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Review Article

A review: Gastroretentive drug delivery system (grdds)

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ABSTRACT

One novel approach in this area is GRDDSs (Gastro Retentive Drug Delivery System). GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. These includes floating system, swelling and expanding system, bio/mucoadhesive system, high density system and other delayed gastric emptying devices. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits, demerits and applications of gastroretentive drug delivery systems.

Introduction

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate.

However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8-12h), and the existence of an absorption window in the upper small intestine for several drugs[1]These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. Attempts are being made to develop a drug delivery system which can provide therapeutically effective plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner.[2]

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. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.[3]Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of drug that are absorbed from the proximal part of the GIT (gastro intestinal tract)or those are less soluble in or are degraded by alkaline pH or they encounter at the lower part of the GIT. GRDDS are beneficial for such drugs by improving their[4]

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone,papaverine)

Physiology of stomach

Anatomically the stomach is divided into three regions Fundus, Body and Antrum (pylorus) The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling

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actions [5,6]. Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as inter digestive myloelectric cycle or migrating myoelectric cycle (MMC) which is further divided in to four phases. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern [7].

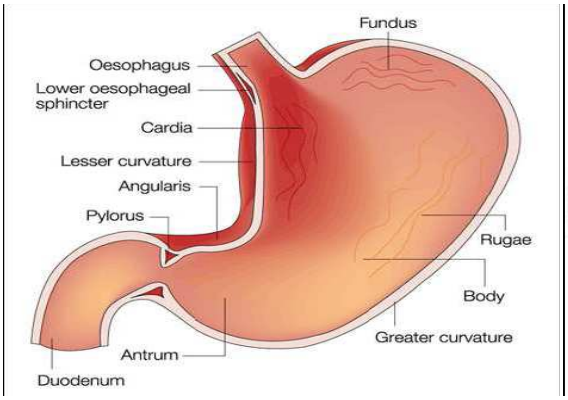


Fig.1 Structure of stomach

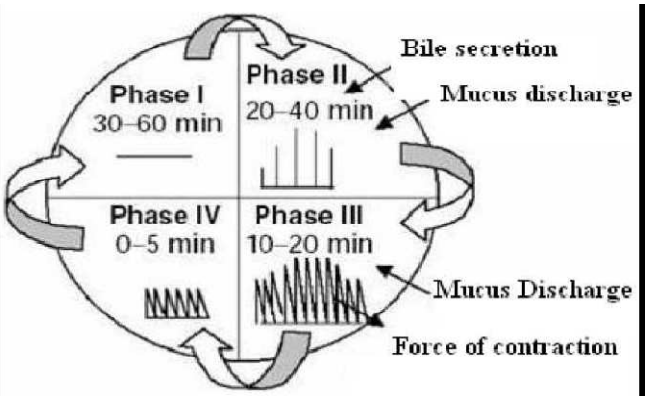


Fig.2 Schematic representation of inter digestive motility

1. Phase 1- (Basic phase) last from 30-60 minutes with rare contractions.
2. Phase 2- (Preburst phase) last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3- (Burst phase) last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.

Gastroretentive drug deliverysystems vs. conventional drugdelivery systems [8]

Sr.No.		Conventional DDs	GRDDs
1.	Toxicity	High risk of Toxicity	Low risk of toxicity
2.	Patient compliance	Less	Improves patient compliance
3.	Drug with narrow absorption window in Small intestine	Not suitable	Suitable
4.	Drug acting locally in the stomach	Not much advantageous	Very much advantageous
5.	Drugs having Rapid absorption through GIT	Not much advantageous	Very much advantageous
6.	Drug which degrades inthe colon	Not much advantageous	Very much Advantageous
7.	Drugs which are poorly soluble at an alkaline pH	Not much advantageous	Very much advantageous
8.	Dose dumping dumping	High risk of dose dumping	No risk of dose dumping

Factors affecting gastric retention time of the dosage form

- **Density**- the density of the dosage form should be less than that of the gastric contents (1.004g/ml)
- **Size-** dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.
- **Shape of the dosage form**- the tetra hedron resided in the stomach for longer period than other devices of similar size. Single or multiple unit formulation- multiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units. , allow co-administration of units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form.
- **Fed or unfed state-** under fasting conditions, the gi motility is characterized by periods of strong motar activity that occurs every 1.5-2 hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.
- **Nature of meal**- feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state,thus decreasing gastric emptying rate and prolonging drug release.
- **Caloric content**-GRT can be increased by 4-10 with a meal that is high in protein and fat.
- **Frequency of feed**- The GRT can be increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.
- **Gender-** mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.
- **Age**- people with age more than 70 have a significant longer GRT.
- Concomitant drug administration- anticholinergic like atropine and propetheline, opiates like codeine can prolong GRT[9-13].

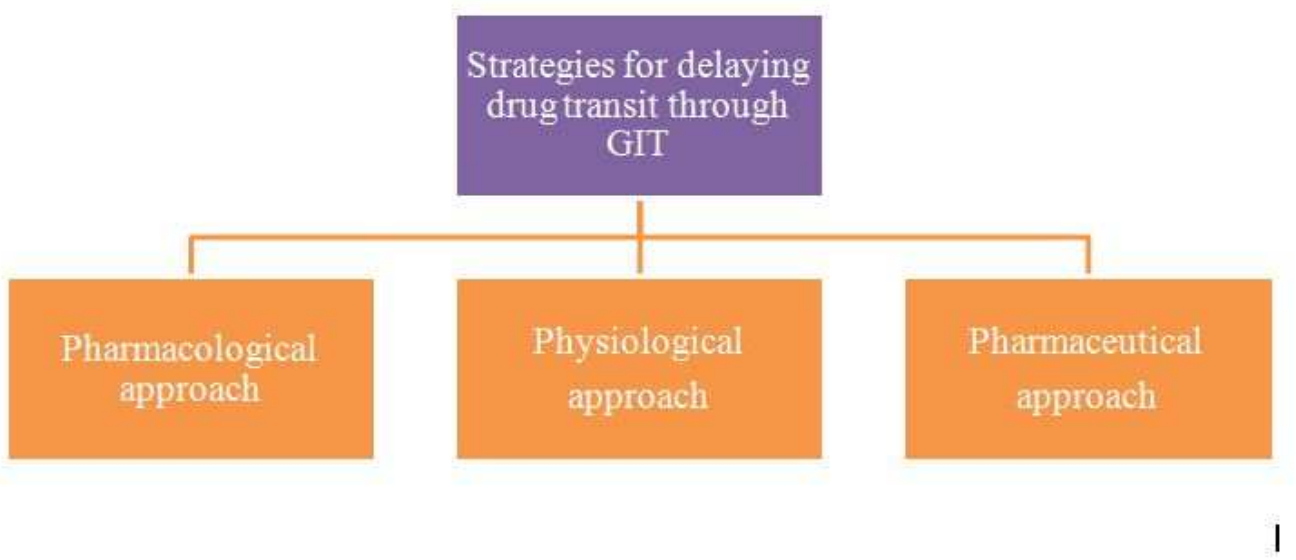
Disadvantages of gastro-retentive drug deliverysystems [8]

- ✓ 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 &NSAID's.
- ✓ Drugs that absorb selectively in colon E.g. Corticosteroid.
- ✓ Drugs that absorb equally well through GIT. E.g. Isosorbide, dinitrate, Nifidipine.
- ✓ Floating drug delivery systems require high fluid level in stomach to float and work effectively.

Advantages of gastro-retentivedrug delivery systems

- ✓ 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.
- ✓ Gastroretentive 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 effects of side effects.
- ✓ 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[14-16].

Strategies for delaying drug transit through GIT



- **Pharmacological approach**

It involves the co-administration or incorporation of a drug into the dosage form. This drug delays gastrointestinal emptying. Examples include antimuscarinics, e.g. propantheline.

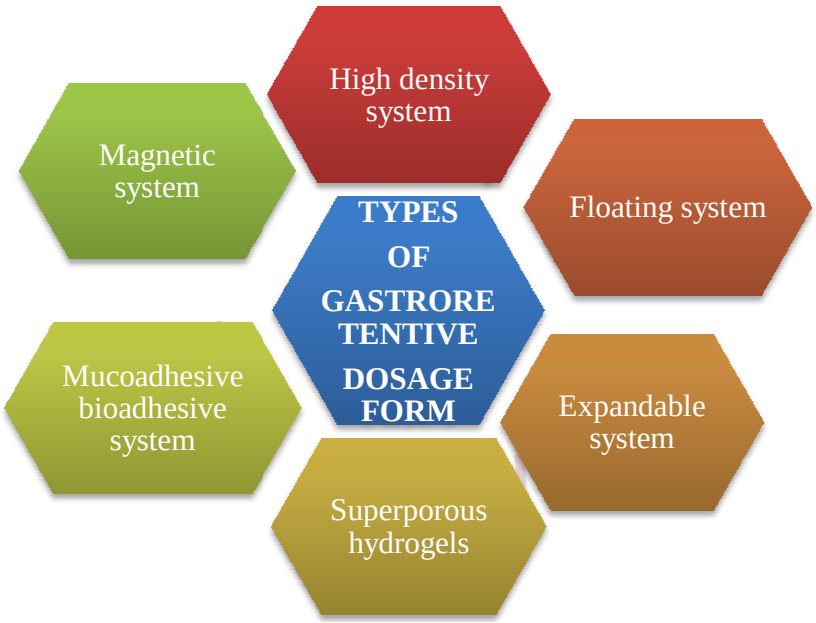
- **Physiological approach**

It is the use of natural materials or fat derivatives such as triethanolamine myristate, which stimulate the duodenal or jejunal receptors to slow gastric emptying[17].

- **Pharmaceutical approach**

First two approaches are not used due to toxicity problems. The various pharmaceutical approaches are:

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 prepared by coating drug on a heavy core or mixed with heavy inert material such as iron powder, zinc oxide, titanium dioxide, barium sulphate. The resultant pellets can be coated with diffusion controlledMembrane [18]These systems have some drawbacks like they are technically difficult to manufacture with a large amount of drug because the dry material of which it is made interacts within the gastric fluid to release its drug contents. One other problem is that no such system is available in the market.

Fig. 3: High density system

- **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. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT. Their dominance over the other types of GRRDS is also evident from the large number of floating dosage forms being commercialized and marketed world-wide.[19]

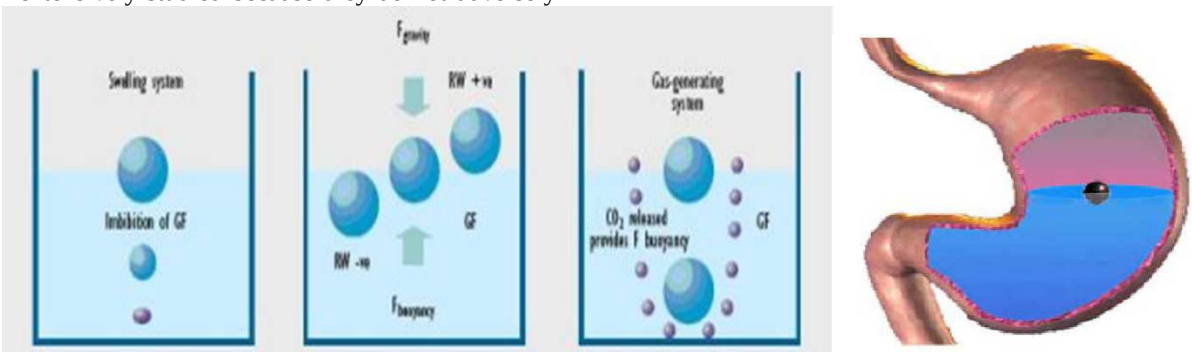


Fig .4a: Mechanism of floating drug delivery system

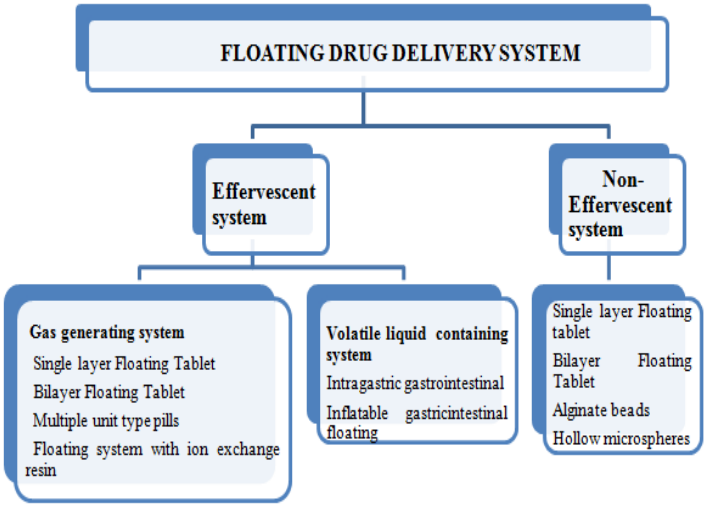


Fig. 4b: Classification of floating system

A) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature[20].These effervescent systems further classified into two types.

1) Gas generating systems
2) Volatile liquid/vacuum systems

1) Gas generating systems

These buoyant delivery systems utilize effervescent reactions betweenCarbonate/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]

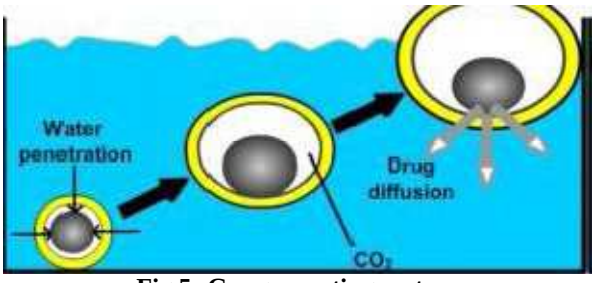


Fig.5: Gas generating system

a) 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]

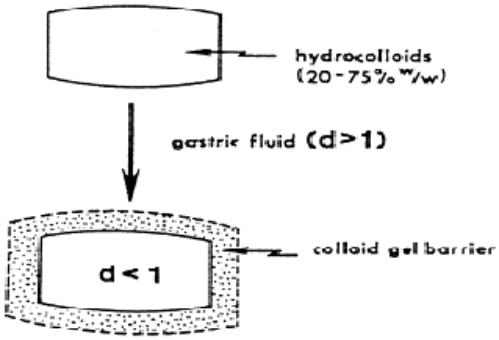


Fig. 6: Single layer floating tablet

b) 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.

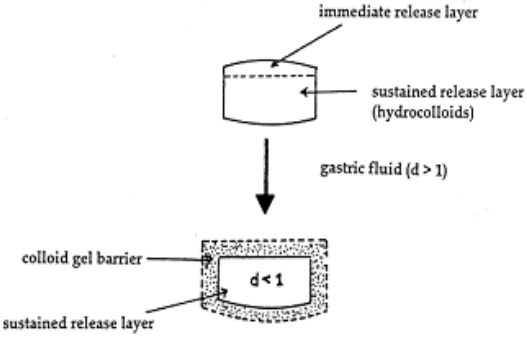


Fig. 7: Bilayer floating tablet

c) 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 atbody 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]

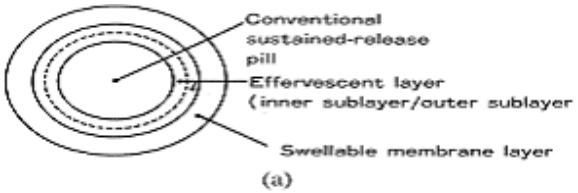


Fig.8: Multiple unit floating tablet

d) **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 and coated with a hydrophobic polymer. The system is so designed that when the beads reach the stomach, chloride ions are exchanged with bicarbonate and drug ions. The generated CO2 is entrapped in the polymeric coated resins and causes the beads to float.[24]

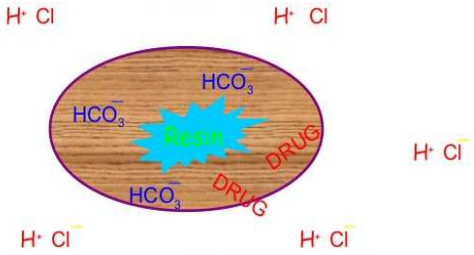


Fig.9: Ion exchange resin

2) Volatile liquid containing system

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

a) 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 microporouscompartment[26]

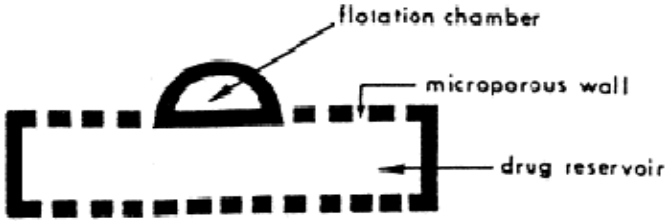


Fig.10: Intragastric floating drug delivery device

b) 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. The inflatable chamber automatically inflates and retains the drug reservoir into the gastric fluid.[27]

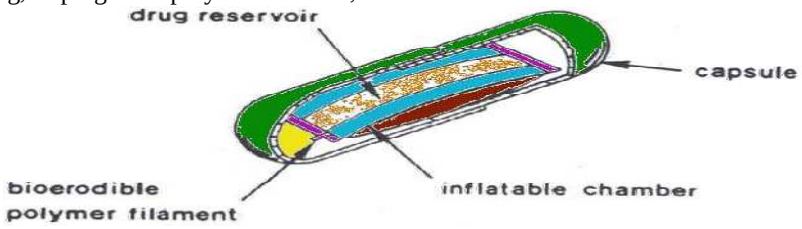


Fig.11: Inflatable Gastrointestinal Delivery Systems

B) **Non-Effervescent FDDS**

The Non-effervescentFDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The mostcommonly used excipients in non-effervescent FDDSare 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 gel-forming 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]

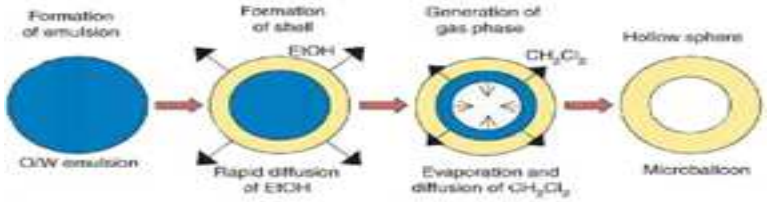


Fig.12: Hollow microspheres

3) 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 vander 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]

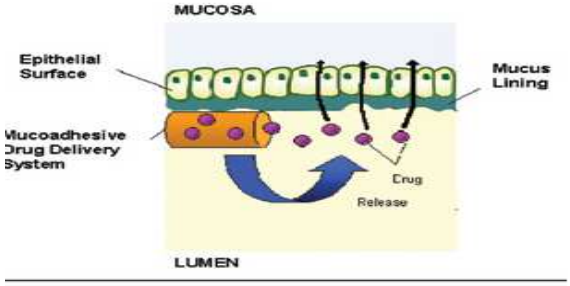


Fig.13: Mucoadhesive systems

a) 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]

b) 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]

c) 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]

.

4) Swelling system

These are the dosage forms, which after swallowingswells to such an extent that their exit from the pylorusis prevented, as a result the dosage form is retained inthe stomach for a prolonged period of time. Thesesystems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter.Controlled and sustainedrelease may be achieved by selection of propermolecular weight polymer, and swelling of thepolymers retard the release [39]. On coming in contactwith gastric fluid the polymer imbibes water andswells. The extensive swelling of these polymers is dueto the presence of physical chemical cross links in thehydrophilic polymer network. These cross linksprevents the dissolution of the polymer and hencemaintain the physical integrity of the dosage form. In the dissolution media themembrane detached from the core and sweeled to forma balloon that kept the unit floating. the size of theunits increased by three to six folds, thus the floatingability as well as the increased dimension offered thesystem gastroretentive property[40]

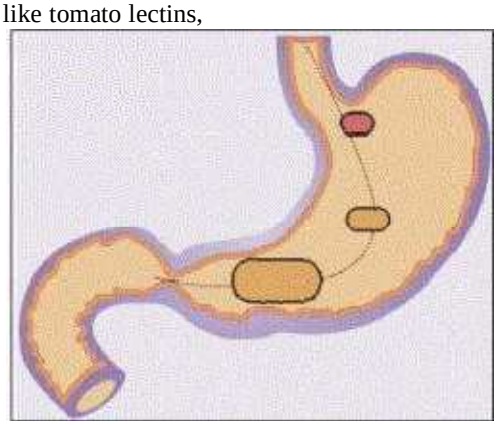


Fig.14: Swelling system

5) 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 co-formulation of a hydrophilic particulate material, Ac-Di-Sol[42].

6) 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]

Conclusion

Gastroretentive drug delivery systems have emerged as current approaches of enhancing bioavailability and controlled delivery of drugs that exhibit an absorption window. Gastroretentive drug delivery approaches comprised mainly of floating, bioadhesive, swelling, magnetic, and high density

systems. These systems not only provide controlled release of the drug but also present the drug in an absorbable form at the regions of optimal absorption. All these drug delivery systems have their own advantages and drawbacks. To design a successful GRDDS, it is necessary to take into consideration the physicochemical properties of the drug, physiological events in the GIT, formulation strategies, and correct combination of drug and excipients.

Conflict of interest statement

We declare that we have no conflict of interest.

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