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REVIEW ON: GASTRO RETENTIVE DRUG DELIVERY SYSTEMS(GRDDS)

1. **Vaibhav Appaso Bhapkar**

Sarsam College of Pharmacy, Palshiwadi, Taluka-Baramati, Dist-Pune

2. **Tanmay Ramdas Chandgude**

Sarsam College of Pharmacy, Palshiwadi, Taluka-Baramati, Dist-Pune

3. **Sanket Balasaheb Hagwane**

Sarsam College of Pharmacy, Palshiwadi, Taluka-Baramati, Dist-Pune

Abstract:

A Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to Restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable Nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to
Achieve peak plasma levels. The purpose of writing this review on gastro retentive drug delivery systems was to Compile the recent literature with special focus on various gastro retentive approaches that have recently become Leading methodologies in the field of site- specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important Factors controlling gastric retention. Afterwards, we have reviewed various gastro retentive approaches designed and developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfordable, Super porous hydrogel and magnetic systems.

Finally, advantages of gastro retentive drug delivery systems were Covered in detail.

Keywords: GRDDS, evaluation parameters, non-floating system, floating system, application.

Introduction:

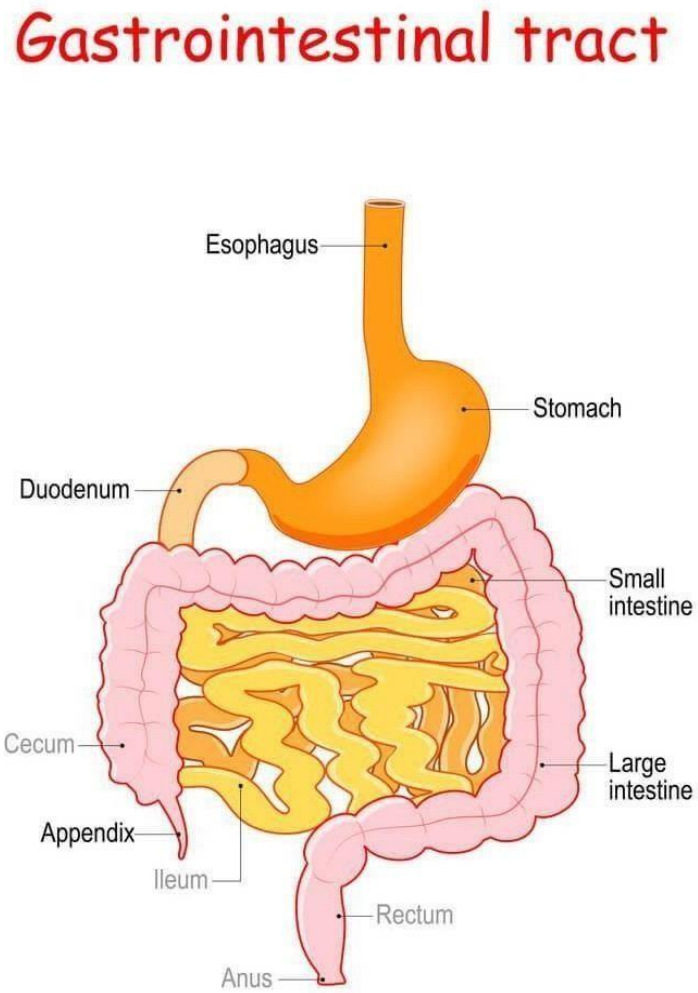
Oral drug delivery systems have dominated other drug delivery systems for human administration Due to their various advantages including ease of administration, flexibility in formulation, Cost- effectiveness, easy storage and transport, and high patient compliance. However, oral drug delivery Systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal System, pH of the commensal flora, gastric
retention time of the dosage form, surface area, and Enzymatic activity . Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolongs the gastric residence time if drugs. Prolong gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in high pH environment. Mucoadhesive systems that causes bio adhesion To stomach mucosa, unfold able, extendable or Swell able system which limits emptying of the dosage forms through the pyloric sphincter of the Stomach, super porous hydrogel system, magnetic System etc.

The main purpose of this review is to provide information on various GRDDS that have been Developed to date, as well as the physiological state of the stomach, suitable drug candidates for GRDDS, factors affecting GRDDS, and in vitro and vivo characterization of GRDDS. In addition, Challenges and future perspectives on GRDDS are discussed. The medicine is therefore given continually to the absorption Point in the gut, i.e. the gastric stomach.
In 1668, 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.

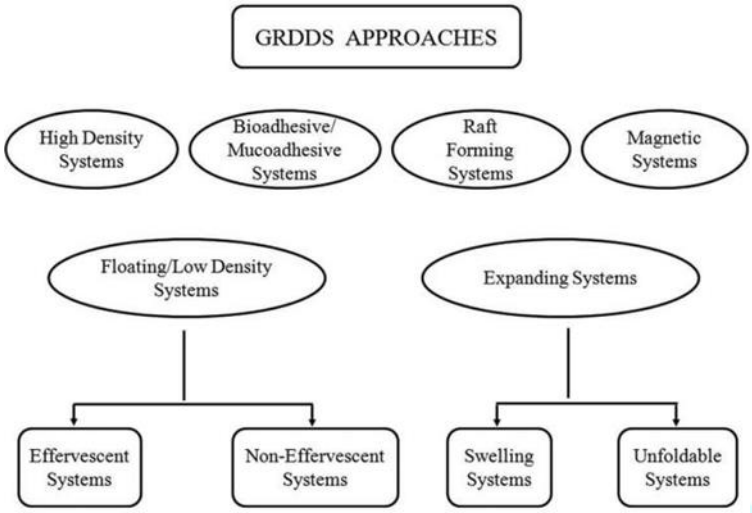
The relatively short gastric emptying time in humans, Which normally averages 2-3 hrs. through the major Absorption zone (stomach or upper part of the intestine), Can result in incomplete drug release from the drug Delivery system leading to diminished efficiency of the Administered dose.

Basic Physiology of gastro intesonal tract-

Anatomically the stomach is divided into three regions Fundus, Body and Antrum (pylorus) The proximal part made One novel approach in this area is GRDDSs (gastro retentive drug delivery system). Dosage forms that can be retained in the stomach are called GRDDS In the GRDDS, the stomach has a crucial role; therefore, a good understanding of the anatomy and physiology of the stomach is a prerequisite for successful development of the gastro retentive dosage form.



Gastroretentive drug delivery systems (GRDDS):



1) **High density approach**:

For preparing such type of formulations, the density of the pellets should be higher than the stomach fluid. It would be at least 1.50 g/ml. These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6 2.8 g/cm3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High density formulations
include coated pellets.

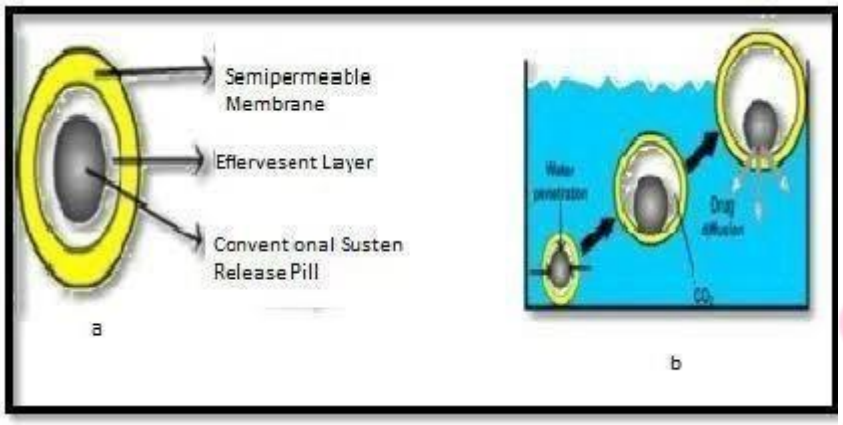
2) **Floating or low Density system:**

By virtue of their low densities, FDDS remain afloat above the Gastric contents for prolonged periods of time and provide continuous release of the drug. FDDS are low density systems that have enough Buoyancy to float over the gastric contents and remain in The stomach for a prolonged period. Floating systems can be classified- a)
Effervescent system

b) Non-Effervescent system

a) Effervescent system

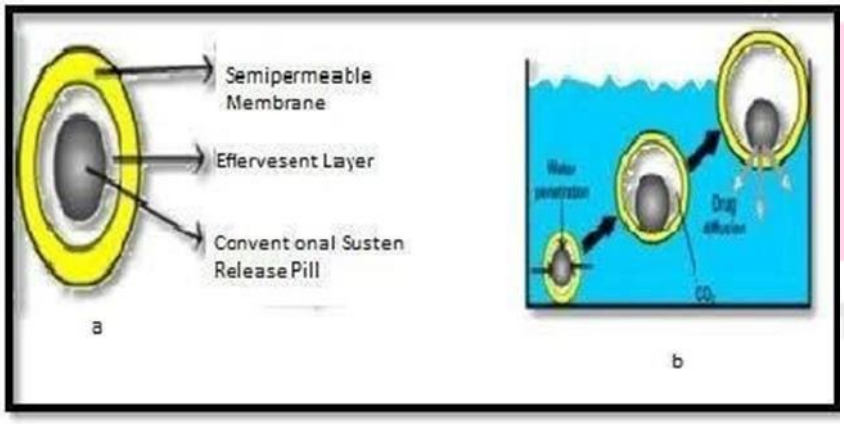
Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consisted of sustained- release pills as seeds surrounded by double layers. The inner layer was made up of effervescent layer containing both sodium bicarbonate and tartaric acid. This system made to float in the stomach by incorporating floating chamber ,which may be filled with vaccum, air or inert gas. This system uses matrices prepare with swelleble polymer and effervescent components.



Effervescent floating systems can be categorized into single- and double-layer effervescent floatingtablets and multiple-unit effervescent floating systems Single layer effervescent tablets are formulated by intimately mixing effervescent agent, polymer, drug, and excipients. However, in bilayer effervescent floating tablets, one layer comprises the drug, polymer, and CO2gas-generating agent,whereas the other layer constitutes an immediate- release drug and excipients without CO2and polymer.

B Non Effervescent system:

Non effervescent systems incorporate a high level (20– 75%w/w) of one or more gel forming, highly swellable, cellulosic hydrocolloids (e.g., Hydroxy ethyl cellulose, Hydroxy Propyl cellulose, Hydroxy Propyl methylcellulose [HPMC], and sodium carboxy methyl cellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablet or capsules.



These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature main ingredients of effervescent system include swellable polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid tarataric acid One drawback of the HBS is that this system, being a matrix

formulation, consists of a blend of drug and low-density polymers. The release kinetics of the drug cannot be changed without changing the floating properties of the dosage form and vice versa.

Bio/Mucoadhesive systems:

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the connection and duration of contact between

the dosage form and the biological membrane .The ability to provide adhesion of a drug delivery system to the gastrointestinal wall provides longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories.

A. Hydration-mediated adhesion

B. Bonding-mediated adhesion

C. Receptor-mediated adhesion

Raft Forming System:

This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formationof CO2 to makethe systemlessdense and float on the gastric fluids. The system contains a gel forming agent (e.g. alginic
acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus dioxide which becomes entrapped within the gel precipitate, converting it into
foam which floats on the surface of the gastric contents, much like a raft on water. Both in vitro and in vivo
studies have demonstrated that alginate-based rafts can entrap carbon dioxide, as well as antacid components contained in some formulations, thus providing a relatively pH-neutral barrier. Several studies have demonstrated that the alginate raft can preferentially move into the oesophagus in place, or ahead, of acidic gastric contents during episodes of gastro-oesophageal reflux; some studies further suggest that the raft can act as a physical barrier to reduce reflux episodes.

Magnetic systems:

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. They guided them to the esophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h. Although these systems seem to work, the external magnet must be
positioned with a degree of precision that might compromise patient compliance.

Expanding Systems:

Its uses were first extended to the veterinary field before being extended to humans. For the system to function properly, it must have three main designs: a small size for easy oral consumption, an enlarged shape in the stomach to hinder passage via the pyloric sphincter, and a smaller system size to aid in evacuation after the
medication has released fully. This device is sometimes called a "plug type system" since it has the ability to block the pyloric sphincter

a) **Swelling Systems:**

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes
referred to as plug type systems because they tend to remain stuck at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting

a polymer with the proper molecular weight and swelling properties.

b) Unfoldable Systems :

Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are

made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bio erodible polymer compressedwithina capsule which extends in the stomach.

Factors Affecting Gastric Retention :

Density

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

Size:

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed with those with a diameter of 6.6 mm.

Shape:

The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and

22.5 kilo pounds per square inch (KSI) are reported to have better GRT, 60 to 100% retention at 24 hours compared with other shapes.

Fed or Unfed State:

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hours.

The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerablylonger.

Single or multiple unit formulation:

Multiple unit formulations show a more conventional release profile and unrelated

impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Nature of the meal:

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

Caloric Content:

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

Frequency of feed:

The GRT can increase by over 400 minutes when consecutive meals are given compared witha single mealdue to the lowfrequencyof MMC.

Gender:

Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates whiledepressionslows it down.

Age:

Elderly people, especially those over 70 years have a significantly longer GRT. Posture GRT can vary between supine and upright ambulatory states of the patients.

Diseased state of the individual:

Biological factors also affect the gastric retention e.g. Crohn's disease, gastrointestinal diseases and diabetes.

Concomitant drug administration:

Anti-cholinergics like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

Advantages:

➢ The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non gastroretentive drug delivery. There are several different factors related to
absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.

➢ For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

➢ They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

➢ Gastroprotective drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

➢ The controlled, slow delivery of drug form Gastroretentive dosage form provides sufficient local action at the diseased site, thus mini mizingor eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effectsofsideeffects.

➢ Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

➢ Gastroretentive drug delivery can minimize the counter activity of the body leading to higher Drug efficiency.

➢ Reduction of fluctuation in drug concentration makes it possible to obtain improved selective receptor activation.

➢ The sustained mode of drug release from Gastroretentive doses form

enables extension ofthe time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

Disadvantages:

➢ Unsuitable for drugs with limited acidsolubility. E.g. Phenytoin.

➢ Unsuitable for drugs those are unstable inacidic environment. E.g. Erythromycin.

➢ Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin sNSAID's.

➢ Drugs that absorb selectively in colon.

E.g. Corticosteroid

➢ Not all medications are compatible with GRDDS. GRDDS, for example, may not hold onto drugsthat easily dissolve in stomachacid.

➢ GRDDS can raise the possibility of a medication's negative effects, particularly if it is released too quickly or too slowly.

➢ GRDDS development and manufacturing may be more expensive than that of other drugdeliverymethods.

Applications:

Sr.no.	Formulation	Drug
1	Tablet	Acetaminophen, Acetylsalicyclic acid, Amoxicillin trihydrate, Atenolol, Ampicillin, Captopril, Cephalexin, Ciprofloxacin, Cinnarazine, Cholrpheniramine maleate, Dilitiazem, Florouracil, Furosemide, Isosorbide mononitrate, Isosorbide dinitrate, Losartan, Metformin hydrochloride, Nimodipine, P-Aminobenzoic acid (PABA), Pentaoxyfillin, Prednisolone, Piretanide, Riboflabin- 5'phosphate, Sotalol, Theophyllin, Verapamil HCl, Ziduvudine
2	Capsule	Chlordizepoxide HCl, Celiprolol HCl, Diazepam, Furosemide, L- Dopa and Benserazide, Misoprostal, Nicardipine, Pepstatin, Propranol, Urodeoxycholic acid
3	Films	Albendazole, Cinnarizine, P-Aminobenzoic acid (PABA), Piretanide, Prednisolone, Quinidine gluconate
4	Microspheres	Griseofulvin, Ibuprofen, Ketoprofen, Nicardipine, Nifedipine, Orlistat, P-nitro aniline, Piroxicam, Rosiglitazone maleate, Terfenadine, Theophylline, Tranilast, Verapamil, amoxicillin
5	Powders	Several basic drugs-Riboflavin, Sotalol, Theophylline.

6	Granules	Diclofenac sodium, Diltiazem, Fluorourocil, Indomethacin, Isosorbide dinitrate, Prednisolone, Ranitidine HCl
7	Beads	Beta-cyclodextrin, Curcumin, Diltiazem HCl, Loratidine, Ranitidine HCl

Conclusion

Currently, gastro-retentive drug delivery systems are used to improve the bioavailability and controlled distribution of drugs that exhibit an absorption window. During gastro-retentive operations, the main drug delivery techniques that were employed were floating, bio-adhesive, swelling, magnetic, and high density systems. More and more drug delivery systems are being created these days with the goal of releasing the medication into the stomach region. Despite the fact that adopting these medication delivery mechanisms has a number of benefits. From a pharmaceutical point of view, future GRDDS techniques could have to focus on a combined strategy to enhance product quality. The right drug and excipient combinations, formulation methods, and physiological processes that take place in the GIT must all be considered. This review's conclusion included a thorough overview of GRDDS delivery, including their most current developments and commercialized goods.

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