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Critical assessment pertaining to Gastric Floating Drug Delivery Systems

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Abstract

Plan: *This review discusses overall approaches of gastroretentive drug delivery systems and limelight on floating drug delivery its formulation development and discusses various evaluation parameters.*
Preface: *Oral drug delivery of nearly half of the drugs gets thwarted owing to the high lipophilic nature .Bioavailability of these drugs being function of their aqueous solubility and dissolution tends to exhibit low magnitude and high intra and inter subject variability. Many drugs have a short biological half life and thus have invents potential in ameliorating GI absorption. To overcome the poor bioavailability and patient complaints much attention has been given to Gastro retentive drug delivery system, although there are various approaches in retaining the drug within the gastric region.*
Outcome: *Floating dosage form can be broadly divided in to effervescences and non effervescences both have its own merits and demerits. To state that a given floating drug delivery system successfully float ,its lag time should be within 5 min. Factors affecting floatation are size, shape, density, single or multiple unit, fed or unfed state, nature and frequent of food, gender, age, patient related etc. Evaluation include buoyancy study, floating and swelling behavior, drug release in additional to conventional evaluation, in vivo evaluation is important since the results may not adequately correlate with in vitro results. The usual reported in vivo floatation studies include x-ray, gamma scintigraphy, gastroscophy, magnetic marker, ultrasonography and octanoic acid breath test.*
Key words: *gastro retention, buoyancy, mucoadhesive, transit time, scintigraphy*

1. Introduction:

The oral ingestion is the predominant and most preferable route for drug delivery may depend upon the factors such as gastric emptying process, gastro intestinal transit time of dosage form, drug release from the dosage form site of absorption of drugs[1]. We have covered a review on gastroretentive and mucoadhesive dosage forms[2].
In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times.

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Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs[2].

Gastric emptying of dosage form 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 .Several difficulties are 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 GIT .Drug absorption from the GIT is a complex procedure and is subject to many variables, it is widely acknowledged that the extent of gastro intestinal 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 aabsorbed[3].

The oral controlled drug delivery systems should be primarily used to achieving more predictable and increased bioavailability of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, useful for drugs acting locally in the GIT, drugs which are poorly soluble and unstable in the intestinal fluids. Among the various gastro retentive systems, gastric floating drug delivery systems (GFDDS) offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time .While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. Floating drug delivery and mucoadhesive systems gained significant attention in the past decade because of its effectiveness in gaining bioavailability, cost-effective compared to other NDDS and better scale up technical opportunities.

1.1. Issues related to gastric emptying:

It is well recognized that the stomach may be used as a ‘depot ‘for sustained release dosage forms, both in human and veterinary applications. Anatomically the stomach is divided into 3 regions: fundus, body and anthrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, where as the anthrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[4].

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fating state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[5].

This is called as the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[5].

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes .It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine .it is also known as house keeper wave. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of concentrations 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 1mm), which are propelled towards the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in showdown of gastric emptying rate.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric emptying residence time and unpredictable gastric emptying rate. Yet another major adversity encountered through the oral route is the first-pass effect, which leads to reduced systemic bioavailability of a large number of drugs. Overall, the relatively brief GI transit time of most drug products, which is approximately 8-12 hours, impedes the formulation of a once daily dosage form for most drugs such as age, race, sex and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore desirable to have a CR product that exhibits an extended GI residence and a drug release profile independent of patient related variables[6].

Table 1: Regional specific characteristics of GIT influencing gastro retention

Region	*Surface area(m^2)*	*Liquid secretion (ml/min)*	*Reaction PH*	*Transit time (hr)*
Oral cavity	About 0.05	0.5-2	5.2-6.8	Short
Stomach	0.1-0.2	2-4	1.2-3.5	0.5-3
Duodenum	About 0.04	1-2	4.6-6	1-2
Small intestine	4500*	0.2	4.7-6.5	1-10
Large intestine	0.5-1	0.2	7.5-8.0	4-20

**Taking microvilli area in to account*

1.2. Need for gastroretentive drug delivery system

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effect and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example material passes through the small intestine in as 1-3 hours. In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT[7]:

I) Drugs acting locally in the stomach
E.g. Antacids and drugs for H.Pylori viz., Misoprostol
II) Drugs that are primarily absorbed in the stomach
E.g. Amoxicillin
III) Drugs that is poorly soluble at alkaline P^H
E.g. Frusemide, Diazepam, Verapamil, etc.

IV) Drugs with a narrow window of absorption
E.g. Cyclosporine, Methotrexate, Levodopa, etc
V) Drugs which are absorbed rapidly from the GIT.
E.g. Metronidazole, tetracycline.
VI) Drugs that degrade in the colon.
E.g. Ranitidine, Metformin HCL.
VII) Drugs that disturb normal colonic microbes
E.g. Antibiotics against H.Pylori.

1.3. Drugs that would benefit from GRDDS

CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine), Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics, Anti-hypertension drugs, Anti-diabetic agents for Type-2 diabetes, Drugs for local treatment of GI infections and gastric enzyme replacement[8].

1.4. Formulation considerations for GRDDS

It must be effective retention in the stomach to suit for the clinical demand

I) it must have sufficient drug loading capacity
II) It must be control the drug release profile
III) It must have full degradation and evacuation of the system once the drug release is over
IV) It should not have effect on gastric motility including emptying pattern
V) It should not have other local adverse effects[9].

2. Approaches to gastric retention

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms, swelling and expanding systems, Mucoadhesive systems, High density systems, Modified shape systems. Gastric emptying delaying devices and co-administration of gastric delaying drugs. Among these, the floating dosage forms have been used most commonly.

A. Floating drug delivery system:

Floating drug delivery systems (or) hydro-dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is slowly released at a desired rate from the stomach. After the release of drug, the residual system is emptied from the stomach. This results an increase in the gastric retention time and better control of fluctuations in the plasma drug concentration.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as hydro dynamically balanced systems(HBS) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices.

These forms are expected to remain buoyant (3-4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of gastric contents.
Among the different hydrocolloids recommended for floating form formulations, cellulose and ether polymer are most popular, especially hydroxy propyl methyl cellulose. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase bouncy[10, 11].
Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intra gastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of x-ray and gamma scintigraphic monitoring of the form transit in the gastrointestinal tract. when a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meals empties. The reported gastric retention times range from 4 to 10 hours.
Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time[12].
The floating drug delivery system (FDDS) can be divided into effervescent systems and non effervescent systems.

I. Effervescent systems:

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas[13].
These are matrix type systems prepared with the help of swellable polymers such as HPMC, methylcellulose, chitosan and various effervescent compounds, e.g. sodium bicarbonate, calcium carbonate, tartaric acid and citric acid. They are formulated in such away that when in contact with the gastric contents, Co_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms[14].

i) Volatile liquid / vacuum Containing Systems:-

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies body temperature to cause the inflation chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in system first contains the drug and the second chamber contains the volatile liquid .These systems are classified into 3 categories

1. Intra gastric floating drug delivery system
2. Inflatable gastrointestinal delivery systems
3. Intra-gastric osmotically controlled drug delivery system

a) Intra gastric floating gastrointestinal drug delivery system:-

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

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 compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

c) Intragastric 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 intragastirc 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 vapor 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 bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

ii) Gas generating systems:

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate Co_2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chime. A multiple unit type of floating pills, which generate co_2, have also been developed.

The system consists of a sustained release pill as seed, surrounded by double layers. The inner layer is an effervescent layer containing sodium bicarbonate and tartaric acid. The outer layer is of a swellable membrane layer containing PVA, shellac etc. Another effervescent system consisting of a collapsible spring, which controls the release of drug from the polymer matrix, has also been developed.

The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus carbon dioxide is released, causing the beads to float in the stomach[15]. Earlier we have reported fabrication of gas liberating Lanzoprazole microsphere[16].

iii) Matrix tablets

Single layer matrix tablet is prepared by incorporating bicarbonates in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug.
Bilayer tabet can also be prepared by gas generating matrix in one layer and second layer with drug for its sustained release effect.
Floating capsule also prepared by incorporating such mixtures. Triple layer tablet also prepared having first swellable floating layer, second sustained release layer of two drugs (metronidazole and tetracycline) and third rapid dissolving layer of bismuth salt. This tablet is prepared as single dosage form for triple therapy of H.Pylori[14].

II. Non effervescent system:

Non effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, poly methacrylate, and polystyrene. The formulation methods includes a simple approach of thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration the dosage form swells in contact with gastric fluids and attains a bulk density of less than one. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. These formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass [17, 18]. Corresponding author have utilized compressed carbon dioxide in the system slurry to produce microspheres with air pockets by which it becomes buoyant[19].

i) Hydro dynamically balanced systems:

Hydro dynamically balanced (HBS), which contains drugs with gel forming hydrocolloids meant to remain buoyant on the stomach content. These are single unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxy propyl methyl cellulose(HPMC),hydroxyl ethyl cellulose(HEC),hydroxyl propyl cellulose(HPC),sodium carboxymethylcellulose (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[4, 17, 18].

ii) Micro porous compartment systems:

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. Gastric fluid enters through the aperture, dissolves the drug for continuous transport across the intestine for drug absorption.[19]

iii) Multi particulate system: Floating beads

Multi particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. Thus multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet[19].

iv) Micro balloons / hollow microspheres:

There are various approaches in delivering substances to the target site in a controlled release fashion. One such approach is using polymeric micro balloons as carrier for drugs. Hollow microspheres are known as the micro balloons.

Hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion evaporation methods to prolong the gastric retention time of the dosage form[20].Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer and polymer ratio and the solvent used for formulation. The micro balloons floated continuously over the surface of acidic dissolution media contain surfactant for more than 12 hours[21]. At present hollow microspheres are considered to be one of the promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

B. Mucoadhesive systems:

Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the gastro retention of drug delivery system (DDS) in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane.

A bio/muco-adhesive substance is a natural or synthetic polymer capable of producing an adhesive interaction based on hydration –mediated, bonding mediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosal surface [22, 23].

C. Swellable systems:

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. On coming in contact with gastric fluid, the polymer imbibes water and swells. These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as plug type systems. Sustained and controlled drug release may be achieved by selection of polymer of proper molecular weight and swelling of the polymer retards the drug release.

D. Expandable system:

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus[24]. As a result, the dosage form is retained in the stomach for a longer period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. As dosage form coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of this polymer is a result of the presence of physical-chemical crosslink's in the hydrophilic polymer network. These crosslink's prevented the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period .On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer[25]. An optimum amount of cross linking is required to maintain a balance between swelling and dissolution .The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion[26]. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration

The expandable GRDFs are usually based on three configurations [27]:

I) A small collapsed configuration which enables sufficient oral intake

II) Expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter.

III) A smaller form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.

The expansion can be achieved by

I) swelling system

II) Unfolding system

E. Self-unfolding systems/Modified shaped system:

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the GRT depending on size, shape and flexural modulus of the drug delivery system[28].

The self unfoldable systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach .A drug can be either contained in a polymeric composition of the gastro retentive system or includes as a separate compartment. Several methods were suggested to provide for the self –unfolding effect[29].

1) The use of hydro gels swelling in contact with the gastric juice.
2) Osmotic systems, comprising an osmotic medium in a semi permeable membrane.
3) System based on low boiling liquids converting into a gas at the body temperature.

F. Magnetic systems:

This system is based on a simple idea that the dosage form contains a small internal magnet and magnet placed on the abdomen over the position of the stomach. Despite numerous reports bout successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept [30, 31].

G. High density systems:

These systems with a density of about 3g/cm3 are retained in the anthrum part of the stomach and are capable of withstanding its peristaltic movements. The only major draw backs with such system is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8g/cm^3. It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc to manufacture such high density formulations [32, 33].

H. Raft forming systems:

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. These systems contains a gel forming agent and alkaline bi carbonate or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids[6]. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. Because raft forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon [25, 26, 27].

I. Super porous hydro gels:

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10nm and 10micro meter .Absorption of water by conventional hydro gel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of dosage form may occur. Super porous hydro gel ,average pore size >100 micro meter, swell to equilibrium size within a minute, due to water uptake by capillary wetting through numerous inter connected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di-Sol (cross carmellose sodium).

3. Factors affecting the gastro retentive systems:

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. Most of approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system[34].

3.1. Dosage related physical factors

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach .Both positions may isolate the dosage system from the pylorus. A density of <1.0gm/cm3 is required to exhibit floating property.
Size and shape have found to have effect on gastro retention. Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm. Tetrahedron and ring shaped devices with a flexible modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

*3.2. Single or multiple unit formulation***:**

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms. For single unit dosage form, either the whole dosage form retains within the stomach, but if fails no drug will be released in the gastric region, thus shows 'all or non hypothesis'.

Table 2: Various reported gastroretentive systems and the APIs and polymers used

Type of Gastro Retentive Systems	Active Ingredients	Polymers
Gastro retentive Tablets	Ofloxacin	HPMCK4M, HPMC 5cps
	Itopride hydrochloride[45,47]	HPMCK15M, HPMC K100M
Floating Tablets	Theophylline	HPMCK15MCR, HPMC K100M
	Cephalexin[45]	HPMCK4M, Xanthan Gum, Guar Gum
	Salbutamol Sulfate[50,52]	HPMC K4M
	Ranitidine Hydrochloride	HPMCK15M, HPMC K100M
	Clarithromycin	HPMC K4M
	Cefuroxime axetil	HPMC K4M, HPMC100LV
	Acetohydroxamic acid & Chlorpheniramine maleate	Eudragit RSPO, Eudragit EPO
	Imatinib mesylate[46,48]	HPMCK4M, HPMC K15M, HPMC K100M,
Bilayered Floating Tablets	Tizanidine hydrochloride	HPMC K 15M, HPMC 100M, Xanthun gum
	Captopril[45]	HPMC K4M, HPMC K15M, HPMC K100M
Bioadhesive Bilayered floating tablet	Rosiglitazone maleate[48]	HPMC
	Imatinib mesylate[49,51]	Carbopol947P, Sodium CMC
Floating microspheres	Acyclovir	Ethyl cellulose
	Cefpodoxime proxetil	Ethyl cellulose, HPMC K15M
	Famotidine[52]	Polymethyl methacrylate
	Ranitidine hydrochloride[47]	Sodium alginate. Pectin pure
	Keterolac trametamol	Eudragit100, Ethyl cellulose, Eudragit S 100, HPMC K4M
	Diltiazem hydrochloride[50,53]	Eudragit RS 100, Ethyl cellulose
	DIltiazem	Alginate, Chitosan, Eudragit
	Verapamil hydrochloride	Eudragit S 100, Cellulose acetate, Acrycoat S 100
	Acetohydroxamic acid	Gellan (Gelrite)
	Metformin hydro chloride	Ethyl celllulose
	Cimetidine [45]	HPMC, Ethyl cellulose
Floating microparticles	Aceclofenac	Eudragit RS 100
	Verapamil hydro chloride[53]	EudragitRS ,Ethylcellulose, Poly methyl Methacrylate
	Ketoprofen	Eudragit S100, Eudragit RL
Micro capsules	Melatonin[49]	Chitosan
Floating micro pellets	Lansoprazole	HPMC, Methyl cellulose, Chitoisan
Floating minimatrices	Aceclofenac[50]	HPMC 15 LV
Hollow microspheres/Microballons	Aceclofenac	Pectin
	Diclofenac sodium	Eudragit S100
	Theophylline	Xanthan gum, Gelatin
	Riboflavin[51]	Eudragit S100

3.3. Fed or unfed state:

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer [25].

3.4. Nature and frequency of meal:

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release[35]. GRT can be increased by 4 to 10 hours with a high calorie meal (in proteins and fats) [36, 37]. The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

3.5. Gender, age, exercise and body posture of subject:

Mean ambulatory GRT in males (3.4 +-0.6 hours) I less compared with their age and race matched female counterparts (4.6+_1.2 hours), regardless of the weight, height and body surface[36]. Elderly people, especially those over 70 years of age, have a significant longer GRT[25]. Vigorous physical activity retards gastric emptying. Gastric emptying is favored while standing and by lying on the right side since the normal curvature of the stomach provides a downhill path where as lying on the left side or in supine position retards it since the contents have to go against gravity [37].

3.6. Emotional state of subject:

The influence of emotional factors on gastric motility and secretion may be either augmentative or inhibitory depending upon whether the emotional experience is of an aggressive or a depressive type[34].

3.7.Gastro intestinal P^H:

Gastric emptying is retarded at low stomach P^H and promoted at higher or alkaline P^H. Chemicals that effect gastrointestinal P^H also alters gastric emptying. The inhibitory effect of various acids on gastric emptying decreases with increase in molecular weight and is in the following order HCL>Acetic>lactic>tartaric>citric acids. With alkaline solutions, a low base concentration (1% $NaHCO_3$) increases the gastric emptying rate more than the 1 of higher concentration (5%).

3.8. Concomitant drug administration and disease state:

Anti cholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time. Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT [7, 24].

4. Evaluation of gastro retentive dosage form:

In general there are several parameters which are commonly applicable for all type of gastro retentive dosage forms eg. Drug content, FTIR, X ray etc. But there are specific evaluation parameters which depending on the type of approach adapted for the gastro retention. Thus mucoadhession studies may not be considered for floating devices. Various parameters that need to be evaluated in gastro retentive formulations include

A) In-Vitro Evaluation:

i) Floating systems:

a) Buoyancy lag time: It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. This parameter can be measured as a part of the dissolution test. The maximum buoyancy lag time for floating dosage form is 5 mins[8].

b) Total floating time:

Test for floatation is usually performed in SGF-Simulated Gastric fluid maintained at 37˚C. The time for which the dosage form continuously floats on the dissolution media is termed as total floating time[38].

c) Specific gravity/density:

It can be determined by the displacement method using Benzene as displacement medium[7].

d) Resultant weight:

Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up/down) is corresponding to its buoyancy force (Fbuoy) and gravity force (Fgrav) acting on dosage form[11].

$F = Fbuoy – Fgrav$, $F = D_f\ g\ V – D_s\ g\ V$, $F = (D_f – D_s)\ g\ V$, $F = (D_f – M/V)\ g\ V$

Where F = Resultant weight of object; D_f= Density of fluid; D_s = Density of solid object; g = Gravitational force; M = Mass of dosage form; V = Volume of dosage form

So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

ii) Swelling systems:

a) Swelling index:

After immersion of swelling dosage form into SGF at 37˚C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness/diameter with time[7, 38].

b) Water uptake:

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. So it is also termed as weight gain[7, 38].

*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:

In vitro dissolution test is generally done by using USP apparatus with paddle The in vitro release of drug from different formulations was examined by using simulated gastric fluid(P^H 1.2, without enzymes) 900 ml as the dissolution medium and maintained at 37˚C at a rotation speed of 50-100 rpm. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and replaced by 5ml of fresh dissolution medium. Samples were assayed spectro metrically at maximum wave length[39].

*C) In-Vivo Evaluation***:** Although many animal models including rabbits have reported for in vivo behavior, human studies are easily and widely acceptable. Type of the study determines the tracing element to be incorporated. We have even reduced the size of the dosage form in order to avoid congestion of the narrow trachea if rabbits are used.

1. *Radiology:* X- ray is widely used for examination of internal body systems. Barium sulphate is widely used Radio opaque marker. So, drug s replaced by $BaSO_4$ and x-ray images are taken at various intervals to view Gastro retention. It is advisable to prepare different concentration of BaSO4 and find out which ratio gives the comparable *in vitro* floatation. Our research experience shows that 20% of the drug if substituted will give satisfactory results. The corresponding author has performed *in vivo* studies on rabbits of a mucoadhesive anticancer single unit dosage form and is in pipeline for patent.

2. *Scintigraphy***:** Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is ^{99}Tc (technetium).

3. *Gastroscopy***:** Gastroscopy is peroral endoscopy used with fiber 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.

4. *Magnetic marker monitoring:* In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.
5. *Ultrasonography: Used sometimes, not used generally because it is not traceable at intestine.*

6. *^{13}C Octanoic acid breath test:* ^{13}C Octanoic acid is incorporated in to GRDDS. In stomach due to chemical reaction, octanoic acid liberates Co_2 is replaced with ^{13}C isotope. So time up to which $^{13}Co_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no Co_2 release .So this method is cheaper than other[7, 38].

5. Merits of gastro retentive drug delivery systems

i) The Gastro retentive systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
ii) Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
iii) This type of drug delivery systems is especially very useful in the in the treatment of the disorders related to the stomach. As the prime objective of such systems is to produce a gastro retentive product or a product which has enhanced retention time in the stomach.
iv) Prolonged gastric retention improves bioavailability, reduces the drug waste, and improves solubility for drugs that are less soluble in a high P^H environment.
v) Gastric retention helps to provide better availability of new product with new therapeutics possibilities and substantial benefits for patients.
vi) All those molecules with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.
vii) This is a primary manner in which the bioavailability of a therapeutic agent can be enhanced, especially all those drugs which get metabolized in the upper GIT.
viii) They also have an advantage over the conventional systems as it can be used to overcome the adversities of gastric retention time as well as the gastric emptying time. As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of emptying because their bulk density is lower than that of gastric fluids.
ix) The duration of treatment through a single dose, this release the active ingredient over an extended period of time.
x) The active entity is delivered to the site of action, thus minimizing or eliminating the side effects [40-44].

6. Conclusion:

Out of several approaches in gastro retention, floating drug delivery is the most extensively preferred technique followed by mucoadhesive technique. Floating drug delivery is aimed to achieve the retention of the drug along with the formulation for an extended period of time in the gastric region. Floatation achieved by non-gas generating formulation approaches will be preferred to gas generation formulations since the later may cause belching, distention etc. which may lead to less patient compliance. To state that a given floating drug delivery system successfully float, its lag time should be within 5 min. It has to be noted that even though the *in vitro* evaluation for retention is successful by means of floatation/ mucoadhession etc. it need not show the same *in vivo* behavior.

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