillary wetting through swell, abundant open pores to create equilibrium within one minute. Furthermore, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by the gastric contraction (Wagh, Ahirrao and Kshirsagar, 2018), (Kumar and Kaushik, 2018).

Super porous Hydrogel Composites (SPHCs), as the second generation of SPHs, possess improved mechanical properties over SPHs, with composite agents such as, Chitosan. Ac-Di-Sol and Carbopol. After preparation of these SPHCs, they can be drilled and filled with drug-polymer mixture to provide drug delivery in sustained fashion (Pawar *et al.*, 2011). Alternatively, these drugs filled SPHCs can also be filled in suitable size hard gelatin capsules for ease of administration (Shah, Prajapati and Patel, 2017)

2.3 Swelling system

Subsequent to being gulped, these dosage forms are swelling to a size that keeps away from their entrance through the pylorus. In this method, As a result, the dosage form is maintained in the stomach for a long time. These systems are at some point referred for plug point system. Since they will as a rule stay halted at the pyloric sphincter. These polymeric cross sections remain in the gastric gloom for a couple of hours even in the few worked state. Proceeded and controlled drug release may be accomplished by selecting a polymer with the right sub-atomic weight and swelling properties (Neumann, Schneider and Koziolek, 2017).

When exposed to gastric fluid, the polymer swallows water and becomes swollen. The broad swelling of these polymers is an aftereffect of the presence of physical-chemical cross links in the hydrophilic polymer organize. These cross-linking prevent the dissolution of the polymer and therefore maintain the physical integrity of the dosage forms (Malik *et al.*, 2014). A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the inflammatory capacity of the system and maintains its physical integrity for a longer period of time.

The swelling system are subcategorized into three steps

a. **Swelling index**
b. **Weight gain and Water uptake**
c. **Continuous monitoring of water uptake**

a. Swelling index: The swelling index after concentration of swelling dosage form into SGF at 37°C, the dosage form is removed out at regular interval and dimensional changes are measured in conditions of increase in tablet thickness / diameter with the time.

b. Weight gain and water uptake: Water uptake is indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as Weight Gain.

Water uptake (WU) is measured in terms of percent weight gain as given by equation below, (Lakshmi and Vidyadhara, 2018)

$$Water\ uptake\ (WU) = \frac{W_t - W_o}{W_o} \times 100$$

Where, W_t = weight of dosage form at time t

W_o = initial weight of dosage form

c. Continuous monitoring of water uptake: Although previous method has advantage of un-disturbance of swollen tablet, but for measuring water uptake one has to remove whole assembly out of beaker, so process in not continuous. In this apparatus, swelling tablet is placed on glass filter as support in one hollow cylinder with smooth surface inside, and one light weight punch is placed on it to prevent floating. This cylinder is placed pre-heated in dissolution medium. Another dissolution medium reservoir beaker is placed on digital balance and both are connected with media filled U tube and medium level is kept equal. As swelling of tablet started, it absorbs water and water level in outer part of cylinder goes down. The decrease in water level is maintained by importing extra medium via U tube from reservoir beaker. As medium is transferred from reservoir, amount of water transferred can be determined by observing loss in weight by digital balance (Rajamma, Yogesha and Sateesha, 2012), (Badoni A., Ojha A., Gnanarajan G., 2012).

2.4 Expandable drug delivery system

Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would achieve the known pharmacokinetic and pharmacodynamics advantages of controlled release dosage form of these drugs (Ullah *et al.*, 2017), (Suresh *et al.*, 2013). The need for GRDFs has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. Several approaches have been proposed to retain the dosage forms in the stomach. The dosage size in the stomach is one of the influential factors of gastric retention time (Shaikh, K. N., Payghan S.A., 2011), (Kumar, Aeila and Sai, 2020).

Expandable drug delivery systems are small for easy swallowing and expand to a larger size after contact with gastric juices, which can prolong the gastric retention time. Thus, an optimal expandable dosage requires the following properties: convenience for oral ingestion, expandable upon contact with the gastric contents, controlled drug release and either a

degradable nature or a reduction in size enabling safe evacuation after drug release (Bahadur, Roy, Chanda, *et al.*, 2016).

Superporous hydrogels that are pH and temperature sensitive, are fast-swelling and have a high swelling capacity are considered to be a novel material for swellable system (Klausner *et al.*, 2003), (Kumar, Doddayya and S, 2012).

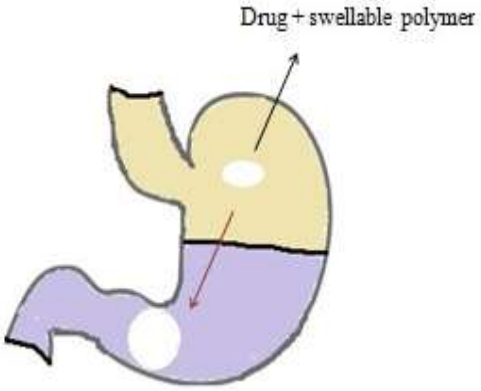

Figure 6: GRDDS based on expandable tablet

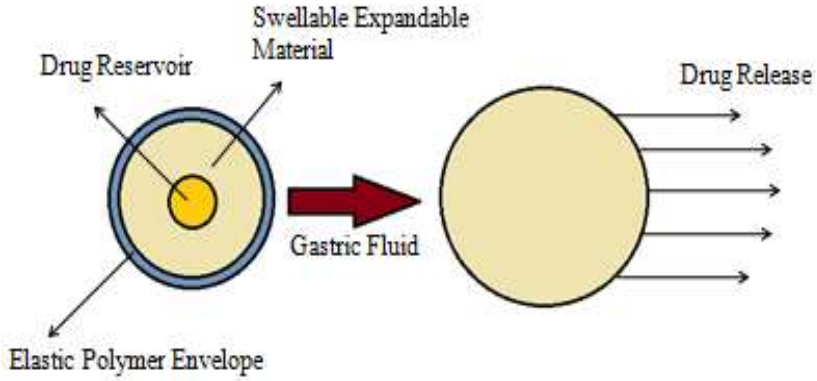

Figure 7: Drug release from swellable system

2.5 Raft forming systems

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. Gelation involves formation of the double helical junction zones followed by aggregation of the double helical segments which form three dimensional networks by complexation with cations and hydrogen bonding (Nakanishi, Kaiho and Hayashi, 1998), (Parikh and Amin, 2008).

The raft floats because of the buoyancy created by the formation of CO_2 and acts as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the esophagus. Usually the system contains a gel forming agent or polymer (e.g. alginic acid), acid neutralizer and

alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids.

Various natural and synthetic polymers can be utilized in the formulation of raft forming drug delivery systems. Natural polymers include alginic acid, guar gum, gellan gum, xyloglucan, pectin, chitosan etc. Synthetic polymers include poly (DL Lactic acid), poly-caprolactone, HPMC etc. (Shah, Prajapati and Patel, 2017)

2.6 Ion exchange resin system

Ion exchange resin system is a system which is formulated to have gastro-retentive properties. Ion exchange resin beads are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions takes place. As a result of this reaction, carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly (Porwal, Dwivedi and Pathak, 2017).

2.7 Magnetic systems

These systems, which have a density of 3 g/cm^3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm^3, such systems can be retained in the lower part of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50 %) and to achieve the required density of 2.4–2.8 g/cm^3. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide, and iron powder may be used to manufacture such high-density formulations (Yadav *et al.*, 2016). This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance (Nayak A.K, 2010), (Bahadur *et al.*, 2018).

2.8 High density systems

High density systems have a density greater than that of gastric fluid commonly used excipients of these systems includes barium sulfate, zinc oxide, iron powder and titanium dioxide. The densities of the tested dosage forms ranged from 0.9 to 5 g/cm^3. The author concluded that high density materials had slower GRTs than high density materials.

Thereafter, the impact of dosage form density on GRT has been studied. The small density pellets are able to resist gastric peristaltic movement due to their retention in the antrum range or fold, increasing the gastrointestinal tract time from 5.8 to 25h. Even though this system has the potential to improve the GRT (Malik *et al.*, 2014). It is difficult to density high density pellets containing high drug dose.

2.9 Alginate beads

The aqueous solution of calcium chloride consist of freeze-dry calcium alginate bead of approximately 2.5 mm diameter prepared by pouring sodium alginate solution, leading to the formulation of calcium alginate precipitation porous system which help the system float on gastric contents. Due to the porous nature, they can maintain floating power for more than 12 hour, when compared with solid beads, which have a short residence time of 1 hour, and these floating beads indicates the resident time of more than 5.5 hours (Malik *et al.*, 2014).

Table 3: Mechanism of various GRDDS

Gastroretentive approaches	Mechanism
Floating systems	System causes buoyancy in gastric fluid. Density of pellets/tablets is lower than the density of stomach fluid.
Bioadhesive systems	A very complex process with several mechanisms, including electrical theory, adsorption, wetting, diffusion, and fracture theories. The interaction between the negatively charged mucosal surface and positively charged polymers might facilitate the bioadhesive process.
Expandable systems	Expansion of the dosage form occurs by swelling or unfolding in the stomach Swelling usually occurs because of diffusion. Unfolding takes place due to mechanical shape memory.
Superporous hydrogel systems	Swells up to 100 times due to water update by capillary wetting through numerous pores.
Raft forming systems	The polymer in presence of mono or divalent cation, absorbs water, swells and forms in situ gel layers, which float above gastric fluid and termed as raft.
Magnetic systems	Consists of the small internal magnet mixed with the drug. Its position inside the stomach is controlled by an extracorporeal magnet.
High density systems	Uses the density of dosage form as a strategy to produce the retention mechanism. Sinking system remains at the bottom of the stomach, where the density of the dosage form is greater than the gastric fluid.

Table 4: Commercially Available Marketed Products of GRDDS

Brand Name	Drug	Dosage forms	Dose	Indications	Company
Cifran O.D	Ciprofloxacin	Tablet	500mg, 1 gm	Systemic treatment of infections	Ranbaxy, India
Madopar	Levodopa and Benserazide	Capsule	100mg and 25mg respectively	Parkinson's disease	Roche Products, USA
Glumetza	Metformin Hydrochloride	Tablet	500mg and 1000mg	Type 2 diabetes	Depomed, Canada
Oflin OD	Ofloxacin	Tablet	400mg	Genito urinary, respiratory, gastrointestinal, skin and soft tissue infections.	Ranbaxy, India

CONCLUSION

Gastroretentive drug delivery systems have developed as current approaches of increasing the bioavailability and controlled delivery of drugs that exhibit an absorption window. Gastroretentive drug delivery system is having various approaches like floating, bioadhesive, swelling, magnetic, and high density systems. These approaches not only provide controlled release of the drug but also improve the bioavailability. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards commercializing this technique. Number of commercial products and patents issued in this field are evident of it.

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