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A REVIEW ON GRDDS RECENT ADVANCES IN DRUG DELIVERY SYSTEMS AND ITS APPLICATION

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ABSTRACT

One such shown technique is the drug delivery system with gastroretentive characteristics, aiming at locally or systemically releasing particular drugs. In the pharmaceutical business, much emphasis has been given to the development of controlled oral release and site-specific medicines to achieve better therapeutic benefits. Drug absorption is a very variable process in the gastrointestinal system and extending gastric dose form retention extends the drug absorption duration. In the upper section of a gastrointestinal system, this technique is especially beneficial for medication usage with a restricted absorption window. This review also provides an outline of the merits, demerits and assessment factors. There are many advantages to the development of the Gastro retention system, such as enhancing drug bioavailability, increasing the solubility of less soluble drugs at high pH, controlling the therapeutic rate thereby reducing the fluctuations incidence and thus reducing the consumption for half-life. This review article focuses on various essential methods for delivering gastroretentive medicines (floating, bioadhesive, high-density, swelling, raft forming, and magnetic systems) in different dosing forms.

KEYWORDS: GRDDS, evaluation parameters, non-floating system, floating system, applications.

INTRODUCTION

The most convenient and recognised approach for the administration of drugs was the oral route. During oral controlled release, huge curative advantages prefer to the advantage of therapeutic advantages, as an attractive issue in the pharmaceutical sector. Gastro-resistant

medicines are new systems in delivery that are of upper hand because of their capacity to maintain their stomach for longer periods. The non-site special release of medication is also a drawback to conventional rapid release tablets.[1,2] On the other hand, certain medicinal products are absorbed from specific places and must be released at this spot solely for maximum absorption. It depends on variables such as the emptying process, dosage form transit length through the digestive system, the release of medication from the dosage form and the site of the absorption. The oral routes remain the most popular way of drug delivery to systemic circulation, due to their simplicity of administration, low drug costs, patient compliance and flexibility in formulation. Estimated 90% of all systemic drugs are administered orally in drugs administered orally; solid oral dosage forms are preferable over liquid oral dosage forms.[3] Tablets are now the most prevalent type of solid dose. Depending on drug release patterns, they might be categorised in two groups, namely immediate release and delayed release. Drug having short halves that are quickly absorbed and eliminated from the gastrointestinal tract quickly eliminates systemic circulation. In order to be successful, these medications must be taken regularly. In addition, medications with a low absorption fencing in the upper portion of the GIT are not suitable for oral, sustained release systems due to the short gastric emptying time of 2.7±1.5 hours (h) and 3.1±0.4 hour of intestinal transit.[6] One method to extend gastric residency is to employ gastroretentive medicines for local or systemic effects. These types of dosage may remain long in the stomach and increase the period of stomach retention. The medicine is therefore given continually to the absorption point in the gut, i.e. the gastric stomach.[7] In 1968, after observing several patients chocked after eating pills, David explained the floating drug distribution process for the first time. Its solution consisted of using tablets of less than 1 g / ml to float on the surface of the water. Since then several approaches for optimum floating supply systems have been developed.[8] Increased interest in novel dosage formulations which remain in the stomach for a lengthy and predictable period of time is manifested in the industry and academic.[9]

The Perks of A Gastroretentive Drugs Delivery System

- Improved bioavailability: The bioavailability of riboflavin and levodopa is considerably greater than the normal forms of dosage as it is absorbed in the upper section of the digestive tract.[10, 11]
- Reduced dose frequency and long-term drug use. This improves compliance with the treatment strategy for the patient. The upper part of gastrointestinal tract can all get local antacids, anti-ulcer medications and antibiotics for H. pylori infection.[5, 12]

- There is no evidence of drug level fluctuation, and the appropriate therapeutic plasma and tissue concentrations are maintained for a long duration. There is a reduction in the chance of failure of the medical therapy as well as unwanted side effects.
- These medicines include Furosemide[13], Captopril[14], and Diazepam, Verapamil, and Cefpodoxime proxetil[15], to name a few. Suitable for the drugs which degrade in the intestine or column.[16]

Risk Factors In the Delivery of Gastroretentive Medication

- Inadequate for medications that are acid-sensitive. Inadequate for better absorbed medications in the lower part of the gastrointestinal tract.
- Problems with the result and dumping wanted.
- Many factors, including motility of the stomach, pH and food presence, affect gastric retention. The dosage form therefore has to be able to resist peristalsis in the stomach.
- Poor connection between in vitro and in vivo.
- The expense of wording is greater.
- It is difficult to withdraw the medicine with toxic, poisonous or hypersensitive effects.

Other Stumbling Block of Specific Types of Gastroretentive Drug Delivery Systems Are Listed In The Table Below

Technology	Stumbling block
Expandable system	Hydrolysable and biodegradable polymers cause storage problems, making it difficult and expensive to make.
Floating system	The ability to float is heavily dependent on the stomach's ability to digest food, and a larger amount of fluid is necessary in the stomach.
High density system	Large amounts of medicines are difficult to integrate. To present, there are no such systems accessible on the market
Mucoadhesive system	Due to the fast turnover of mucus and the peristaltic wave of the stomach, it might get separated from the gastric mucosa. In addition, it may attach itself to the mucus of the intestines
Magnetic system	Patient compliance is an issue

Factors Influencing the Gastroretentive Drug Delivery System

A number of factors have implications for gastric emptying, which could have a major impact on the release and absorption of a medicine, the development of a drug delivery system with an extended gastric residence and drug release profile independent of the patient's related variables is desirable.[18]

The factors that influencing the gastric emptying and hence the gastric retention of the drugs includes.

- Concomitant adiminstration of drugs such as anticholinergic agents e.g., atropine, propantheline and opiates delay the gastric emptying while the prokinetic agents like metoclopramide and cisapride enhance the gastric emptying process.[19]
- Density, size and shape of the dosage form.[20, 21, 22]
- Intake of food with drugs: the nature of the food, calorie content and its frequency of intake have considerable effect on the retention of drugs in stomach.[23, 24]
- Fasting or fed state of the stomach: During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. In the fed state this cycle is delayed and hence the gastric emptying rate is slowed.[25, 26]
- Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn's disease.[27, 28]

Different Perspective of the Grdds

Various ways of retaining oral dose forms in the stomach were employed. Some are defined as single components and others as multi-piece dosing forms. Gastroretentive drug delivery system may be widely classified as a floating and non floating system.

A. Floating drug delivery system (FDDS)

Unlike the high-density drug delivery system, floating systems have a density that is smaller than the gastric content, such that the system is buoyant in the stomach for a long time without altering gastric content. Floating systems for medication delivery are sometimes referred to as a low density system. Figure 1 shows the mechanism of floating of this system.

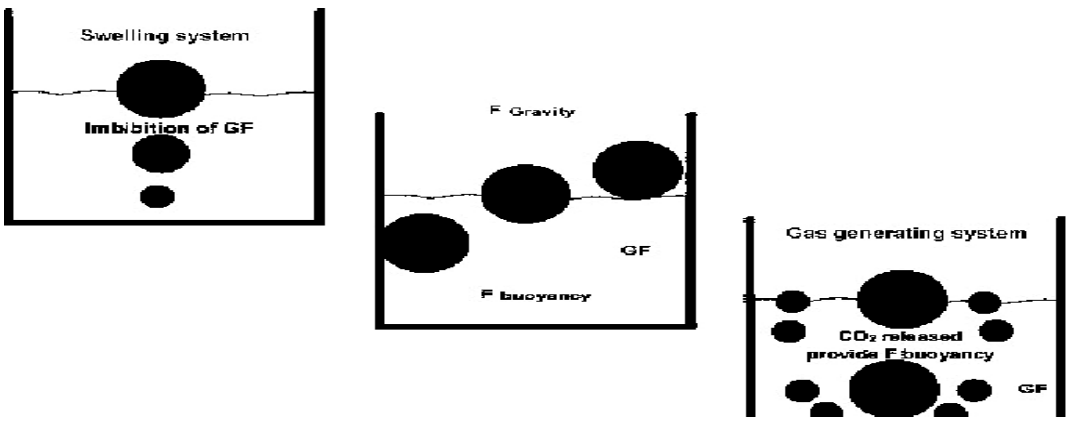

Fig. 1: The mechanism of floating system.

Floating drug delivery system can be divided into.

a. Effervescent system

b. Noneffervescent system

i. Alginate beads

ii. Microporous compartment

iii. Hydrodynamically balanced system

iv. Microbaloons

B. Non-floating system

These gastro retentive drug delivery systems do not float in the stomach however they remain retained there by different mechanisms. Non-floating system is further divided into:

- a. High density (sinking) drug delivery system
- b. Unfoldable system
- c. Magnetic system
- d. Bioadhsive or mucoadhesive system

C. Superporous hydrogels

- 1st generation superporous hydrogel (**CSPHs)**
- 2nd generation superporous hydrogel (**SPHCs)**
- 3rd generation superporous hydrogel (**SPHHs)**

A. Floating Drug Delivery System

a. Effervescent System

This system comprises of swellable polymers such like sodium bicarbonate, disodium glycine, cytroglycine, citric acid and tartaric acid. This is an effervescent material. The mechanism releases carbon dioxide in contact with gastric fluid which causes the formulation to float within the stomach.[32] For gas production, it is stated that the optimum citric acid and sodium bicarbonate ratio is 0.76:1.[9] It is also split as tablets with a single matrix unit or numerous pills. A single matrix tablet unit might be of one or many layers. Floating system with ion exchange resins has also been reported. Effervescent system and drug release from such system is shown in figure 2.

Fig. 2: Drug release from effervescent system.

b. Non-effervescent system

In this system, gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene are used. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Superporous hydrogels are an excellent example working in this approach. The dosage form swells significantly to several times of original volume upon contact with gastric fluid, the gastric contraction pushes the dosage form to the pylorus but due to larger size of the dosage form, the contractions slips over the surface of the system, due to which the dosage form pushes back into the stomach[33] (Fig. 3).

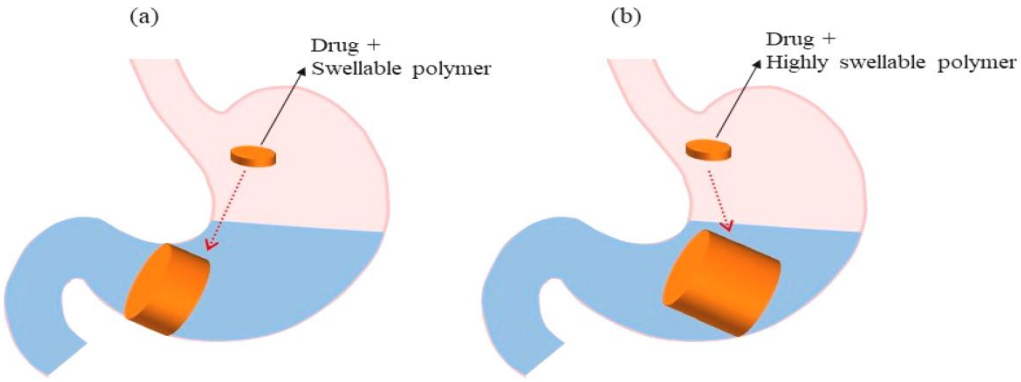

Fig. 3: Gastric retention of highly swellable gastro retentive drug delivery system.[34]

Non-effervescent system can be further divided into: hydrodynamically balanced system, Microbaloons, alginate beads, and microporous compartment.

Alginate beads

The development of multi-unit floating dosage forms has been used freeze-dried calcium alginates. The spherical beads of around 2.5 mm in diameter can be produced by dropping sodium alginate solution into an aqueous calcium chloride solution.[35] These beads are separated from one other and air dried. This leads to the development of an aporous system in the stomach.

Microporous compartment

This device contains a drug reservoir inside a microporeal compartment with pores on top and bottom walls (Fig. 4). The contained caught air floats the supply system floats over the stomach content. The gastrical fluid enters the aperture and disbands the medication and transports the dissolved medicine for absorption in the stomach and nearby section of the small intestine.

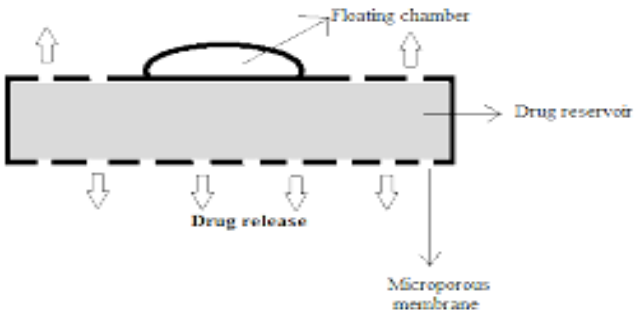

Fig. 4: Microporous compartment.

Hydrodynamically balanced system

The hydrodynamically balanced system was first designed by Sheth and Tossounian.[36] Hydrodynamically balanced system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This system contains one or more gel forming cellulose type hydrocolloid e.g., hydroxypropyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, agar, carrageen or alginic acid. It also contains matrix forming polymers such as polycarbophil, polyacrylate and polystyrene. When such system comes in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface (Fig. 5).

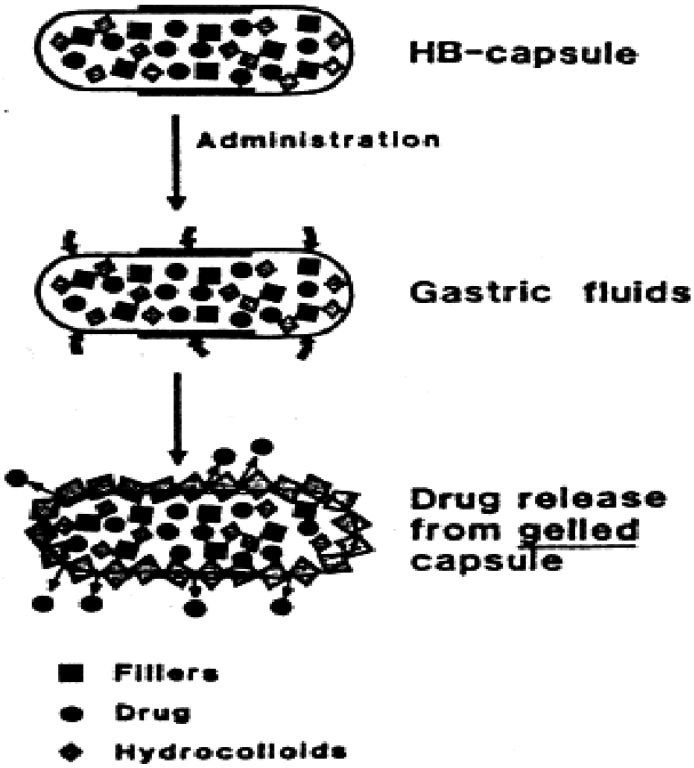

Fig. 5: Hydrodynamically balanced system.

Microbaloons

Hollow microspheres (Microbaloons), loaded with drug in their outer polymer shells, and are prepared by emulsion-solvent diffusion method. The steps involved in this method are summarized in figure 6. The ethanol: dichloromethane solution (1:1) and an acrylic polymer are poured into an agitated aqueous solution of polyvinyl alcohol at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane form an internal cavity in the microsphere of the polymer with the drug. The Microbaloons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.[37]

B. Non-floating system

a. High Density (Sinking) Drug Delivery System

In this approach formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide and titanium oxide so that the density of the formulation exceeds the density of the normal gastric content.[38] These materials increase the density up to 1.5-2.4 gm/cm3. Depending on density, the GI transit time of pellets can be extended from an average of 5.8 to 25 hours. But effectiveness of this system in human beings was not observed.[30] and no formulation has been marketed.

b. Unfoldable system

The drug delivery system unfolds and increases in size and it remains lodged at sphincter avoiding its exit from the stomach. For this the system should be small enough to be swallowed but unfold itself when it comes in contact with gastric fluid, and after a certain period of time its size should become small so that it will be easily evacuated. The unfoldable systems are made up of different biodegradable polymers.

c. Magnetic system

In this system, the dosage form contains a small magnet and another magnet is placed on the abdomen over the position of the stomach. The external magnet should be placed with a degree of precision which may decrease the patient compliance.

d. Bioadhsive system

The gastric retention time is extended by adhering the bioadhesive system to gastric mucosa membrane (Fig. 6). The adherence of the delivery system to the gastric wall increases residence time thereby improving bioabailability. The chemicals used for the mucoadhesion purpose include polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose, gliadin etc.[39] Novel adhesive material derived from fimbrae of bacteria or its synthetic analogues have also been tried for the attachment to the gut. However, gastric mucoadhesive force does not tend to be strong enough to resist the propulsion force of stomach wall. The continuous production of mucus and dilution of the gastric content is another limitation for such type of system. Many investigators have tried out a synergestic approach between floating and bioadhesion system.

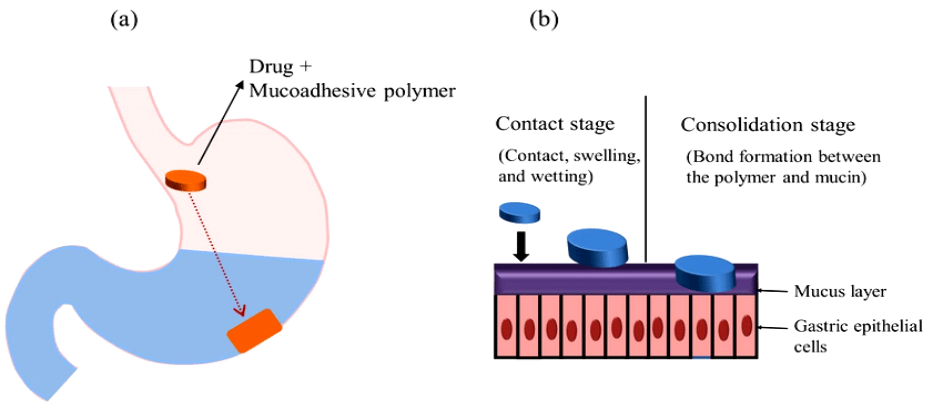

Fig. 6: Bioadhesive system.

C. Superporous Hydrogels[48]

A superporous hydrogel is a 3-dimensional network of a hydrophilic polymer that absorbs water in large amount in a short period of time due to the presence of interconnected microscopic pores. SPHs are a new type of hydrogel that have numerous super size pores inside them and the swelling occurs by capillary wetting but rarely by diffusion. Certain ingredients, including initiators, cross linkers, foam stabilizers, foaming aids and foaming agents, are added into monomer diluted water in the preparation of SPHs. Superporous hydrogel do not have only fast swelling, but also properties like slipperiness, biodegradability biocompatibility, high swelling capacity, high mechanical strength, and stability in acidic condition of the stomach.

This approach to improve gastric retention time super porous hydrogels of average pore size 100micrometer, swell to equilibrium size within a minute dur to rapid water uptake by capillary wetting through numerous interconnected open pors. They swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.

Probable Candidates For Grdds[24, 49, 50]

Following are the probable candidates, but not limited to, for gastro retentive drug delivery system.

- Drugs required to exert local therapeutic action in the stomach: antacids, anti-H.pylori agents, misoprostol
- Drugs that have narrow absorption window in stomach or upper parts of the small intestine, e.g., furosemide, riboflavine-5-phosphate, metformin hydrochloride, ciprofloxacin, alfuzosin hydrochloride, ofloxacin, norfloxacin, domperidone etc.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin tirhydrate
- Drugs unstable in the lower part of GIT, e.g., captopril
- Drugs insoluble in intestinal fluids, e.g., quinidine, diazepam
- Drugs that degrade in the colon, e.g., Ranitidine hydrochloride, metronidazole.

Improbable Drug Candidates for Grdds[51]

- Drugs having very limited acid solubility, e.g., Phenytoin.
- Drugs that exhibits instability in the gastric environment, e.g., Erythromycin.

Marketed Products of Grdds[52]

Following are some gastroretentive products which are available in market:

Brand name	Active Ingredient Pharmaceuticals	Dosage form
Cifran OD®	Ciprofloxacin	Tablet
Oflin OD Madopar® Conviron®	Ofloxacin LDopa and Benserazide Ferrous sulfate	Tablet Capsule Colloidal gel
Valrelease® Topalkan® Liquid Gavison	Diazepam Aluminium-magnesium antacid Al hydroxide and Mg carbonate	Capsule Liquid Liquid

Evaluation Parameters of Grdds[53]

Evaluation parameters of GRDDS generally include.

1. Drug-excipient interaction

It is done by using FTIR and HPLC. Appearance of a new peak and/or disappearance of original drug or excipient peaks indicate the drug excipient interaction.

2. Floating lag time

It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds.

3. In vitro drug release and duration of floating

It is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37±2OC in simulated gastric fluid of pH 1.2. Aliquots of the samples are collected and analyzed for the drug content. The time for which the drug remains floating on the surface of the medium is the duration of the floating time.

4. In vivo evaluation of gastric retention

Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ-scintigraphy and X-ray.

- In γ-scintigraphy, a small amount of stable isotope is compounded in the dosage forms during its preparation. The inclusion of a γ-emitting radio-nuclide in a formulation allows indirect external observation using a γ-camera or scinti scanner.
- For x-ray, barium sulfate is used as a contrast medium. It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form.

In addition, gastroscopy and ultrasonography studies can be included in the in vivo evaluation of GRDDS. Gastroscopy comprises of per-oral endoscopy, used with a fibereoptic and video systems. Ultrasonograpohy is not routinely used in the evaluation of GRDDS. In vivo plasma profile can also be obtained by performing the study in suitable animal model.

5. Water uptake study

It is done by immersing the dosage form in simulated gastric fluid at 37OC and determining the dimensional changes, such as diameter and thickness, at regular interval of time. After the stipulated time the swollen tablets are weighed and water uptake is measured in the terms of percentage weight gain, as given.

WU= (Wt-Wo) X100/Wo

In which, Wt and Wo are the weight of the tablet after time t and initially, respectively.

The tablets are also evaluated for hardness, friability, weight variation etc. which are applicable for conventional instant release tablets. For the multiple unit dosage forms like microsphere following tests are also essential apart from the above tests.

- Morphological and dimensional analysis: It is done with the aid of scanning electron microscopy and optical microscope.
- Percentage yield of microsphere.
- Entrapment efficiency: The drug is extracted by suitable method and analyzed to find out the amount of drug present.

CONCLUSION

In recent years, retention technologies for the supply of medicines to the gastrointestinal system have been extensively explored. A gastro-retentive oral pharmaceutical approach can assist to decrease the dose frequency of different medicine and is undoubtedly beneficial for pharmaceuticals in the stomach or upper intestine. However, several barriers have to be overcome to get the most of the system. Because the human gastrointestinal tract is unpredictable, numerous scientists are still investigating the best approach to use it. Some of them were successful, while others failed. In order to be effective in formulating medicines and excipients, a good GRDDS must take into account the physiological event in the gastrointestinal tract.

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