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A Comprehensive Novel Approach to Floating Drug Delivery System

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ABSTRACT

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, low cost of therapy, patient compliance and flexibility in formulation etc. Oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research and patient literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today

Keywords: SRDDS, Absorption window, gastric emptying time etc.

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INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, low cost of therapy, patient compliance and flexibility in formulation etc. Oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research and patient literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today.[1]

The gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms. There are many difficulties faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa . Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed.[2]

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[3]

Thus, control of placement of a drug delivery system in a specific region of the GIT i.e. gastro retention, a means to address local targeting in the gastric region, offers numerous advantages, such as

- Prolongation of gastric residence time leads to better dug absorption.
- Improvement of bioavailability.
- Reducing frequency of dosing.
- Reducing the adverse effects in other body sites.
- Overall reduction in the health care cost.

Gastro retentive drug delivery system (GRDDS) has been desirable especially for drugs

- Those are locally active in the stomach.
- Those have absorption window in the stomach.

- Those are unstable in the intestinal or colonic environment.
- Those have low solubility at high pH value. [6]

Anatomy Of The Stomach: -

Stomach is an organ with capacity for storage and mixing. It is located just below the diaphragm in the epigastric and left hydrochondriac region of the abdomen. The stomach is anatomically divided into three parts:

- Fundus
- Body
- Pylorus (Or antrum).

They are capable of displaying a large expansion to accommodate food without much increase in intragastric pressure. Stomach lining is devoid of villi and it consists of considerable number of gastric pits that contribute to storage capacity of the stomach. There are two main secretions: mucus and acid, produced by specialized cell in stomach lining. Mucus is secreted by goblet cells and gastric acid by parietal cells (oxyntric) The Mucus spread and cover the rest of GI tract.

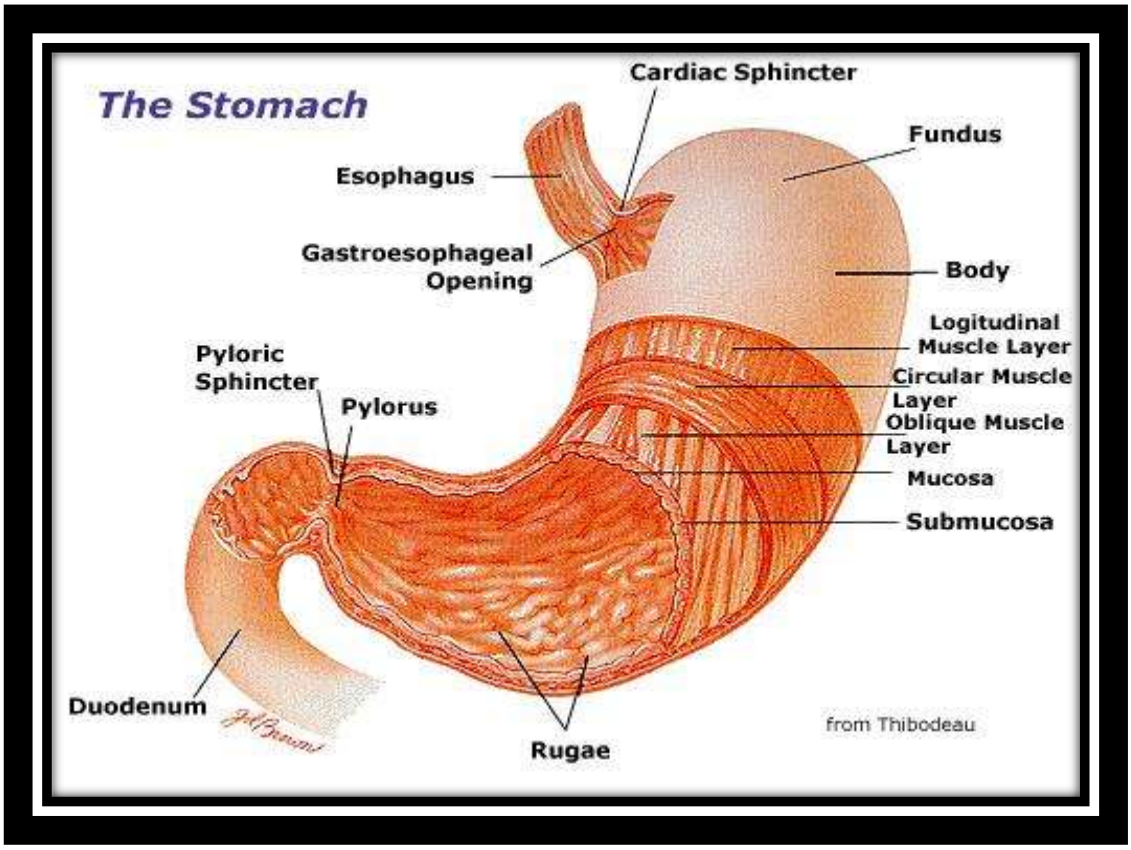

Figure: 1 Anatomy of stomach

Stomach Physiology:[7,8]

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube,

with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae. There are images to four major types of secretary epithelial cells that cover the surface of the stomach and

extend down into gastric pits and glands:

- Mucous cells: secrete alkaline mucus that protects the epithelium against shear stress and acid.
- Parietal cells: secrete hydrochloric acid.
- Chief cells: secrete pepsin, a proteolytic enzyme.
- G cells: secrete the hormone gastrin.

The physiology and disease state of stomach has a direct effect on design of controlled drug delivery system because drug is absorbed from and enters into site of action. Factors such as pH, nature and volume of gastric secretions and gastric mucosa play an important role in drug release and absorption.

Gastric pH

Gastric pH is an important consideration in selecting a drug substance, excipients, and drug carriers for designing intragastric delivery systems. Environmental pH affects the performance of orally administered drugs. The pH of stomach in fasted condition is about 1.5 to 2 and in fed conditions it is usually 2 to 6. A large volume of water administered with oral dosage form changes the pH of stomach to pH of water initially. This change occurs because stomach does not have enough time to produce sufficient quantity of acid before emptying of liquid from the stomach.

Gastrointestinal motility patterns: - [8,9]

Based on fasted and fed state of the stomach, two distinct patterns of GI motility and secretions have been identified. As a result, the bioavailability of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic contractile events, commonly known as migrating myoelectric complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into four consecutive phases;

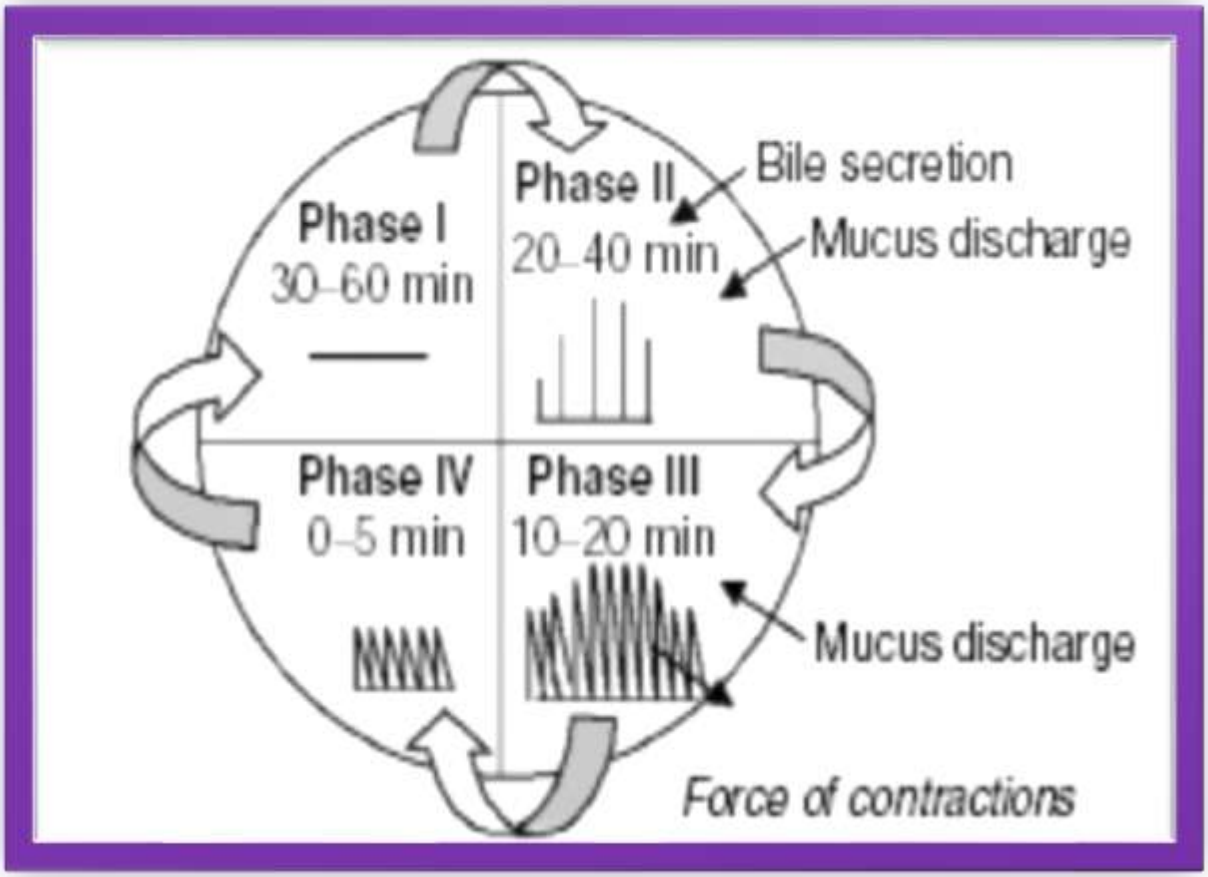

Figure 2: Gastrointestinal motility patterns

Phase I(Basal phase)	Period of no contractions
Phase II: (Preburst phase)	Period of intermittent contraction
Phase III (Burst phase):-	Period of regular contraction at the maximal frequency lasting from 4 to 6 min.
Phase IV	Period of transition between Phase III and Phase I and IV lasts from 0 to 5 minutes.

Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and the small intestine. A complete cycle of these four phases has an average duration of 90 to 120 minutes.

Gastric Volume: -[10,11]

The stomach of an adult is about 10 inches (25 centimeters) long and can easily expand. The distended position holds 2 to 4 liters of food. The stomach can expand to hold up to 4 L (4.2 qts.) of food, more than 50 times its empty volume. The resting volume of stomach is about 25-52 ml. This volume is important for dissolution of dosage forms. As the volume is large, emptying is faster. Gastric emptying of small volumes like 100 ml or less is governed by Migrating Myoelectric Complex (MMC) cycle whereas large volumes of liquids like 200 ml or more are emptied out immediately after administration. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids.

Types of Gastroretentive dosage forms:-

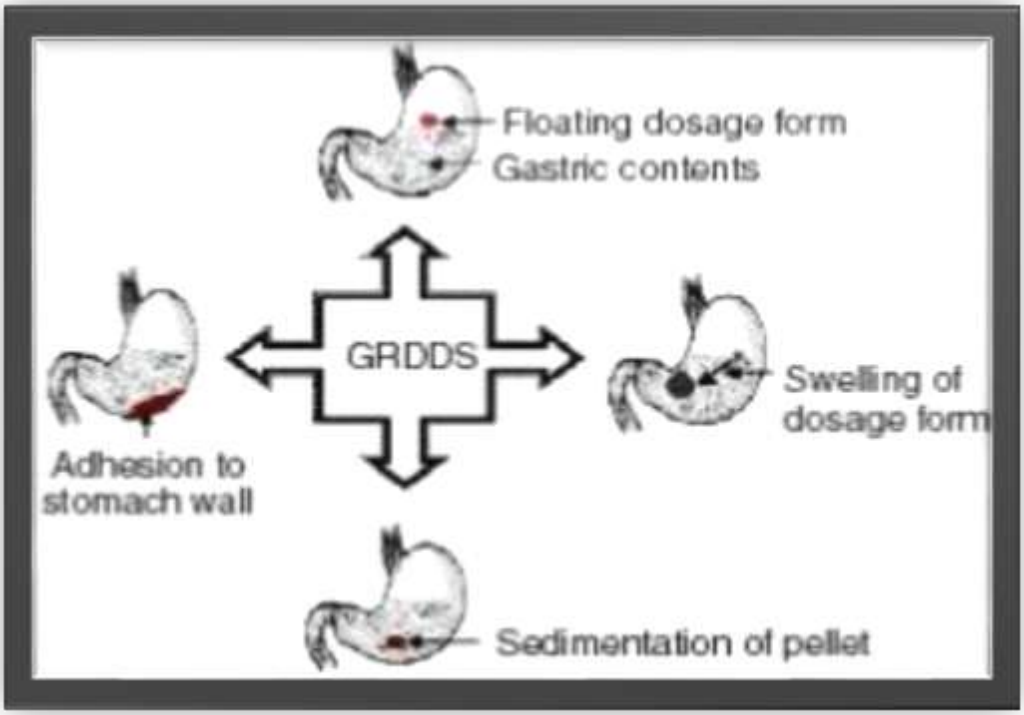

Figure 3: Various approaches of gastroretentive drug delivery system.

Bioadhesive or mucoadhesive system:-[12,14].

Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass metabolism. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation.

Expandable systems:- [15]

These are the dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus . As a result, the dosage form retains in the stomach for a longer period of time These systems may be named as ‘plug type systems.

The expandable GRDFS mainly based on three configurations; Small collapsed configuration which enables convenient oral intake, expanded form that is obtained in the stomach and prevents passage through pyloric sphincter,

Finally another small form achieved in the stomach; when retention is no longer required thereby enabling evacuation. The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occur because of osmosis. Unfolding takes place due to DFs

mechanical shape memory i.e. the GRDF is fabricated in a larger size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, In the stomach, the carrier is dissolved and the GRDF unfolds or opens out, to achieve extended configuration.

Raft forming system:- [16]

The raft forming system is one of the approaches which involve the formulation of effervescent floating liquid with in situ gelling properties, which has been assessed for sustaining drug delivery and targeting. Moreover, the gels formed in situ remained intact for more than 48 h to facilitate sustained release of drug.

The mechanism of the raft forming system involves the formation of continuous layer called a raft. The system involves the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The layer of the gel floats on the gastric fluid because it has bulk density less than the gastric fluid, as low density is created by the formation of CO2. So the system remains buoyant in the stomach. When the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased gastro retention time and a better control of the fluctuations in plasma drug concentration.

Magnetic systems:-[17,18]

This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach.

The dosage form is formulated along with ultrafine ferrite, and magnetic field is applied externally.

Floating or Low density system:-[19]

Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions.

Technological Development In Fdds:-

Based on the mechanism of buoyancy, two distinctly different types, i.e. no effervescent and effervescent systems have been utilized in the development of FDDS.

EFFERVESCENT FDDS

Effervescent system is prepared with swellable polymer such as methocel or effervescent components like sodium bicarbonate or citric acid or tartaric acid.

Multiple-unit oral floating drug delivery system[18]

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 an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sub layers the sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer. When the swollen pills are formed, like balloons, they have a density much lower than 1.004 gm/cm3. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swellable membrane layer.

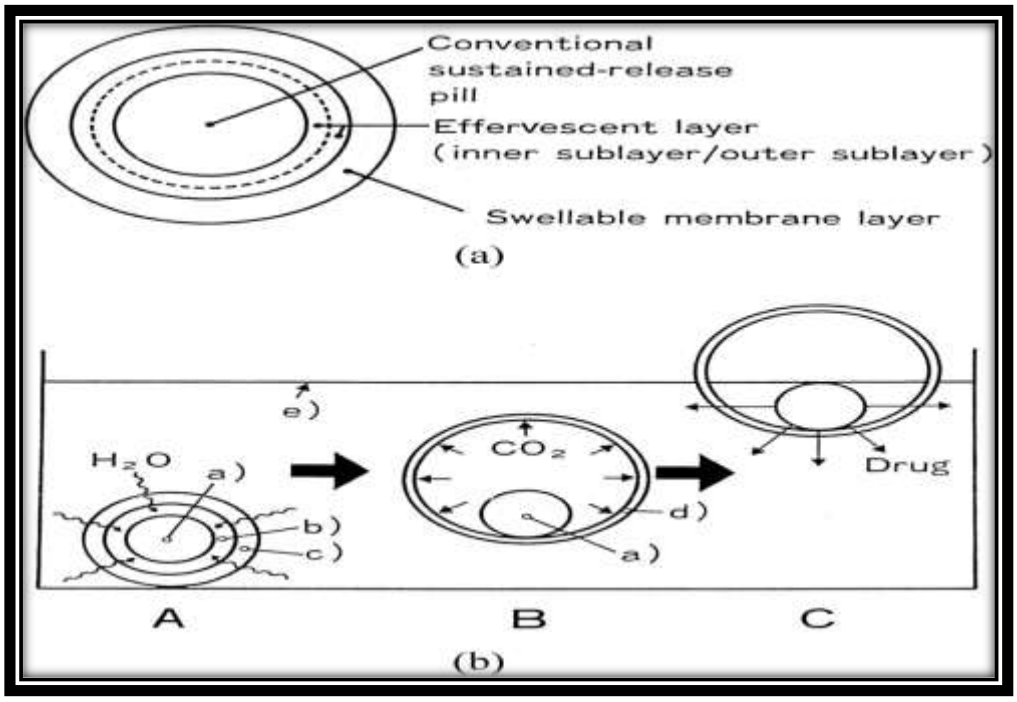

Figure 4. Multiple Unit Oral Floating DDS

Osmotically controlled drug delivery system:-[20,21]

Another approach in developing gas-generating floating systems are the *osmotic controlled systems* also called *volatile systems*. These systems consist of two compartments; incorporated into bio-degradable capsule. One compartment (osmotic active compartment) contains osmotic salt and liquefied or solidified gas (cyclopentane , diethyl ether etc) which at body temperature gasifies and enables flotation of the system This compartment is surrounded by semi-permeable membrane which allows entrance of gastric fluid in the compartment and development of osmotic pressure. The other compartment contain active compound, which is released in controlled manner (also through semi-permeable membrane) due to osmotic pressure created by the osmotic compartment. Volatile systems could be designed without being related to osmotic activity. These systems consist just of chamber of liquefied/solidified

gas which allows flotation and polymeric chamber which release the active compound in controlled manner.

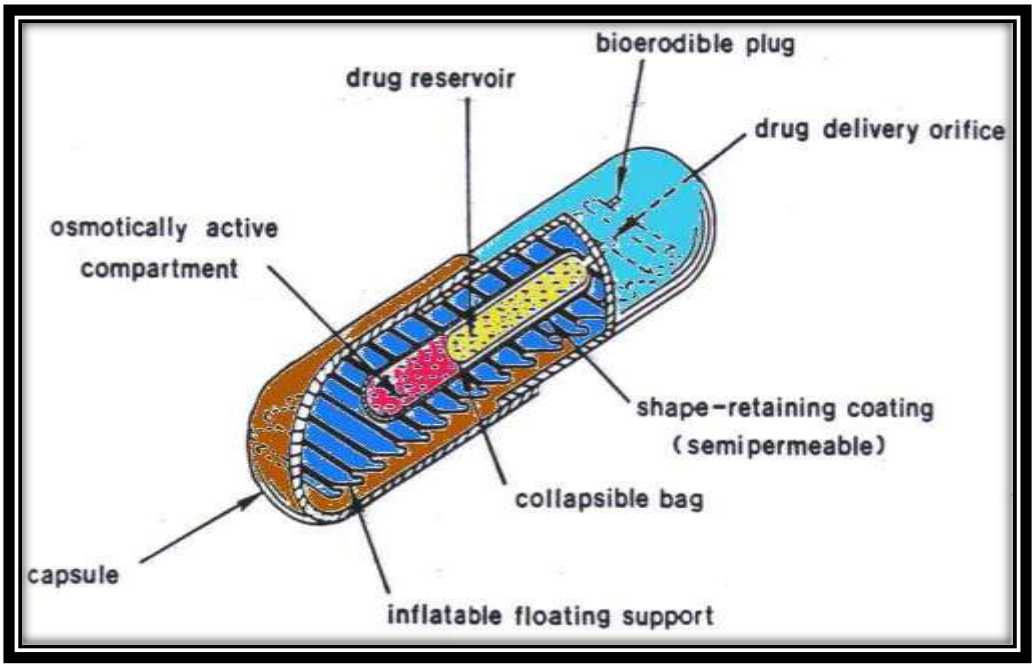

Figure: 5 Osmotically controlled drug delivery system

Inflatable gastrointestinal delivery systems: -[23]

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 compartment in the stomach. the drug continuously released in gastric fluid.

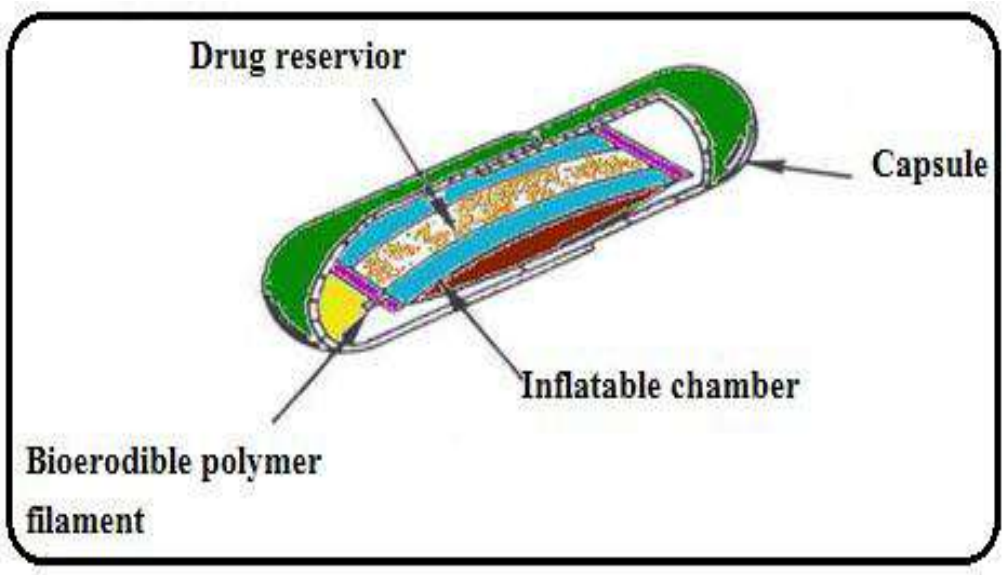

Figure: 6. Inflatable gastrointestinal drug delivery system

NON EFFERVESCENT FDDS:-[19,24]

The most commonly used excipients in no effervescent FDDS - are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier .The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface of the dosage form. The resultant gel structure then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the immediate adjacent hydrocolloid layer becoming hydrated. As a result, the drug dissolves in and diffuses out with the diffusing solvent, creating a 'receding boundary within the gel structure.

Hydrodynamically balanced system: -[8,25]

Hydrodynamically balanced systems (HBSs) are able to improve absorption of drugs especially those that are absorbed from stomach and small intestine. HBSs contain drug with gel-forming hydrocolloids meant to remain buoyant in the stomach content. They are mainly single-unit dosage forms, and are usually composed of one or moregel-forming hydrophilic polymeric substances and an active pharmaceutical ingredient.

Hydroxypropyl methylcellulose(HPMC), hydroxyl ethyl cellulose(HEC) hydroxyl propylcellulose(HPC),sodiumcarboxymethylcellulose(NaCMC),polycarbophil,polystyrene polyacrylate, agar carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydro dynamically balanced system capsule. The capsule shell dissolves in contact with gastric fluids; the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug. The working principle of HBS system shown in fig;

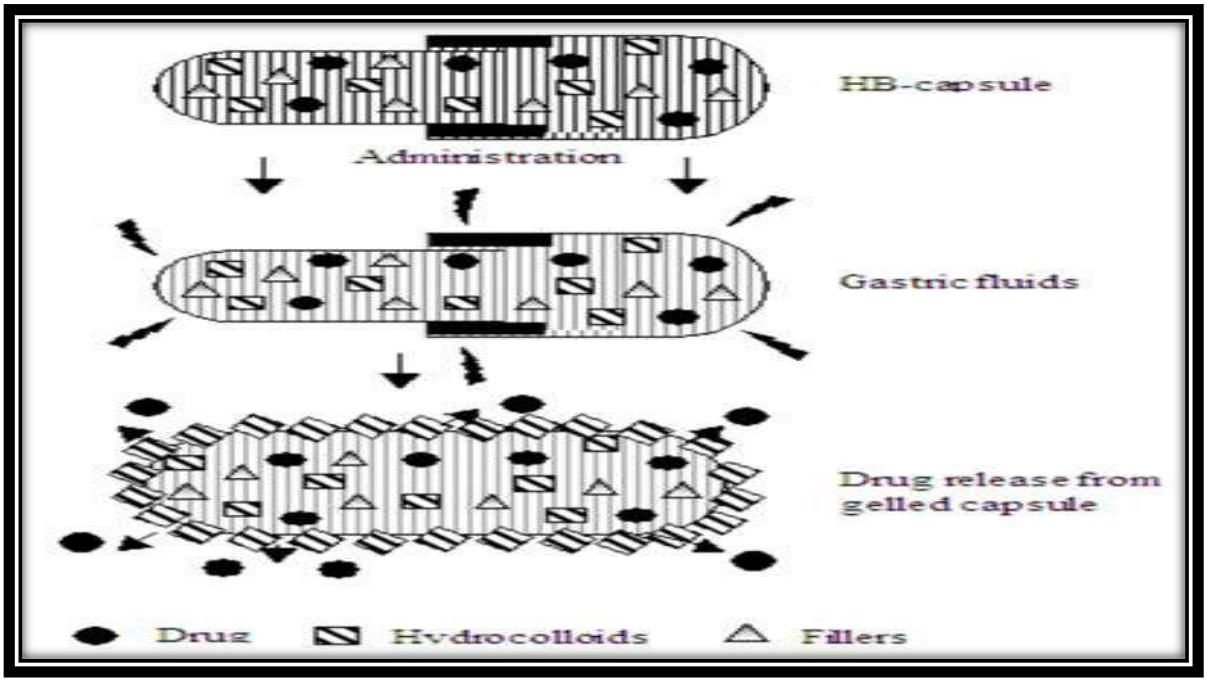

Figure:7 Hydrodynamically balanced system

Hollow microspheres: -[26]

Hallow microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. These microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometers. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in the stomach for prolonged periods. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent di f fusion method.

Alginate beads:[27]

Generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. This is made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared.

Intragastric floating drug delivery system:[28]

These system 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.

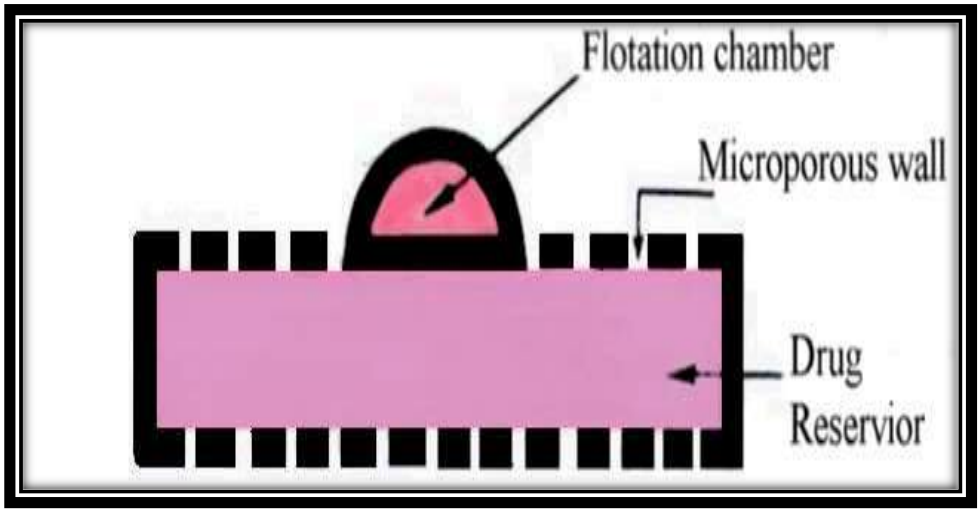

Figure :8 Intra Gastric Floating Gastrointestinal Drug Delivery Device

Bilayered tablet: -

A bilayer tablet contain two layers

i. Immediate release layer and

ii. Sustained release 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.

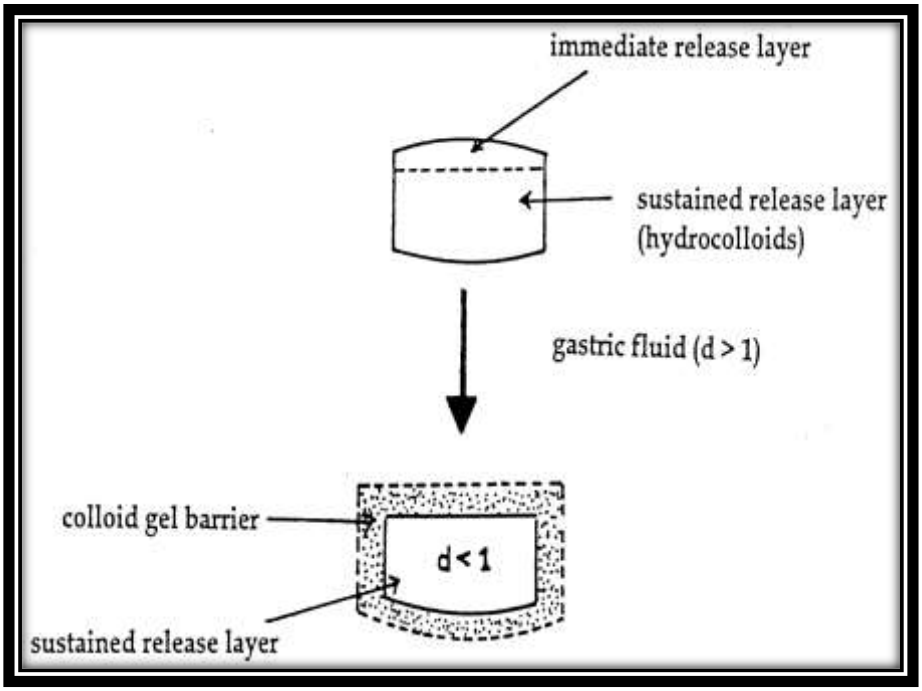

Figure: 9 Intragastric floating bilayered tablet.

POLYMERS AND OTHER INGREDIENTS: -[7]

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg: Acacia, pectin, Chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M andK15M),Gellan gum(Gelrite®), Sodium CMC,MC, HPC

Inert fatty materials(5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

Release rate accelerants (5%-60%): :eg lactose, mannitol

Release rate retardants (5%-60%): :eg Dicalcium phosphate, talc, magnesium stearate

Buoyancy increasing agents (upto80%) : eg. Ethyl cellulose

Low density material: : eg Polypropylene foam powder (Accurel MP1000®).

DRUGS USED IN THE FORMULATIONS OF STOMACH SPECIFIC FLOATING DOSAGE FORMS

Floating microspheres – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen ,Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast and Terfinadine

- Floating granules - Diclofenac sodium, Indomethacin and Prednisolone
- Films – Cinnarizine , Albendazole
- Floating tablets and Pills - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate , Para-aminobenzoic acid, Piretanide , Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline and Diltiazem HCl.

ADVANTAGES OF FLOATING DOSAGE FORM:[3]

(1) These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

(2) The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

(3) The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.

(4) Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.

(5) Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

(6) Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product(29.5%).

LIMITATIONS OF FLOATING DRUG DELIVERY SYSTEMS

(1) A high level of fluid in the stomach is required for drug delivery to float and work efficiently.

(2) Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.

(3) Drugs such as nifedipine, which under goes first pass metabolism may not be desirable for the preparation of these types of systems.

(4) Drugs which are irritant to Gastric mucosa are also not desirable.

(5) The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.

APPLICATION OF FLOATING DRUG DELIEVERY SYSTEM:

Enhanced Bioavailability:

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

Site-Specific Drug Delivery: -

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duode-num. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was in-creased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

Sustained Drug Delivery:

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Eg. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARDIS capsules using rabbits. 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)

Minimized adverse activity at the colon:

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Reduced fluctuations of drug concentration:

Continuous input of the drug following CRGRDF administration produces blood drug concentrations Within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

Absorption enhancement:

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

CONCLUSION:

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves

bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Thus, control of placement of a drug delivery system in a specific region of the GIT i.e. gastro retention, a means to address local targeting in the gastric region, offers numerous advantages.

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