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A Review Article on Gastroretentive Drug Delivery System

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Abstract: ***In recent years, gastroretentive drug delivery systems (GRDDS) have gained attention in the field of oral drug delivery systems. Oral controlled release and site-specific drug delivery systems have piqued the interest of pharmaceutical researchers seeking to improve therapeutic advantage. Gastroretentive drug delivery systems are one of these novel approaches to prolong gastric residence time, thereby targeting site-specific drug release in the stomach for local or systemic effects. Controlled-release dosage forms have been extensively used to improve therapy with several important drugs. Conventional oral dosage forms pose low bioavailability problems because of their quick gastric transition. To comprehend the various physiological challenges associated with achieving gastric retention, important factors controlling gastric retention from the stomach, especially for drugs that are less soluble in the intestine's alkaline pH. There are various gastroretentive approaches designed and developed until now, i.e., high density (sinking), floating, bio-or mucoadhesive, expandable, unfoldable, super porous hydrogel, and magnetic systems. Also, drugs that produce their local action in the stomach get quickly emptied and don't get sufficient residence time in the stomach. The system is useful for drugs that are unstable in the intestine or have low solubility or permeability in the small intestine.***

Keywords: Gastroretentive, Controlled release, Hydrogel, Mucoadhesive, Permeability

1. Introduction

An optimum GRDFs (Gastroretentive dosage forms) can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner, and finally is easily metabolised in the body. This in turn improves bioavailability, reduces drug wastage, improves solubility of drugs that are less soluble at high pH environment. They also help in achieving local delivery of drugs to the stomach and proximal small intestine and helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real in vivo time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal (GI) tract may be very short and highly variable in certain circumstances [1]. A major constraint in the oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular segment of GIT only or are absorbed to a different extent in various segments of GIT. Such drug candidates are said to have an 'absorption window'. But, in case of 'narrow absorption window' drugs, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. Again after crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically minimizes the time available for drug absorption after it, which is then accompanied by lesser bioavailability. Thus, the success of oral controlled drug delivery has faced some difficulties related with physiological adversities, like short gastric residence time (GRT) and unpredictable gastric emptying time (GET) [2]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e., gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options.[3] Many technological attempts have been made to devise various controlled release gastroretentive drug delivery systems namely, high density (sinking) systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5], mucoadhesive systems that causes bioadhesion to stomach mucosa [6], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [7], superporous hydrogel systems [8], magnetic systems [9] etc.

Drugs that are good candidates for Gastroretentive Drug Delivery System

1. Drugs acting locally in the stomach E. g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach E. g. Amoxicillin
3. Drugs that are poorly soluble at alkaline pH E. g. Furosemide, Diazepam, Verapamil, etc.
4. Drugs with a narrow window of absorption E. g. Cyclosporine, Methotrexate, Levodopa, etc.
5. Drugs which are absorbed rapidly from the GItract. E. g. etonidazole, tetracycline.
6. Drugs that degrade in the colon.
7. E. g. Ranitidine, Metformin HCl.
8. Drugs that disturb normal colonic microbes E. g. antibiotics against Helicobacter pylori

Advantages of Gastroretentive Drug Delivery System.

Improves patient compliance by decreasing dosing frequency.

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Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

Gastric retention time is increased because of buoyancy.

- Enhanced absorption of drugs which solubilise only in stomach.
- Drug releases in a controlled manner for prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect.
- Better therapeutic effect of short half-life drugs can be achieved.

Limitations of the Techniques of Gastroretention

More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions.

1) The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
2) Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique. Similarly retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
3) Not suitable for drugs that may cause gastric lesions e. g. Non-steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.
4) The mucus on the walls of the stomach is in a state of constant renewal, resulting in Unpredictable adherence.
5) In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.

Gastrointestinal Tract

The GIT is a muscular tube like structure which extend from mouth to anus. It takes nutrients in and eliminates waste by secretion, absorption, motility, digestion, and excretion, which are known as physiological processes. The gastrointestinal tract is divided into three main parts according to their structure-• Stomach • Small intestine • Large intestine

Anatomy of stomach

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and the body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.12 Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.

Diagram of stomach

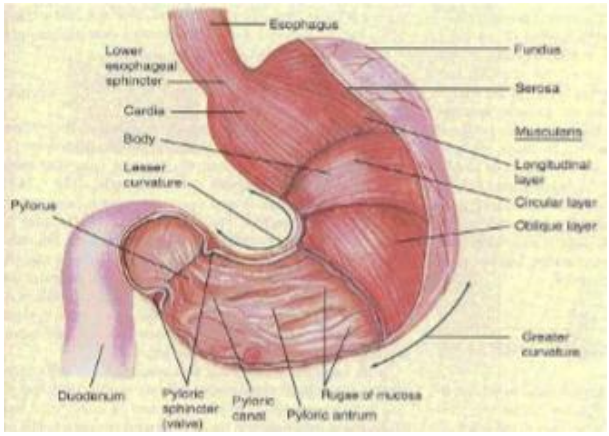

Figure 1: Diagram of human stomach

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Phase Time	Time	Comments
Phase I(basal phase)	last for 30-60 minutes minutes	rare contractions
Phase II (pre burst phase)	last for 20-40 minutes	intermediate c ontractions, as phase progresses intensity and frequency also increase gradually
Phase III (burst phase)	Last for 0-5 minutes	Intens e and regular contraction occurs during this phase for short period of time. Due to this undigested food sweeps out from stomach down to small intestine
Phase IV	Last for 10-20 Minutes	occurs between phase III and I of consecutive cycles

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in a slowdown of gastric emptying rate.14 The events are summarised in fig 2.

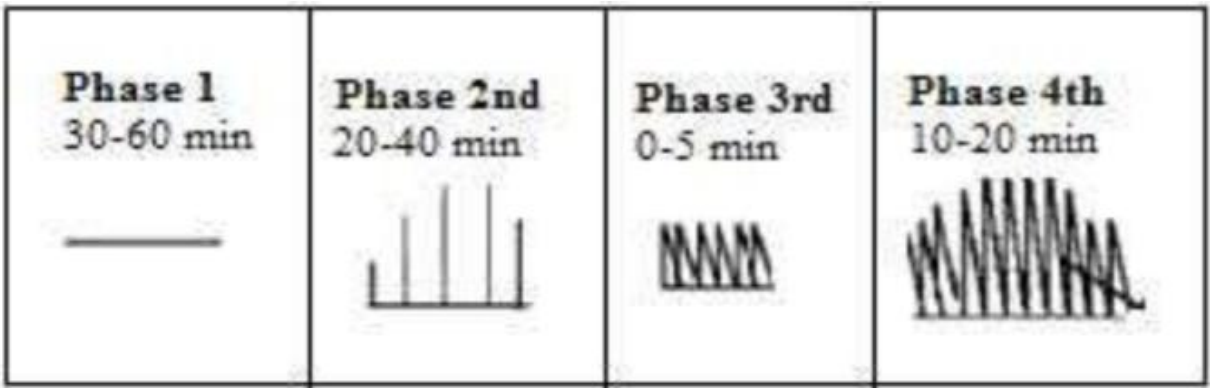

Figure 2: Migrating Myoelectric cyc

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 delivery systems [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

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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.

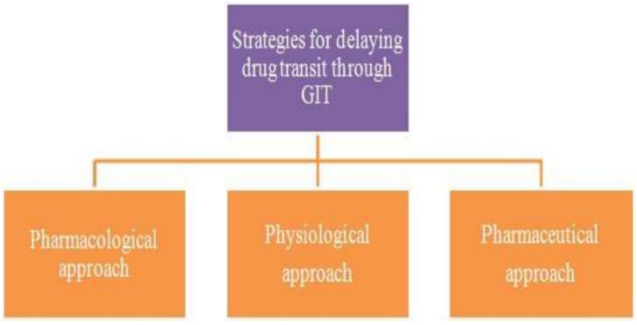
✓ Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

✓ 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 of the 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.

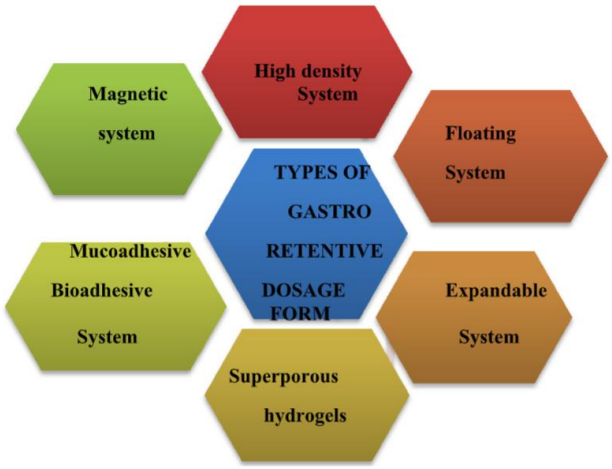
- **Physiological approach**

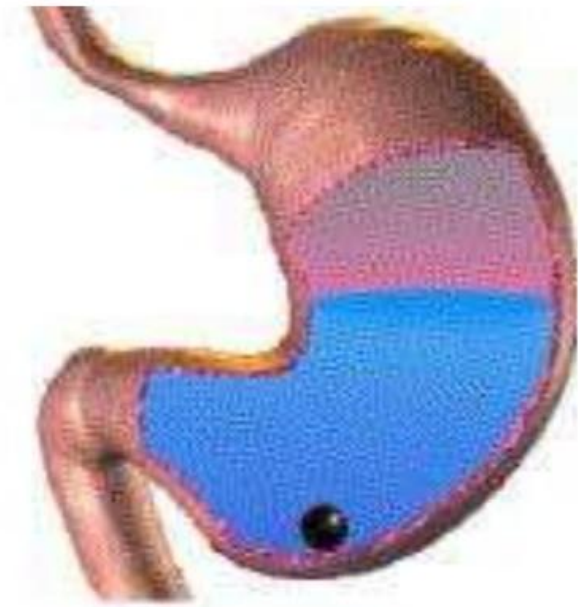
It is the use of natural materials or fat derivatives such as triethanolamine myristate, which stimulate the duodenal or jejunal receptors to slow gastric emptying [17].

- **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

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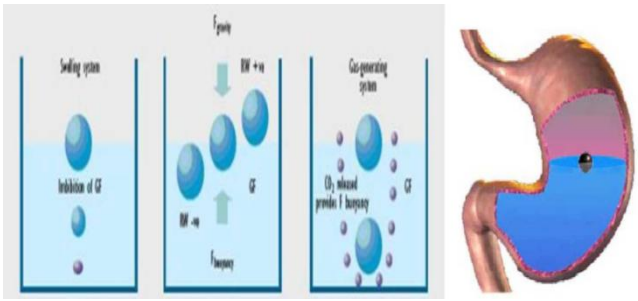
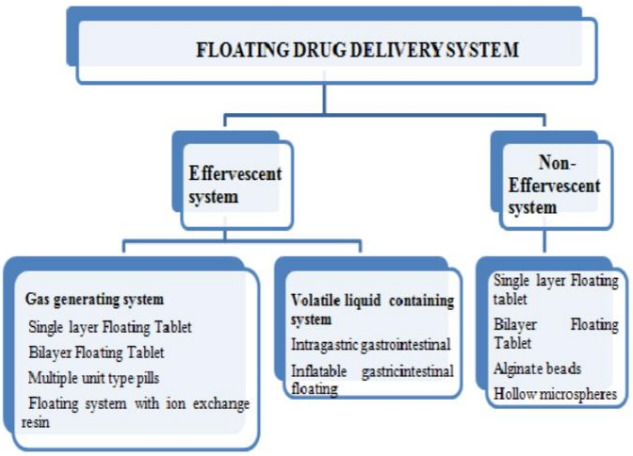


Mechanism of Floating Drug Delivery System



Classification of floating system

A) Effervescent System

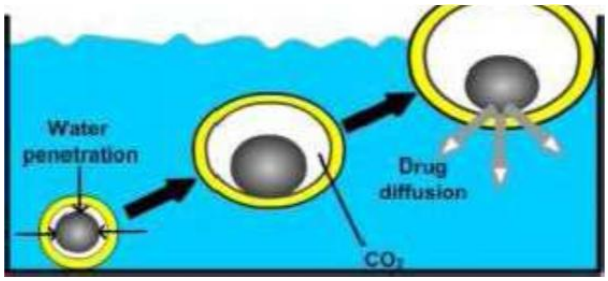
Effervescent systems include use of gas generating agents, carbonates (e. g. Sodium bicarbonate) and other organic acid (e. g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of system and making it float on the gastric fluid. An 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

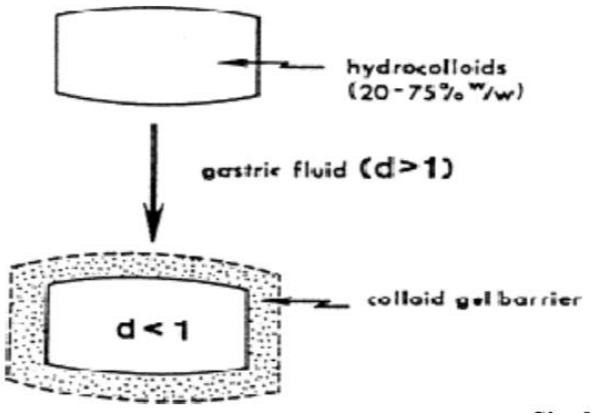
1) Gas generating systems

These buoyant delivery systems utilize effervescent reactions 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]



a) Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

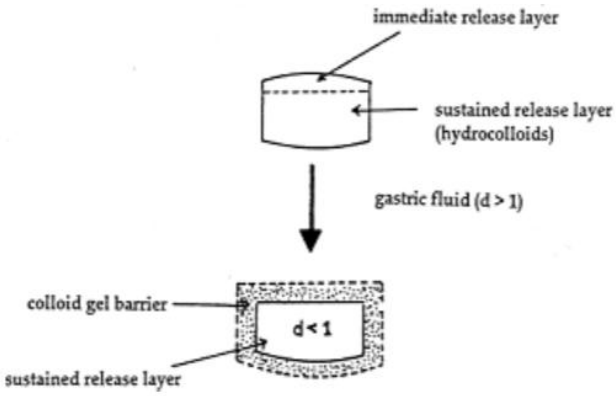
These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired 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]



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.



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 medium at body temperature, it sinks at once and then forms membrane layer. When the system is immersed in dissolution 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]

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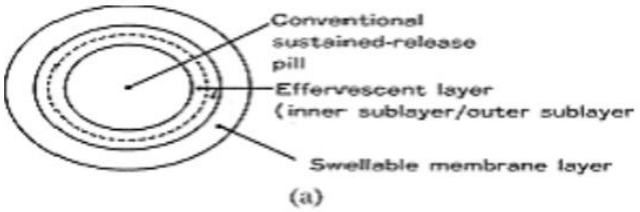
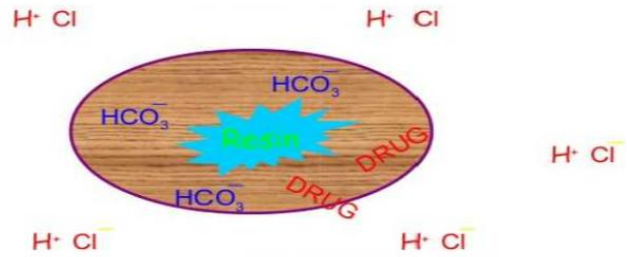


Multiple Unit Floating System

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 are exchanged with bicarbonate and drug ions. The generated CO2 is entrapped in the polymeric coated resins and causes the beads to float. [24]



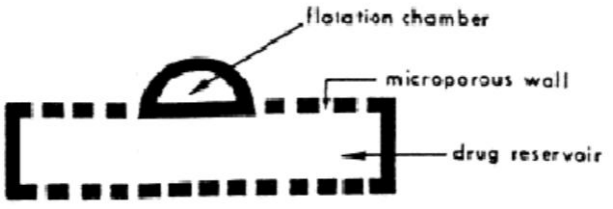
Ion Exchange Resin

3) Volatile liquid containing system

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a 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 a bioerodible 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]

a) Intragastric Floating Gastrointestinal Drug Delivery System

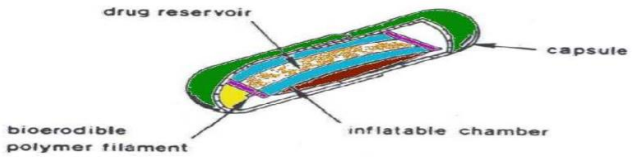
These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment [26



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]



Inflatable Gastrointestinal Delivery Systems

B) Non-Effervescent FDDS

The Non-effervescent FDDS 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 and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive 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 float in gbeads gave a prolonged residence time of more than 5.5 hours. [30].

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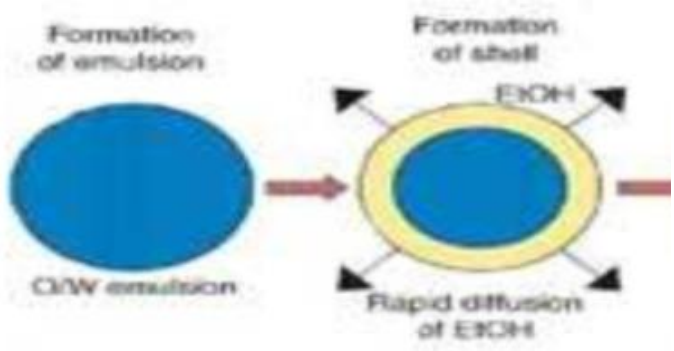
d) Hollow microspheres (microballoons)

Hollow microspheres loaded with drug in their outer 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]



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 layer makes mucoadhesive polymers very useful exicipientsin the GRRDS. These polymers can be natural such as sodium 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]

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

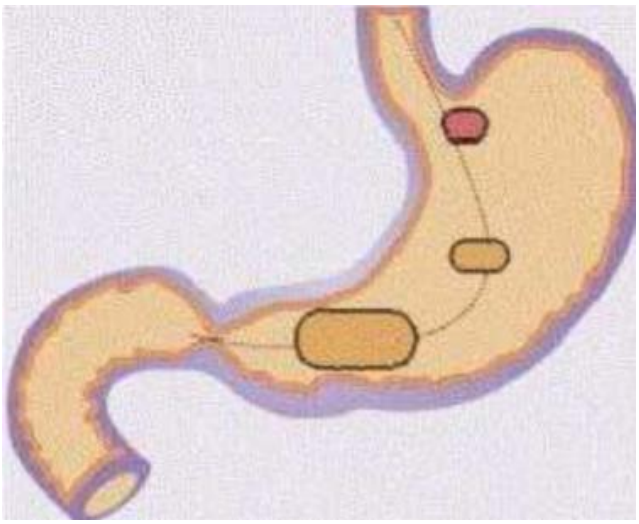
Adhesion of polymers to mucus/epithelial cell surface involves varying bonding mechanism. Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucusa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive 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 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 due to the presence of physical chemical cross links in the hydrophilic polymer network. These cross links prevents the dissolution of the polymer and hence maintain the physical integrity of the dosage form. In the dissolution media the membrane detached from the core and swelled to form a 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



Swelling System

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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]

2. 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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