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GASTRIC RETENTION – AN INNOVATIVE APPROACH TO INCREASE BIOAVAILABILITY

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ABSTRACT

Oral sustained release dosage forms have been developed and are in use since past few decades due to their considerable therapeutic advantages. However, this approach has not been adopted for a variety of important drugs, notably the ones having a narrow absorption window in the upper part of the gastro intestinal tract, i.e., stomach and the proximal small intestine. The main problems faced are the relatively short transit time of the dosage form in these anatomical segments. Usually after a period of less than 2 hours, the sustained release dosage form would ordinarily leave the absorbing upper gastrointestinal tract and move into non absorbing segments of the GIT leading to short absorption phase accompanied by lesser bioavailability. An alternative proposed to improve the bioavailability of narrow absorption window drugs is by confining the pharmaceutical dosage form within the stomach region to enable them to have an extended absorption phase. After oral administration, such a dosage form would be retained in the stomach for a longer period of time with consequent release of drug in a sustained manner. This mode of drug delivery known as Gastoretentive Drug Delivery System is highly effective not only in case of narrow absorption window drugs but also in case of drugs having solubility and stability problems at higher pH, or drugs required to carry out local action in the stomach. In this review article prominence have been given to factors influencing gastric retention, suitability of drug candidates for GRDDS,current technical trends, mechanisms involved, recent modifications in evaluation of GRDDS along with its future prospectus.

Keywords: Gastroretentive Drug Delivery System, Gastric Residence Time, Effervescent, Non- effervescent, Mucoadhesion, *H. Pylori*, Peptic Ulcer

INTRODUCTION

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 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 patent 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.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible mannerat a predetermined rate **[1].** Some of these systems may not work as planned due to the several physiological difficulties, such as inability to restrain and localize the drug delivery system within desired region of gastrointestinal tract GIT and highly variable nature of gastric emptying process **[2]**.

Gastric retention may not be favourable for all the drug candidates; however certain candidates get benefited by incorporation into GRDDS (Gastro retentive drug delivery system) like drugs which have absorption window or the drug candidates that suffer instability or solubility problems at higher pH, also prolonged local availability of antibacterial agents may increase their effectiveness in treating H. Pylori related peptic ulcers which is believed to be the causative bacterium for chronic gastritis and peptic ulcers. Brief discussion on the need for gastric retention of a delivery system is as under **(Figure 1)**.

Need For Gastro-Retention of A Drug Delivery System

Gastric retention of a drug delivery system is desirable under various circumstances.

For example, GRDDS can improve the controlled delivery of drugs:

- That have absorption window, by continuously releasing the drug for a prolonged periodof time before it reaches its absorption site **[3]**. Fig1 shows absorption through absorption window of narrow absorption window drug.
- That have low solubility or are degraded by the alkaline pH **[4, 5]**.
- That are required to treat certain conditions in the stomach and proximal small intestine which in turnmay lead to improved bioavailability, therapeutic efficacy and possible reduction of the dose size **[6, 7]**.
- Prolonged local availability of antibacterial agents may increase their effectiveness in treating H.Pylorirelated peptic ulcers **[8]**.

Factors Affecting Gastric Retention Time of a Dosage Form

Dosage Form Related

Density

Dosage forms having a density lower than that of the gastric fluid can float on the surface of the fluid, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm^3 is required to exhibit floating property.

Shape

Gastric residence of a dosage form was found to be effected by shape of the dosage form. The different shapes studied were ring, tetrahedron, cloverleaf, disk, string and pellet. The tetrahedron was found to reside in the stomach for longer periods than other devices of a similar size, likewise extended gastric retention was observed with rigid rings. Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) were found to have a better gastric residence time as compared with other shapes **[9]**.

Single or Multiple Unit Dosage Form

Multiple unit dosage forms permit a larger margin of safety against dosage form failure compared with single unit dosage forms. These formulations show a more predictable release profile and insignificant impairing of performance due to failure of units **[9]**.

Meals

The rate of gastric emptying depends on nature of meal and its caloric content.

Nature of Meal

If indigestible polymers or fatty acid salts are taken, the motility pattern of the stomach is changed to fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric Content of Meal

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

Fed or Unfed State

Under fasting conditions, GI motility is characterized by periods of strong motor activity or the MMC that occur every 1.5-2 hours. However, in the fed state, the MMC is delayed and GRT is considerably longer.

Frequency of Feed

The GRT can be increased by over 400 minutes, when successive meals are given, compared with a single meal due to the low frequency of MMC.

Volume of GI Fluid

Resting volume of stomach is 25-50ml. When volume is large, emptying is faster. Fluids taken at the body temperature leave the stomach faster than the colder or warmer fluids.

Patient Related Factors

Gender

Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of weight, height and body weight.

Age

Greater the age (especially more than 70) longer the GRT.

Posture

GRT can vary between spine and upright ambulatory states of a patient.

Concomitant Drug Administration

Sometimes concomitant drug administration can either increase or decrease the GRT depending upon the drug. For example, Anticholinergic like atropine, Propantheline, Prokinetic agents like Cisapride, Metachlopramide decrease GRT.

Disease State

GRT in patients also depends on disease state of the patient particularly those diseases which can influence GRT e.g., Gastric ulcer, diabetes, hypothyroidism increase GRT while duodenal ulcers, hyperthyroidism decrease GRT **[10]**.

Approaches To Gastric Retention

Gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion **[11, 12]**, flotation **[6]** sedimentation **[13, 14]**, expansion **[15, 16]**, modified shape systems **[17, 18]** or by the simultaneous administration of pharmacological agents **[19]** that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail.

Floating System

Floating drug delivery systems (FDDS) systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Floating sustained release dosage forms are able to maintain their low

apparent density; while the polymer hydrates and builds a gelled barrier at the outer surface thus presenting most of the characteristics of hydrophilic matrices so are known as hydrodynamically balanced systems (HBS). The FDDS can be divided into effervescent and non-effervescent systems.

Effervescent System

These are matrix type of systems containing swellable polymers such as Methylcellulose and Chitosan and various effervescent compounds, e.g., Sodium bicarbonate, Tartaric acid and Citric acid. They systems in contact with the gastric contentsliberateCO_2which gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

I. Volatile Liquid or Vacuum Containing Systems

a) Intra-Gastric Floating Gastrointestinal Drug Delivery System

In these systems vacuum, air or harmless gas is filled in the floatation chamber and the drug reservoir is encapsulated inside a micro porous compartment **(Figure 2)**.

b) Inflatable Gastrointestinal Delivery Systems

In these systems drug reservoir (drug reservoir can be drug impregnated polymeric matrix) is loaded in the inflatable chamber containing a liquide.g. Ether, Cyclopentanethatgasifies at body temperature to cause the inflatation of the chamber in the stomach. The whole system is then encapsulated in a gelatine capsule. The Device may also consist of a bio-erodible plug made up of Polyvinyl alcohol(PVA), 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 **(Figure 3)**.

c) Intra-Gastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two

components; drug reservoir compartment and an osmotically active compartment.The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach **(Figure 4) [20]**.

II. **Gas-Generating Systems**

Gas-generating systems utilize effervescent reactions between Carbonate, bicarbonate salts and citric, tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. In these buoyant systems matrices is prepared with swellable polymers like Methocel, polysaccharides like Chitosin, effervescent components like Sodium bicarbonate, Citric acid and Tartaric acid or chambers containing a liquid that gasifies at body temperature are used. The optimal ratio of citric acid and Sodium bicarbonate for gas generation is reported to be 0.76:1 **[21]**. A brief presentation of mechanism of floating system is given in **Figure 5**.

III. Matrix Tablets

Single layer, bilayer and also triple layer matrix tablets have been prepared.

Non-Effervescent Systems

I. Colloidal Gel Barrier System

The hydrodynamically balanced system (HBS) was first design by Sheth and Tossounian **[22]** in 1975. In these systems hydrocolloids are used to make the dosage form

buoyant on stomach contents. Mostly one or more gel forming highly swellable cellulose type hydrocolloids are used e.g., HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymers such as Polycarbophil, Polyacrylates and Polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.

II. Micro-Porous Compartment System

In micro-porous compartment system a drug reservoir is held inside a micro-porous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the un-dissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

III. Alginate Beads

Alginate beads (multiple unit dosage forms) can be prepared from freeze-drying calcium alginate. Here sodium alginate solution is dropped into aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated and frozen in liquid nitrogen and freeze dried at -40^0C for 24 hrs, leading to the formation of porous system, which can float over 12 hours **[23]**.

IV. Floating Microspheres: (Hollow Micro-Balloons)

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow 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 up to 1mm. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug

is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration **(Figure 6) [24]**.

Bioadhesive Systems

Bioadhesion is an interfacial phenomenon in which a substance is held to biological membrane or mucus. In case of polymer attached to the mucin layer of the mucosal tissue, the term 'mucoadhesion' is employed. 'Bioadhesive' is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of time. In Bioadhesive drug delivery systems the dosage form adheres to the epithelial surface in the stomach thereby prolonging its gastric retention **(Figure 7) [25]**.

Expandable Systems (Swelling and Unfolding Systems)

Swelling systems are retained in the gastrointestinal tract due to their mechanical properties. As the dosage form absorbs the GI fluid due to the osmosis, it swells up and is unable to pass though pyloric sphincter. These systems may be referred to as plug type systems because of their tendency to remain lodged in the pyloric sphincter **(Figure 8)**. In swelling systems sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Swelling of these polymers is due to the presence of physical–chemical cross links in the hydrophilic polymer network. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. Higher the degree of cross-linking smaller is the swelling ability of the system and higher the physical integrity for a prolonged period **(Figure 9)**. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. Unfoldable systems are made of biodegradable polymers. They are available in different geometrical forms **(Figure 10)**.

High Density Systems

High density systems have specific gravity greater than that of the gastric fluid ($1.004 gm/cm^3$).These systems due to their high density are retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. In high density systems drug is coated with heavy inert material like barium sulphate, zinc oxide, titanium dioxide and iron powder resulting in pellets with density up to $3 g/cm^3$ approximately **[27]**, **(Figure 11) [28]**.

Magnetic Systems

In magnetic systems the dosage form is retained in the specific portion of GIT due to the external applied magnetic field. In these systems the dosage form contains certain excipients as a part of formulation which behave as a small magnet, which helps it to be retained in the specific site in GIT under the influence of external field. The external magnet must be positioned with a degree of precision that might compromise patient compliance **[29]**.

Super Porous Hydrogel Systems

In these swelling systems super porous hydro gels of average pore size >100 micro meters, which can swell to equilibrium size within a minute due to the rapid water uptake by capillary wetting through numerous interconnected open pores, are used. Super porous hydrogel due to their superabsorbent nature, were mechanically too weak for gastro retentive application. The mechanical strength of super porous hydrogel was substantially increased by making super porous hydrogel composites. The composite materials used were hydrophilic particulate materials, commonly used as disintegrants in pharmaceutical tablets. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction **[30]**.

Raft Systems

These systems contain a gel forming solution (example Sodium alginate solution containing carbonates or bicarbonates) which on contact with gastric fluid swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles. Each portion of the liquid swells forming a continuous liquid called as a raft **(Figure 12)**. The raft floats on the gastric contents because of low bulk density created by entrapped CO_2. These systems are typically used to deliver antacids (such as aluminium hydroxide or calcium carbonate to reduce gastric acidity) and the drugs for gastro intestinal infections and disorders **[31]**.

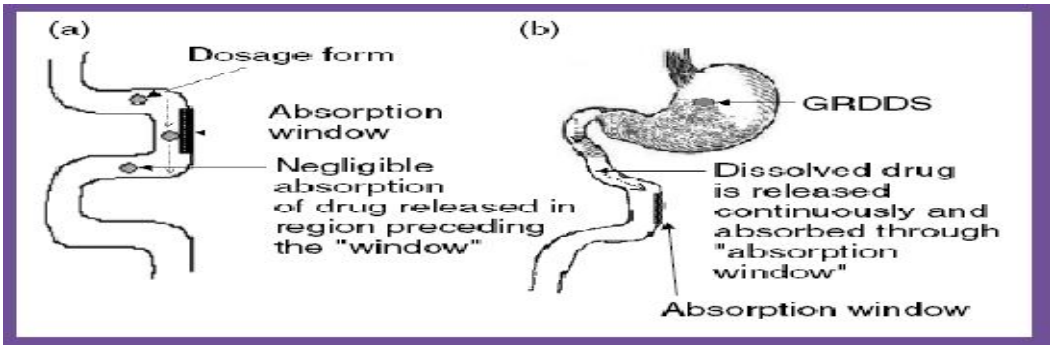

Figure 1: Comparison of (a) Conventional Dosage Form (b) Gastro Retentive Drug Delivery System [8]

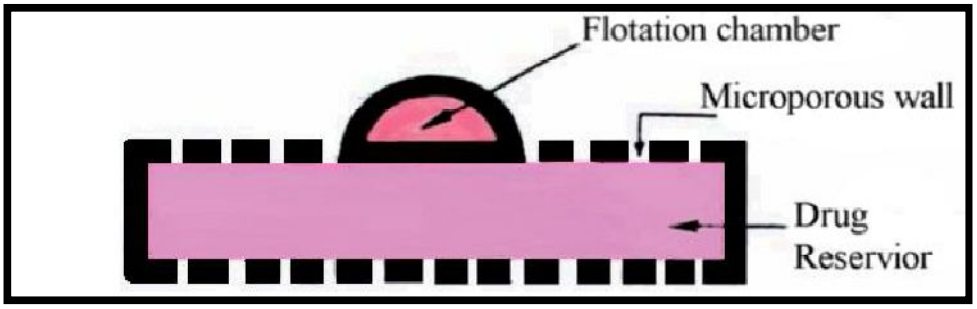

Figure 2: Intra-Gastric Floating Gastrointestinal Drug Delivery Device [20]

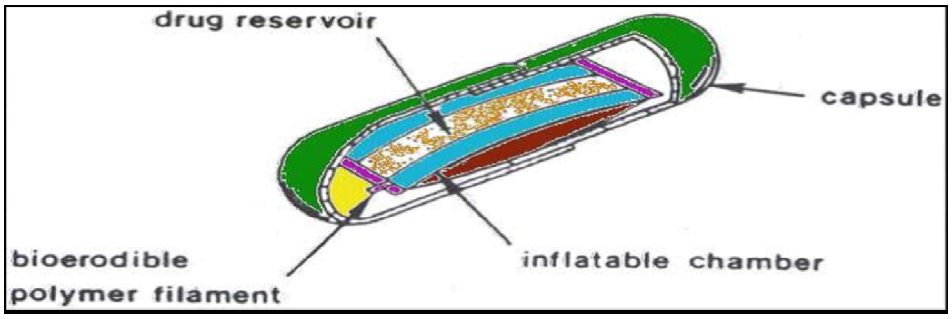

Figure 3: Inflatable Chamber [20]

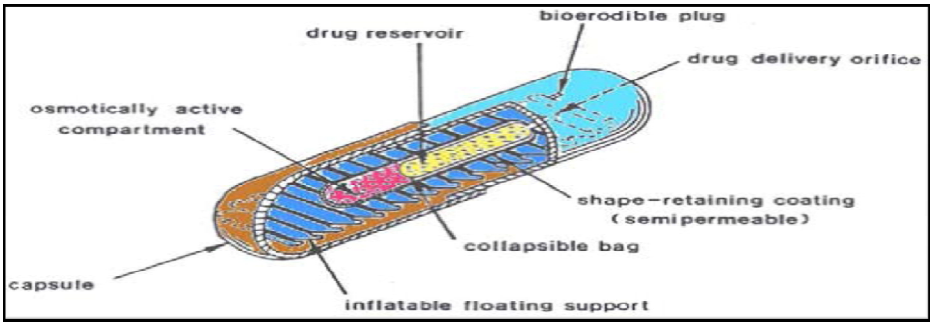

Figure 4: Intragastricosmotically Controlled Drug Delivery System [20]

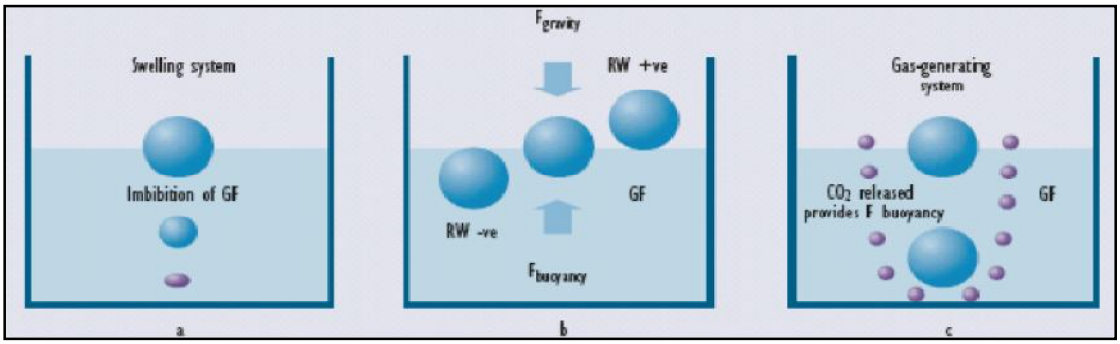

Figure 5: The Mechanism of Floating System [21]

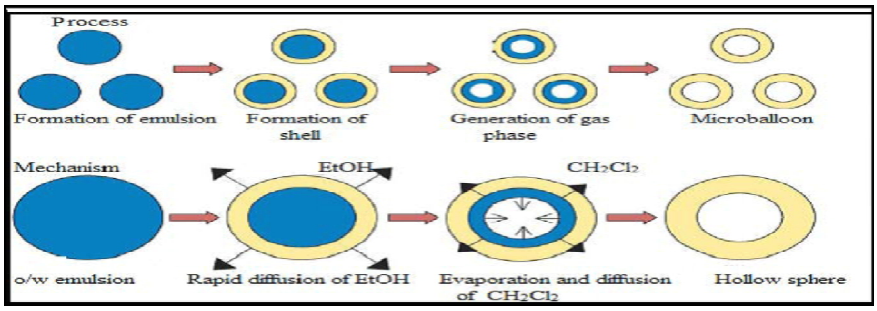

Figure 6: Synthesis of Floating Hollow Micro Balloons [24]

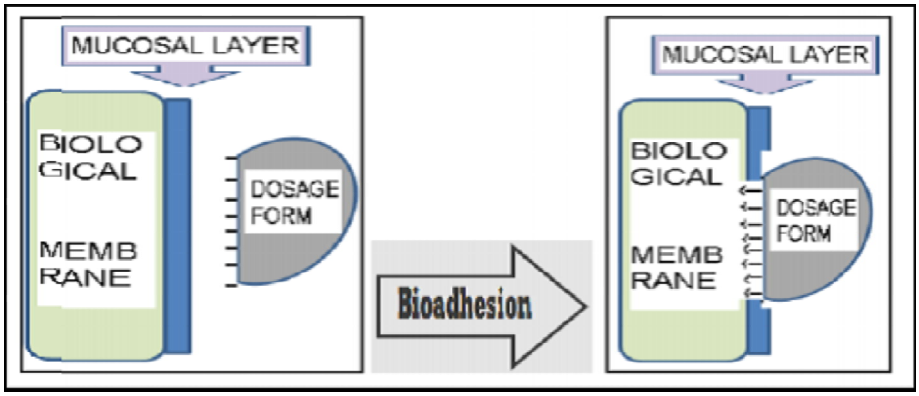

Figure 7: Mucoadhesivesystems [25]

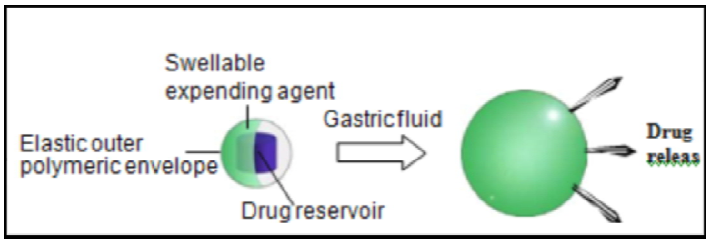

Figure 8: Swelling System

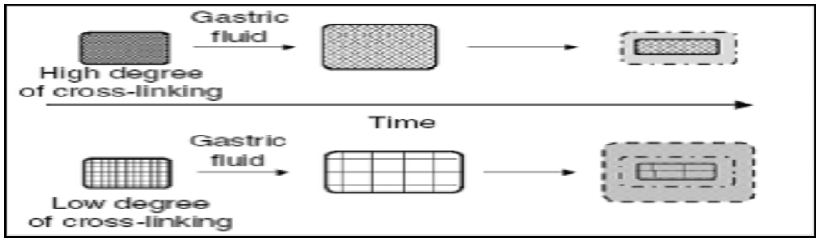

Figure 9: Relation Between the Degree of Cross Linking of the Polymeric Chains and the Swelling Behaviour of the Swelling System [26]

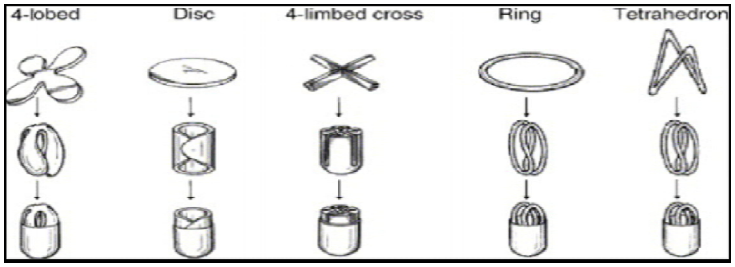

Figure 10: Various Geometrical Forms of Unfolding System [21]

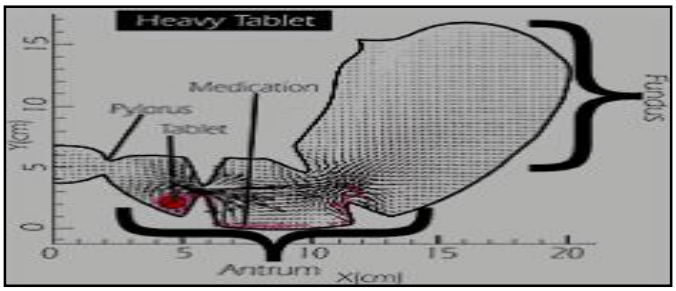

Figure 11: High Density System [28]

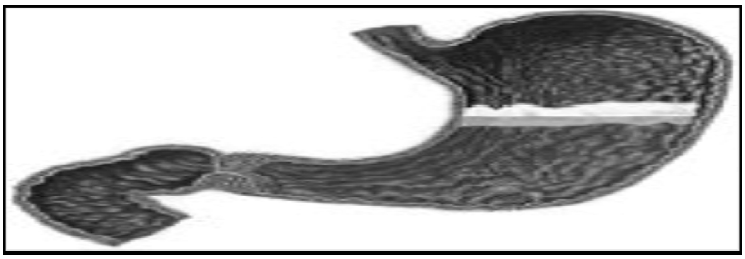

Figure 12: Schematic representation of the Barrier Created by a Raft Forming System [31]

Incorporation of Passage Delaying Food Agents

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release.

Potential Drug Candidates For Stomach Specific Drug Delivery System

- Drugs which are locally acting in the stomach e.g. Misroprostol, Antacids etc.
- Drugs with absorption window **[3, 32]** e.g., of drugs with narrow absorption window: L-dopa, Para-aminobenzoic acid, Furosemide, Riboflavin, Cyclosporine, Methotrexate, and Ofloxacin etc.
- Drugs primarily absorbed from stomach and upper part of GI tract,

e.g., Calcium supplements, Chlordiazepoxide and Cinnarazine etc.

- Drugs that degrade in the colon, e.g., Ranitidine HCl, Metronidazole, Captopril etc.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate, Tetracycline, Clarithromycin etc.
- Drugs that exhibit low solubility at high pH values (e.g. Diazepam, Chlordiazepoxide, Verapamil, Ofloxacin etc.

Drugs Those are Unsuitable for Stomach Specific Drug Delivery Systems

- Drugs that have very limited acid solubility e.g. Phenytoin etc.
- Drugs that suffer instability in the gastric environment e.g. Erythromycin etc.
- Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and Corticosteroids etc.

Advantages of Gastroretentive Drug Delivery System [10, 33, 34]

- **Enhanced Bioavailability:** Gastroretentive dosage forms enhancesthe bioavailability of drugs especially the ones having absorption window **[35]**.
- **Sustained Drug Delivery, Reduced Frequency of Dosing:** Drugs with relatively short biological half-life, sustained and slow release may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance and improves therapy.
- **Targeted Therapy for Local Ailments in the Upper GIT:** The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach but are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
- **Reduced Fluctuations of Drug Concentration:** Gastro retentive dosage form minimizes the fluctuation of drug concentration. Therefore, concentration dependent adverse effects that are associated with peak concentration can be prevented. This feature is of special importance for drugs with narrow therapeutic index **[36]**.
- **Extended Time Over Critical (Effective) Concentration:** Sustained mode of drug release enables extension of the time over a critical concentration and thus enhances the pharmacological effects, and improves the clinical outcomes.

- **Minimize Adverse Activity in Colon:** Minimize adverse effects of the drugs that disturb the colonic microorganisms because retention of drugs in the stomach minimizes the drug that reaches colon.
- **Enhance First Pass Biotransformation:** When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input **[37]**.
- **Improve Receptor Activation Selectivity:** FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations**[37]**.
- **Delivery of Sparingly Soluble and Insoluble Drugs:** Administration of gastroretentive dosage will result in dissolution of the drug in the gastric fluids. The drug present in the gastric fluid would be available for the absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage form, if it remains in the solution form even at an alkaline pH of the intestine.
- **Delivery of Drugs During Vigorous Intestinal Movement:** Advantageous in case of vigorous intestinal movement and short transit time as might occur in certain type of diarrhea.
- Minimize loss of valuable drug substance which has high solubility and low permeability or those which utilize carrier mediated transport in the gut, in turn improves efficiency in treatment.
- Slow release of the drug minimizes the counter activity of the body leading to higher drug efficiency.
- Less inter- and intra-subject variability.

Disadvantages of Gastroretentive Drug Delivery System

- The major disadvantage of gastro retentive floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.

- Drugs that are absorbed equally well throughout the GI tract does not benefit from incorporation into a gastric retention system e.g., Isosorbidedinitrate, Nifedipine.
- There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- Drugs that may irritate the stomach lining are not suitable candidates.
- Drugs which are unstable in its acidic environment should not be formulated as gastro retentive systems.
- Not suitable for drugs that have solubility or stability problem in GIT.

Future Prospectus

- Floating dosage form offers various future potential as evident from several recent publications. Several narrow absorption window drugs may benefit from compounding into a GRDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment. This all can be conceivable with GRDDS **[38]**.
- Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The floating concept can also be utilized in the development of various anti-reflux formulations.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease?
- Combination therapy to treat H. Pylori infection in a single GRDDS needs to be developed.

Evaluation of Gastroretentive Dosage Form

Evaluation of Powder Blend

(a) Angle of Repose (b) Bulk Density (c) Percentage porosity

Evaluation of Tablets

(a) Weight variation (b) content uniformity (c) Hardness & friability (d) Particle size analysis and surface characterization (for floating microspheres and beads) etc. All these tests are performed in the same way as in case of conventional dosage forms. Only the important tests which are of concern in case of GRDDS are discussed below.

A. In-Vitro Evaluation [39, 40]

i. Floating Systems

Floating systems are evaluated for buoyancy lag time, floating time, specific gravity and resultant weight.

a) Buoyancy Lag Time: it is time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium.

b) Floating Time: The time for which the dosage form continuously floats on the dissolution media maintained at 37±0.5^{0}C at given RPM is termed as floating time.

c) Specific Gravity (Density) can be determined by the displacement method using Benzene as displacement medium.

d) Resultant Weight: Resultant weight F of a dosage form is given by

$F = F_{buoy} - F_{grav}$; $F = D_f\ g\ V - D_s\ g$; $F = (D_f - M/V)\ g\ V$

Where, F = resultant weight of object; F_{buoy}= buoyancy force acting on dosage form; F_{grav} = force of gravity acting on dosage form; D_f= Density of Fluid; D_S = Density of Solid object; g = Gravitational force; M = Mass of dosage form; V = Volume of dosage form.
When D_s, density of dosage form is lower, F is positive, gives buoyancy and when D_s is higher, F will negative shows sinking

ii. Swelling Systems

a) Swelling Index: Dimensional changes in dosage form with time in simulated gastric fluid maintained at 37±0.5^{0}C.

b) Water Uptake: Changes in weight of a dosage form with time in simulated gastric fluid maintained at 37±0.5^{0}C.

Water uptake(WU) = (Wt – Wo) * 100 / Wo

Where, Wt = weight of dosage form at time t

Wo = initial weight of dosage form

B. In-Vitro Dissolution Tests

Invitro dissolution tests are performed in USP apparatus with paddle in the same way as that of conventional tablets but as the system floats on the surface, so to have proper force acting on the dosage form and to avoid sticking of the system to the surface of vessel or paddle in case of swelling systems, various modification in dissolution assembly are made which are as follows:

a) To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

b) Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage

form and also affects drug release.

c) Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

d) Other method suggests placing dosage form between 2 ring/meshes.

e) In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

f) None of the above dissolution systemsshowedco-relation with the in-vivo conditions. So a novel dissolution test apparatus,Rossett-Rice test Apparatus,with modification was proposed**[39]**.

C) In-Vivo Evaluation [39, 40].

a) Radiology: BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view Gastric Retention.

b) Scintigraphy: Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

c) Gastroscopy: Gastroscopy is peroral endoscopy used with fibre optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) Magnetic Marker: Dosageform is magnetically marked with iron powder inside, and images are taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e) Ultrasonography: Ultrasonographyis also used to detect presence of dosage

form in stomach but not in intestine.

f) **^{13}C Octanoic Acid Breath Test:** In this test ^{13}C Octanoic acid is incorporated into GRDDS. As octanoic acid comes in contact with gastric fluid, $^{13}CO_2$ gas is liberated which comes out in breath. Time up to which $^{13}CO_2$ gas is observed in breath can be considered as gastric retention time of dosage form.

CONCLUSION

After oral administration many factors determine the bioavailability of drugs, the most important amongst them being the absorption site of a drug, pH stability/solubility profiles and dissolution rate. In line with the review as discussed above it is concluded that gastric retention of drugs (GRDDS) can prove as a promising technique to deliver absorption window drugs, and drugs meant to have local action in the stomach(eradication of H. Pylori infection) together with drugs having stability or solubility problems at higher pH.

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