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GRDDS: A Promising System to Increase Gastric Residence of Drug

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Abstract:

GRDDSS can enhance the controlled administration of medications with an absorption window by continually releasing the medication over a protracted length of time before its absorption window. Dated march 19, 2015. This review's goal was to explore, gather, and concisely describe contemporary and older literature, focusing on strategies presently being used to extend gastric residency duration (accepted: 21 march 2015; available online: 31 march 2015). Among them is floating and other tools for delayed stomach emptying. The current study briefly discusses the gastro retentive drug delivery system, including categorization, formulation considerations for GRDDS, variable high-density stomach retention, the floating system, swelling, expanding benefits, demerits, and uses.

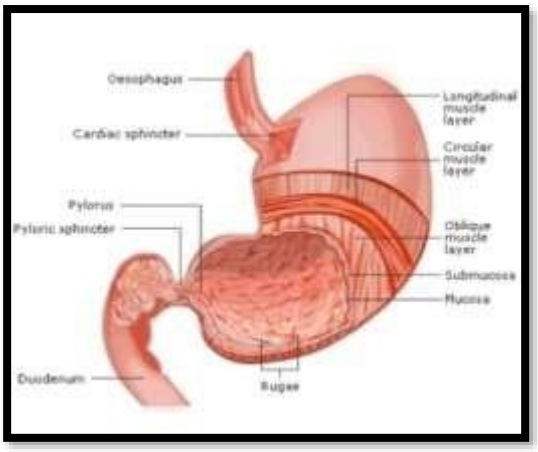
Keywords: system, swelling and expanding system, bio/mucoadhesive system, high density system.

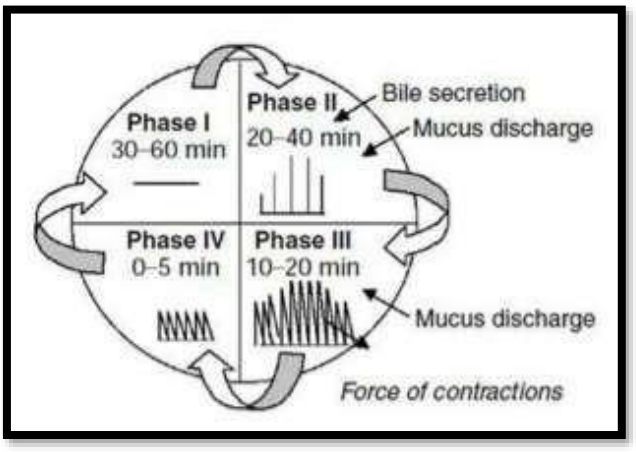
1. Introduction:

Oral medication administration has traditionally been the main method of drug perioderous oral delivery systems have been created during the several decades to serve as drug reservoirs from which the active ingredient may be delivered over a certain time period at a planned and regulated pace. However, there are a number of physiological issues with this method. include a variable and unexpected stomach emptying rate, a quick gastrointestinal transit time (812h), and the presence of a drug-specific absorption window in the upper creating a medication delivery system that can provide therapeutically efficiency prolongs the time that the medication is in the plasma, lowers the frequency of dosage, and decreases a medication controlled that can provide therapeutically efficient prolonging the time that the medication is in the plasma, lowering the frequency of dosage, and decreasing fluctuations in controlled and reproducible manner.[2]

2. Anatomy of The Stomach:

The stomach is anatomically separated into three parts: Fundus, Body, and Antrum (pylorus). The closest component produced GRDDSs are a cutting-edge strategy in this field (gastro retentive drug delivery system). GRDDs are dosage forms that can be retained in the stomach. By constantly releasing the drug for a long time before it reaches its absorption site, GRDDSs can enhance the controlled administration of medications with an absorption window. [3] In To achieve therapeutic benefits from drugs that are absorbed from the proximal part of the GIT (gastro in gastrointestinal are less soluble in alkaline pH, are degraded by it, or come into contact with at the lower part of the GIT, it may be desirable to prolong the gastric retention of the drugs). GRDDS are advantageous for such medications by increasing their Bioavailability, Therapeutic effectiveness and potential dosage decrease. [4] Long-term maintenance of therapeutic levels at the same level, resulting in less variation in the therapeutic levels lessen drug waste. The antrum acts as a pump for stomach emptying by pushing medications that are less soluble in high pH environments, such as weakly basic pharmaceuticals like domperidone and papaverine. The fundus and body act as a reservoir for undigested materials while the antrum is the primary site for mixing movements.





Both when one is fasting and when one is eaten, the stomach empties. The term "inter-digestive myoelectric cycle" or "migrating myoelectric cycle" (MMC), which is further broken into four phases, refers to a sequence of electrical events that occur during the fasting condition and cycle through the stomach and intestine every 2-3 hours. When a mixed meal is consumed, the pattern of contractions switches from fasting to a fed condition, which is also known as a shift in the digestive motility pattern [7].

- Phase 1 (Basic phase) duration is between 30 and 60 minutes, with irregular contractions.
- Phase 2 (pre burst phase) lasts for 20 to 40 minutes with sporadic contractions and action potential.
- Phase 3 (burst phase) lasts for 10 to 20 minutes and is characterized by brief, strong, and regular contractions.
- Phase 4 lasts between phase 2 and cycle 1 of two successive cycles, lasting 0 to 5 minutes.

3. Factors Impacting The Dosage Form's Duration In The Stomach After Ingestion :

- Density: The dosage form's density should be lower than that of the contents of the stomach (1.04g/ml).
- Size: A dosage form with a diameter of more than 7.5mm spends more time in the stomach than one with a 9.9mm diameter.
- Tetrahedron-shaped dosage forms stayed in the stomach longer than other devices of comparable size. Single or multiple-unit formulations are both effective, however, multiple unit formulations have a more predictable release profile, allow coadministration of units with differing release profiles or containing incompatible drugs, and have a higher margin of safety against dosage form failure.having a dose form of one unit.
- Whether you are fed or not, the GI motility is characterised by bursts of vigorous motar activity that happen around every 1.5 to 2 hours while you are fasting. The MMC removes undigested matter from the stomach, and if the timing of the formulation and the MMC are the same, the unit's GRT might be relatively brief. In contrast, when the MMC is delayed in the fast state, the GRT is longer.
- The nature of the meal—feeding the stomach with indigestible polymers or fatty acids—can alter the pattern of stomach motility to a fed state, slowing down gastric emptying and extending medication release.
- A meal heavy in protein and fat can raise calorie content-GRT by 4–10%.
- The GRT can climb to over 400 Hz in terms of feed frequency.because to the low frequency of MMC, the difference between a single meal and subsequent meals is minimal.
- Regardless of height, weight, or body surface, the mean ambulatory GRT in males (3.4 hours) is lower than that in their age- and race-matched female counterparts (4.6 hours).
- Age: Individuals older than 70 have much longer grts.
- Concomitant drug administration of opiates like codeine and anticholinergic drugs like atropine and propetheline can extend GRT [9–13].

4. Gastro-Retentive Medication Delivery Techniques Have Drawbacks [8] :

- Unfit for medications with a low acid solubility. Such as phenytoin.
- Unsuitable for pharmaceuticals in an environment that is unstable and acidic. Consider erythromycin.
- Drugs with a delayed release that irritate or induce stomach lesions. Like aspirin and nsaids. Drugs that preferentially absorb in the colon Consider a corticosteroid.

- Drugs with comparable GIT absorption. For instance, isosorbide, dinitrate, and nifidipinehigh stomach fluid levels are necessary for flotation and efficient operation of floating medication delivery devices.

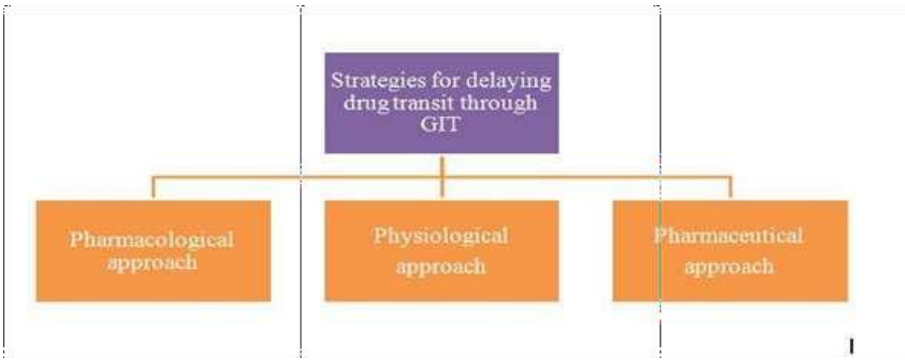
5. Gastro-Retentive Medication Delivery Methods Have Advantages :

- When compared to the administration of non gastroretentive drug delivery, the bioavailability of therapeutic drugs can be greatly increased, especially for those that are processed in the upper GIT. The amount of medication absorption is influenced by several distinct parameters connected to drug absorption and transit in the gastrointestinal tract (GIT).
- Sustained release may provide a flip-flop pharmacokinetics for medications with a short half-life and allow for less frequent dosage with better patient compliance.
- Additionally, they have an advantage over their traditional technique in that it may be utilised to get around the problems with the gastric retention time (GRT) and stomach emptying.time (GET) (GET). Because their bulk density is smaller than that of the stomach fluids, these devices are anticipated to stay buoyant on the gastrointestinal fluid without influencing the intrinsic rate of employing.
- In the stomach and small intestine, gastroretentive drug delivery can result in a prolonged and sustained release of medications from dosage forms that provide local treatment. As a result, they are helpful for treating conditions of the stomach and small intestine. The regulated, gradual administration of medication form
- A gastroretentive dose form offers sufficient local activity at the location of the illness, minimising or completely eliminating the need for systemic medication exposure. The negative consequences of side effects are lessened by this site-specific medication administration.
- Dosage forms that are gastroretentive reduce the variability of medication concentrations and effects. The unfavourable consequences that depend on concentration can be presented that are connected to peak concentrations. This feature is especially crucial for medications with a limited therapeutic index.
- Therapeutic distribution that is gastroretentive can reduce the body's counteractivity and increase drug effectiveness.
- Improved selective receptor activation is achievable by reducing medication concentration fluctuations.
- The extended period over a critical concentration is made possible by the prolonged mode of drug release from gastroretentive dosages, which boosts the pharmacological effects and enhances the chemical outcomes [14–16].

6. Gastroretentive Drug Delivery Systems Vs. Conventional Drug Delivery Systems [8] :

Parameters	Gastroretentive Drug Delivery System	Conventional Drug Delivery System
Risk of toxicity	Lower	Higher
Patient compliance	High compliance level	Less compliance level
Dose dumping	High risk	No risk
Drugs	**Beneficial for drugs:**	**Not beneficial for drugs:**
	That have rapid GI absorption	That have low GI absorption
	Degrade in colon	Degrade in colon
	That show local action in the stomach	That show local action in the stomach

7. Strategies for Delaying Drug Transit Through GIT:



- **Pharmaceutical strategy :**

It entails administering a medicine concurrently or incorporating it into the dosing form. This medication slows gastric emptying. Antimuscarinics, such as propantheline, are examples.

- **Physiological strategy :**

To decrease gastric emptying, it is necessary to employ natural substances or fat derivatives like triethanolamine myristate, which activate the duodenal or jejunal receptors[17].

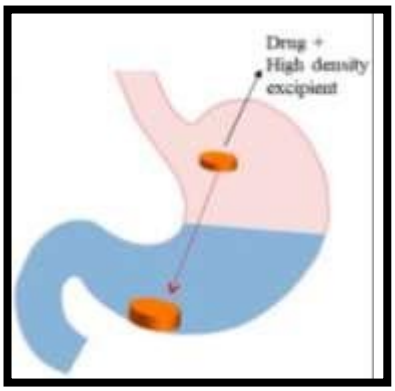
- **Pharmaceutical strategy :**

The first two methods are not employed because of toxicity issues.

The several pharmaceutical methods include :

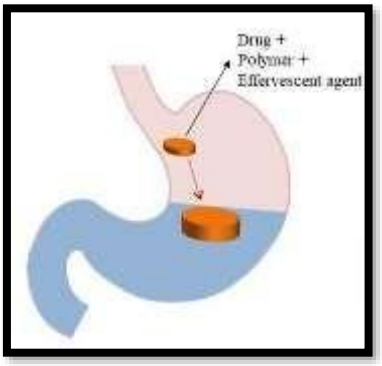
TYPES OF GASTRORETENTIVE DOSAGE FORM

High Density System :

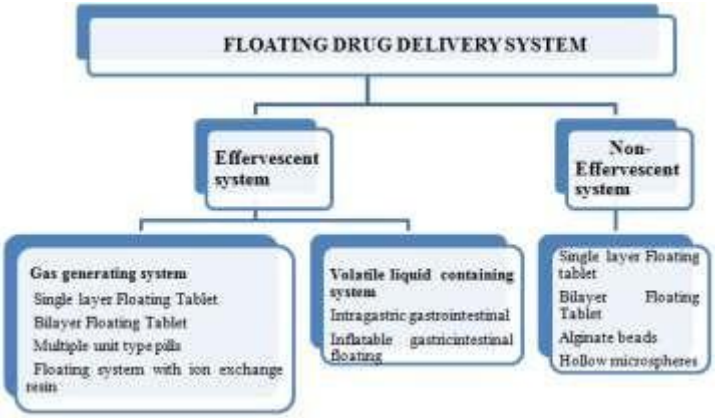


This approach involves formulation of dosage forms with density that must exceed density of normal stomach content (1.004g/ml). These formulations are made by coating the medicine on a substantial support or by combining it with substantial inert substances as iron powder, zinc oxide, titanium dioxide, or barium sulphate. Diffusion-controlled membrane may be applied on the resulting pellets [18]. Because the dry material from which these systems are produced interacts with the stomach fluid to release the medicine they contain, they are technically challenging to make with a high amount of drug. Another issue is that there isn't a system like that on the market.

Low Density Or Floating System :



Due to their low densities, FDDS maintain their buoyancy above the stomach contents for extended periods of time and offer continuous medication release.(These systems in particular have received a great deal of attention since they don't impair the GIT's motility. The overwhelming volume of floating dosage forms that have been developed and are now being sold globally demonstrates their supremacy over the other types of GRRDS. [19]



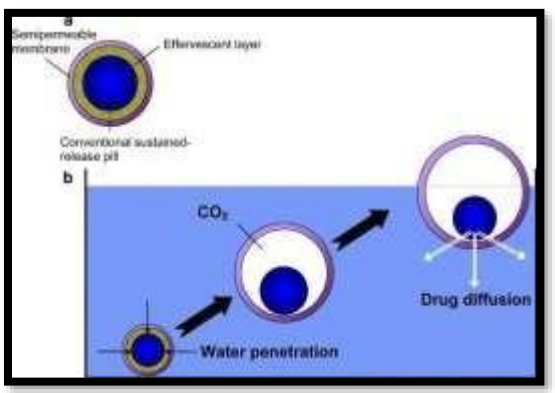
Effervescent System :

Carbonates (such as sodium bicarbonate) and other organic acids (such as citric acid and tartaric acid) contained in the formulation are used in effervescent systems to create carbon dioxide (CO2) gas, which lowers the system's density and causes it to float atop the stomach juice. The inclusion of a matrix with a liquid part that produces gas that evaporates at body temperature is an alternative[20]. There are two further categories for these effervescent systems.

A) Gas-Powered Equipment

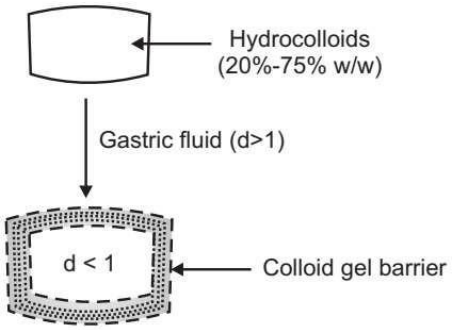
B) Vacuum/Volatile Liquid Systems

A) Gas-Powered Equipment :



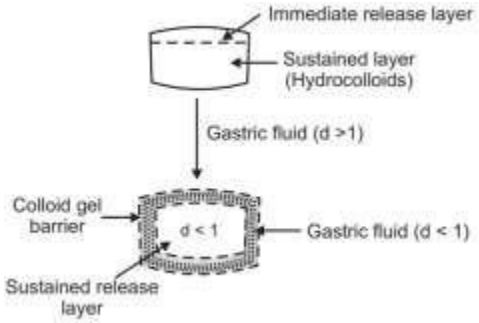
These buoyant delivery systems utilize effervescent reactions between Carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over gastric content.[21]

- **Single Layer Floating Tablets Or Hydrodynamically Balanced System (HBS) :**



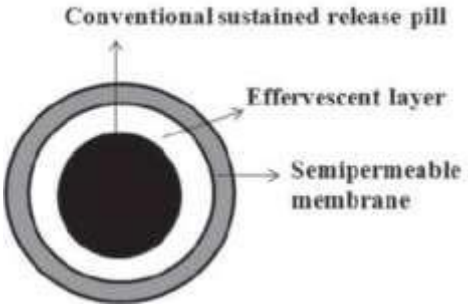
These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the grt and a better control over fluctuation in plasma drug concentration[22].

- **Bilayer Floating Tablets :**



These are also compressed tablet as shown in Fig and containing two layer i.e.(1)Immediate release layer (2) Sustained release layer.

- **Multiple Unit Type Floating Pills :**



These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the systems[23].

- **Ion Exchange Resin :**

Ion-exchange resins, a multiple-unit type of oral floating dosage system has been prepared to prolong gastric emptying time of dosage form. The system is composed of beads of drug-resin complex, which are loaded with bicarbonate ions.

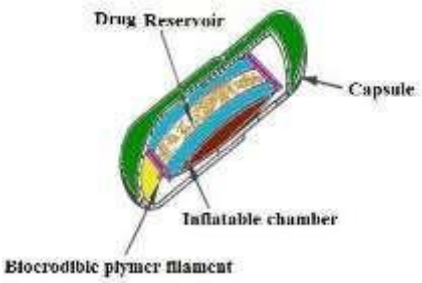
B) Volatile Liquid Containing System :

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which containsa liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of abioerodible plug made up of Poly vinyl alcohol, Polyethylene etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach[25].

- **Intragastric Floating Gastrointestinal Drug Delivery System :**

These 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 microporous compartment[26]

- **Inflatable Gastrointestinal Delivery Systems :**



In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber.

Non-Effervescent FDDS :

The Non-effervescentFDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides andmatrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well asbioadhesive polymers such as Chitosan.[28,29]The various type of this systems are as follows:

A) Single Layer Floating Tablets :

They are formulated by intimate mixing of drug with gelforming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

B) Bilayer Floating Tablets :

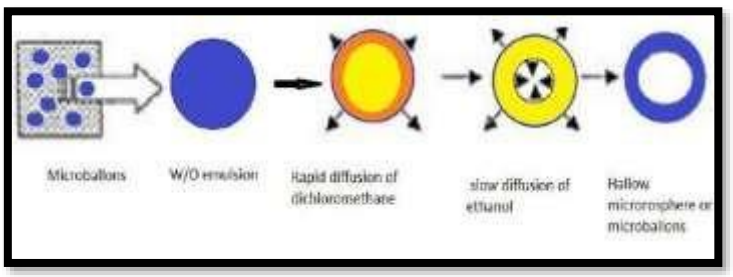
A bilayer tablet contain two layer immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant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

C) Alginate Beads :

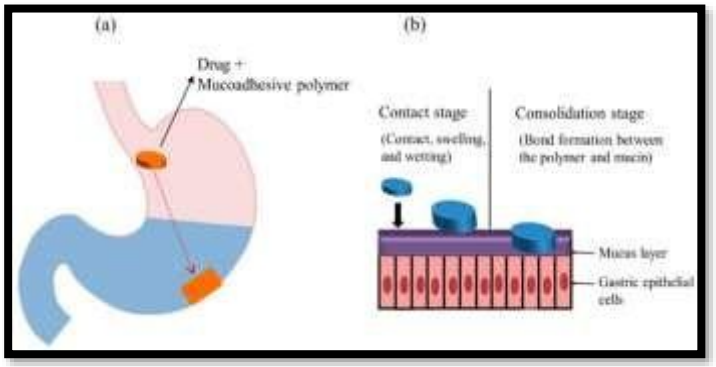
Multi-unit floating dosage forms have been developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then 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 floatingbeads gave a prolonged residence time of more than 5.5 hours.[30].

D) Hollow Microspheres (Microballoons) :

Hollow microspheres loaded with drug in theirouter polymer shelf were prepared by a novel emulsion solvent diffusion method22. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into anagitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h[31,32]



Mucoadhesive Systems :



Mucoadhesive drug delivery systems contain a mucoadhesive polymer that adheres to the gastricmucosal surface and prolong its gastric retention in the git. The capability to adhere to the mucus gel layermakes mucoadhesive polymers very useful exicipientsin the GRRDS. These polymers can be natural such assodium alginate, gelatin, guar gum etc semisynthetic polymers such as HPMC, carbopol, sodium carboxymethyl cellulose [33]the adhesion of polymers withmucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymer become sticky and mucoadhesive upon hydration. Bonding mediated involves mechanical or chemical bonding. Chemical bonds may involve ionic or covalent bonds or van der Waal forces between the polymer molecule and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers can be cationic or anionic or neutral [34,35]

- **Hydration – Mediated Adhesion :**

Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolonged gastroretention of the bio/muco-adhesive delivery system is further controlled by the dissolution rate of the polymer.[36]

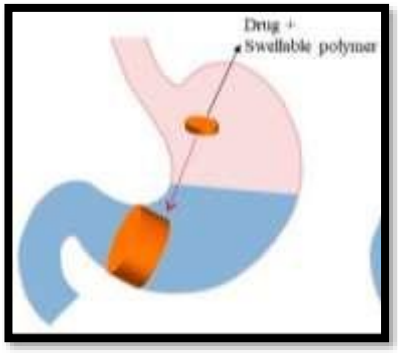
- **Bonding –Mediated Adhesion :**

Adhesion of polymers to mucus/epithelial cell surface involves varying bonding mechanism. Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucusa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive intractions (i.e. Van der Walls intractions) and stronger specific intraction, which include on the cell surface. The receptor mediated hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (--OH) and the carboxylic groups (--COOH)[37]

- **Receptor -Mediated Adhesion :**

Certain polymers have the ability to bind to specific receptor sites events serves as a potential approach in bio/muco- adhesion, hence enhancing the gastric retention of dosage forms. Certain plant lectins, like tomato lectins, interact specifically with the sugar groups present in mucus or on the glycocalyx [38]

Swelling System :



These are the dosage forms, which after swallowing swells to such an extent that their exit from the pylorusis prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. These systems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of The polymers retard the release [39]. On coming in contact with gastric fluid the polymer imbibes water And swells. The extensive swelling of these polymers is dueto the presence of physical chemical cross links in The hydrophilic polymer network. These cross links prevents the dissolution of the polymer and Hencemaintain the physical integrity of the dosage form. In the dissolution media the membrane detached from the core and sweeled to forma balloon that kept the unit floating. The size of the units increased by three to six folds, thus the floating ability as well as the increased dimension offered the system gastroretentive property[40]

Superporous Hydrogels :

These are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states [41] during which the premature evacuation of the dosage form may occur. Superporous hydrogel have a pore size >100µm which swell to equilibrium size with in a minutes, due to rapid intake of water by capillary wetting through inter connected open pores. They swell to a larger size and have sufficient mechanical strength to withstand the pressure by gastric contraction. This is achieved by coformulation of a hydrophilic particulate material, Ac-Di- Sol[42].

Magnetic System :

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time.[43]

8. Applications Of GRDDS [44] :

Sustained Drug Delivery :

The GRDDS is used for dosage form retained in stomach for longer period for the drug release3d in the stomach or intestine. (Example: new sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

Reduced Undesirable Activity At The Colon :

The drug maintenance in the hydro dynamically balanced system (HBS) is affected by the present drug in the intestine and also their action is restricted. These properties may be shows good GRDF formulations for antibiotics like beta-lactam which are absorbed only in the small intestine and results in the formulation of microorganism's resistances.

Enhanced Bioavailability :

The drug riboflavin bioavailability is enhanced by Control Release Gastro retention delivery formulation (CRGRDF) Other than non-GRDF CR dosage forms. There are several different processes, related to absorption and transit of the drug in gastrointestinal tract, that act concomitantly to influence the magnitude of absorption.

Absorption Enhancement :

For the development of a floating system some drugs have poor bioavailability at the target site of GIT and regulate absorption.

Site-Specific Drug Delivery Systems :

The site-specific drug conveyance frameworks imply that the medications are caught up in the small digestive tract and the stomach site. For the controlled way of the medication at the site of the stomach shows better therapeutics impacts. This prompts the base symptoms and furthermore decreases dosing recurrence like Riboflavin and Furosemide.

9. Marketed Preparations Of GRDDS [45] :

Brand Name	**Active Ingredient(S)**
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA And Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum –Magnesium Antacid
Almagate Flatcoat ®	Aluminum –Magnesium Antacid
Liquid Gaviscon ®	Ferrous Sulfate
Conviron	Ferrous Sulfate

10. Conclusion:

Current methods for improving bioavailability and regulated administration of medications that have an absorption window include gastroretentive drug delivery devices. The basic methods used for gastroretentive drug administration are floating, bioadhesive, swelling, magnetic, and high density systems. These devices do notdrugs should not only be released in a regulated manner, but they should also be presented in absorbable form in the absorption-optimal areas. Each of these medication delivery methods has benefits and downsides of its own. The physicochemical qualities of the drug, physiological processes in the GIT, formulation techniques, and the appropriate mix of drug and excipients must all be taken into account when designing an effective GRDDS.

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