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A Review on Updates to Increase the Residence Time of Drug in the Stomach for Gastro Retentive Drug Delivery System

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ABSTRACT: Orally-administered controlled-release drug delivery systems are associated with the shortcomings of relatively short residence times in the human stomach as well as highly variable gastrointestinal (GI) transit times. Thus, considerable intra-individual and inter-individual differences in the bioavailability of drugs are observable. There are numerous drug substances which may benefit from prolonged and controlled GI passage times. As a solution to the problem, gastroretentive drug delivery systems (GRDDS), which feature an enhanced gastric residence time (GRT), were developed. Several approaches are currently used including Floating Drug Delivery System (FDDS), swelling and expanding system, polymeric bioadhesive systems, modified-shape systems, high density system and other delayed gastric emptying devices. The drugs having absorption window in the upper part of Gastro Intestinal Tract (GIT) have enhanced bioavailability when formulated through these techniques. The recent technological development for enhancing GRT including the physiological and formulation variables affecting gastric retention, patented delivery systems, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail.

Despite the extensive research performed in the field of GRDDS, the development, the production, and the evaluation of floating devices are still challenging. The purpose of writing this review was to compile recent literature on pharmaceutical approaches used in enhancing the Gastric Residence Time (GRT). Enhancing the GRT may explore new potentials of stomach as drug-absorbing organ.

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INTRODUCTION

Introduction to Drug Delivery System

Historically, oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations. However, it is a well-accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12 or even 24 hr. is possible for many drugs that are absorbed uniformly from GI tract. Nevertheless this approach is not suitable for a variety of important drugs characterized by narrow absorption window in the upper part of GI tract i.e. stomach and small intestine. The design of oral controlled drug delivery systems should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose [1, 2, and 3].

The controlled release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these are classified as:

A. Continuous release system: These systems release the drug for a prolonged period of time along the entire length of Gastro Intestinal Tract (GIT) with normal transit of the dosage form. The various systems under this category are:
a) Dissolution controlled release systems
b) Diffusion controlled release systems
c) Dissolution and diffusion controlled release systems
d) Ion-Exchange resins – drug complexes
e) Slow dissolving salts and complexes
f) pH –dependent formulations
g) Osmotic pressure controlled systems
h) Hydrodynamic pressure controlled systems.

B. Delayed transit and continuous release system: These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage is fabricated to retain in the stomach and hence the drug present therein should be stable at gastric pH. Systems included in this category are:
a) Altered density systems
b) Mucoadhesive systems
c) Size-based systems

C. Delayed release systems: The design of such systems involve release of drug only at a specific site in the GIT. The drugs contained in such system have following category:
a) Destroyed in the stomach or by intestinal enzymes.
b) Known to cause gastric distress.
c) Absorbed from a specific intestinal site, or
d) Meant to exert local effect at a specific GI site.

The two types of delayed release systems are:
a) Intestinal release systems
b) Colonic release systems [4].

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems5. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period, enhancement of activity of duration for short half-life drugs, elimination of side effects, reducing frequency of dosing and wastage of drugs, optimized therapy and better patient compliances [5, 6].

The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely.
a) The physiochemical characteristics of the drug.
b) Anatomy and physiology of GIT and
c) Characteristics of dosage forms.

Good fundamental understanding of the anatomic and physiological characteristics of the human GIT is required to modulate the gastrointestinal transit time of a drug through Floating Drug Delivery System (FDDS) for maximal gastrointestinal absorption of drugs and site-specific delivery.

Types of floating drug delivery system

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are:

A. Single unit

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract [7].

a) Noneffervescent systems

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers(e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules[8]. For the preparation of these types of systems, the drug and the gel forming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

b) Effervescent systems or gas generating systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

B. Multiple units

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the inter subject variability in absorption and the probability for dose dumping is lower [9].

a) Noneffervescent systems

A little or no much report was found in theliterature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the

possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

b) Effervescent systems

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 hr. was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 h.[10].

c) Floating microspheres

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, eudragit S and cellulose acetate, are used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer plasticizer ratio [11].

C. Raft forming systems

The basic 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. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids [12].

BASIC PHYSIOLOGY OF THE GASTROINTESTINAL TRACT

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms[13]. Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. As a result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), preburst (Phase II), and burst (Phase III)intervals (**Fig. 1**) Phase I, the quiescent period, lasts from 30 to 60 min and is characterized by a lack of secretory, electrical, and contractile activity. Phase II exhibits intermittent action for 20–40 min during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large, and regular contractions, termed housekeeper waves, that sweep off undigested food and last 10–20 min. Phase IV is the transition period of 0–5 min between Phases III and I. This series of electrical events originates in the foregut and continues tothe terminal ileum in the fasted state, repeating every 2–3 hrs. Feeding sets off a continuous pattern of spike potentials and contractions called postprandial motility. The particular phase during which a dosage form is administered influences the performance of peroral CRDDS and GRDDS. When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional quickly after administration and able to resist the onslaught of physiological events for the required period of time [14].

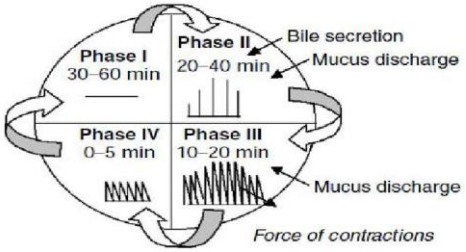

Fig. 1: Sub division of migrating motor complex (MMC)

Potential drug candidates for stomach specific drug delivery systems

1. Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. l-dopa, paraaminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

Drugs those are unsuitable for stomach specific drug delivery systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

Factors affecting gastric retention

a) Density

GRT is a function of dosage form buoyancy that is dependent on the density. Density of the dosage form should be less than the gastric contents (1.004gm/mL).

b) Size and shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo ponds per square inch (KSI) are reported to have better GIT ≅90 to 100 % retention at 24 hrs. compared with other shapes [15].

c) 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.

d) Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every1.5 to 2 hrs. 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.

e) Nature of the meal

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

f) Caloric content

GRT can be increased between 4 to 10 hrs. With a meal that is high in proteins and fats.

g) Frequency of feed

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

h) Gender

Mean ambulatory GRT in meals (3.4±0.4 hrs.) is less compared with their age and race-matched female counterparts (4.6±1.2 hrs.), regardless of the weight, height and body surface.

i) Age

Elderly people, especially those over 70 years have a significantly longer GRT.

j) Posture

GRT can very between supine and upright ambulatory states of the patients [16].

k) Concomitant drug administration

Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

l) Biological factors

Diabetes and Crohn's disease.

Approaches to prolong gastric retention

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts(**Fig. 2**).

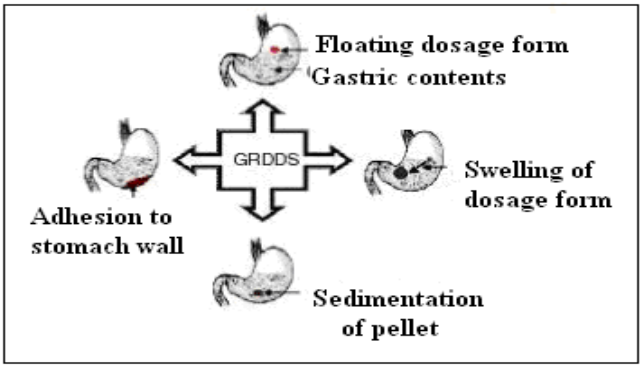

Fig. 2: Different gastric retention systems

Researchers have proposed various mechanisms to retain drug delivery systems in the stomach for an extended period of time. An overview of the different techniques is given below.

a) Co-administration of (pharmacologically active) substances

A prolonged GRT of drug delivery systems is achievable by the simultaneous administration of (pharmacologically active) substances which slow down the gastric motility[17].The passage controlling excipients may be incorporated in the dosage form and when the substances are released, they delay the GI transit of the drug delivery device. An in vivo study has demonstrated that the GI transit time can be modulated by the administration of drug substances. The pre-treatment with metoclopramide enhances; whereas, pre-treatment with propantheline delays the gastric emptying process. The effect of the GI-motility-altering APIs has been investigated on the absorption of subsequently-administered metformin in human subjects [18].

Dietary components (e.g. certain amino acids, fats, peptides) are known to prolong the time period that a dosage form remains in the gastric region [19]. For example, the co-administration of fatty acid salts (e.g. salts of myristic acid) delayed the gastric emptying in humans. The effect of ammonium myristate was studied in vivo following the administration of a commercially available sustained-release nitrofurantoin capsule formulation. The renal nitrofurantoin excretion was assessed in order to investigate indirectly the influence of ammonium myristate on the absorption of the API. The addition of a GI-passage-controlling agent was found to improve the drug bioavailability and to reduce the inter-individual variations [20, 21].

b) Bioadhesive and mucoadhesive systems

Bioadhesive (i.e. immobilization at intestinal surfaces) and mucoadhesive (i.e. immobilization restricted to the mucus layer) systems prolong the relatively short GRT of orally-administered drug delivery systems by adherence of the dosage form to the mucous membrane of the stomach or the epithelial surface of the remaining GI tract [21, 22]. There are different theories to explain the mechanism of bio/mucoadhesion: the electronic theory, the adsorption theory, the wetting theory, and the diffusion-interlocking theory [23].The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism.

These mechanisms are:

1. The wetting theory, which is based on the ability of bioadhesive polymersto spread and develop intimate contact with the mucous layers.
2. The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
3. The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4. The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material.

Several polymers have been analyzed regarding their bio/mucoadhesive potential. Chitosan, cholestyramine, poly(acrylic acid) (e.g. Carbopol®, polycarbophil), Gantrez® (polymethyl vinyl ether/maleic anhydride copolymers), cross-linked dextran gel (e.g. Sephadex®), dextran, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, sodium alginate, sucralfate, tragacanth, poly(alkyl cyanoacrylate), and polylactic acid are used for preparation of bio/mucoadhesive systems [24].

The gastroretentive potential of bio/mucoadhesive GRDDS has been evaluated in vivo in human. Using "-scintigraphy, the influence of polycarbophil on the GRT of a pellet formulation was investigated in fasted subjects. The pellets were found to be rapidly emptied from the stomach [25].

Akiyama et al. compared the GI transit time of sustained-release adhesive and non-adhesive microspheres in fed and fasted volunteers. The GI transit was pharmacokinetically assessed by analyzing the furosemide plasma concentrations and the riboflavin concentrations in urinary excretions. The microspheres, based on the bioadhesive substance carboxyvinyl polymer, showed an extended gastric retention due to the adherence of the dosage form to the gastric and/or intestinal mucosa [26].

The *in vivo* "-scintigraphic studies of Säkkinen et al. did not provide a clear evidence whether formulations containing microcrystalline chitosan can be used as gastroretentive delivery platform. In a few volunteers the microcrystalline chitosan granules were retained in the GI tract for an extended time period compared to the reference formulation of lactose granules [27].

It is difficult to target specifically the GI walls. The use of bio/mucoadhesive substances bears the risk of the dosage forms to attach to the esophageal walls. This results in injuries or possible occlusion of the esophagus [28].

Due to the regular renewal of the mucosal surface, the adhesion duration is limited. In the stomach and the intestine, the mucus is constantly secreted and digested from the luminal surface. In the human stomach, the turnover time from the production to the removal of the mucus layer is estimated to range from 4 to 5 h. The bio/mucoadhesive drug delivery systems may be encased by a mucus shell. In addition, the efficacy of the delivery approach is influenced by the gastric peristalsis because it may hinder the adhesion of the dosage forms to the GI walls [28].

c) Size-increasing systems

The size-increasing GRDDS are based on the principle of expansion of the pharmaceutical dosage form in the stomach to dimensions larger than the pyloric sphincter. Consequently, the gastric emptying of the drug delivery system through the pylorus is retarded. The size-increasing systems exhibit three

configurations. The initial size of the dosage form should be small to facilitate swallowing ("collapsed" configuration) [30]. The delivery approach bears the risk of causing severe injuries or obstruction of the esophagus due to a premature expansion of the dosage form during swallowing. After contact with the gastric juice, the size of the device increases rapidly to prevent uncontrolled stomach emptying through the pylorus. The diameter of the human pyloric sphincter is reported to be 12.8±7 mm. It is thought about establishing a threshold value for the size of dosage forms above which a significant gastric retention may be observable. Researchers have suggested setting a minimum tablet size of 13 mm as cut-off value. The cut-off value is supported by experimental observations: it was discovered that non-disintegrating tablets with a size of 13 mm were retained in the stomach for a prolonged time period compared to 7 mm tablets. The expanded dosage form needs to be rigid enough to withstand the mechanical destruction forces acting in the stomach. On the other hand, the device should not affect the gastric motility, inhibit the gastric emptying, or show local adverse effects (e.g. puncture of the GI walls) [31].

After release of the API, the GRDDS need to be present again in a small configuration to allow clearance from the stomach in order to prevent permanent stomach retention. The delivery approach has the potential risk of life-threatening complications due to the occlusion of the pylorus or due to the accumulation of dosage forms after multiple administrations. The size-increase of dosage forms is achievable by different principles. They are explained and illustrated, by means of examples, in the section below:

(i) Expanding, swelling systems

In the stomach, the expanding, swelling systems increase in size to such an extent that their passage through the pyloric sphincter into the intestine is prevented and their GRT is prolonged. Due to their tendency to remain stuck at the pyloric sphincter, the dosage forms are referred to as "plug-type-systems" [32].

Enzyme-digestible hydrogels, based on poly vinyl pyrrolidone (PVP) cross-linked with functionalized albumin, have been prepared to extend the GRT of APIs. The swelling and degradation properties of the system were controllable by the albumin cross-linker content and by adjusting the degree of albumin alkylation. The concept of hydrogels has been further investigated and superporous hydrogels, which exhibit gastroretentive properties due to rapid swelling of the delivery system, were developed (**Fig. 3**). The fast swelling of the superporous hydrogels to equilibrium size within minutes is achieved by liquid uptake due to capillary wetting through inter-connected pores. The addition of composite material (e.g. croscarmellose sodium) during the synthesis improves the mechanical properties of the hydrogels [33]. Omidian et al. have invented novel superporous hydrogel hybrids with advanced mechanical, elastic, and swelling properties [34].

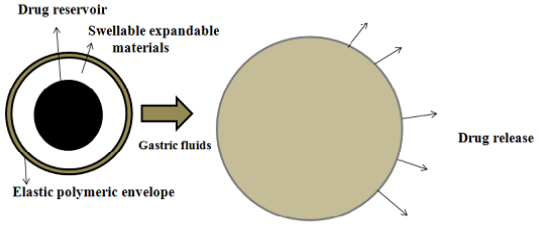

Fig. 3: Drug release from swellable systems

A GRDDS composed of a swellable tablet core which is coated with a porous membrane been investigated. The inner core consisted of the API, the expanding agents (e.g. PVP, Carbopol®), and calcium carbonate. For the permeable tablet coating, different ratios and types of Eudragit® were studied regarding sufficient elasticity to withstand the expansion pressure during swelling and to allow the disintegration of the dosage form after drug release [35].

An expanding system, which exhibits a very high swelling ratio (2 to 50-fold volume increase), has been patented by Theeuwes et al. Due to its large size, the device was, on the one hand, retained in the stomach for an extended time period and, on the other hand, it influenced the gastric motility pattern. The GRDDS are supposed to maintain the stomach in the fed state and thereby delay the onset of the "housekeeper waves" which would empty the dosage form from the stomach. The device consists of tiny, drug-containing pills with a release-controlling wall dispersed within a hydrogel reservoir. The stomach emptying is enabled due to erosion of the device [36].

(ii) Modified-shape systems

Several unfolding GRDDS with different geometry, size, erodibility, and mechanical properties have been patented. For example, the dosage forms exhibit the following geometries: cloverleaf, planar disc, planar multilobe, pellet/sphere, ring, solid stick, and string. For a convenient oral administration, the devices are packed into gelatin capsules. In the stomach, the capsule dissolves and releases the drug delivery device. It unfolds to a sufficiently large size preventing the emptying through the pylorus. The developed GRDDS are claimed to exhibit sufficient resistance to the forces present in the GI tract. After a predetermined period of time, the erosion of the device occurs; thus, enabling the stomach emptying of the dosage form [37, 38, 39].

d) Magnetic systems

The magnetic systems are composed of a dosage form, containing a small internal magnet or a mass of magnetic material, and an extra-corporal magnet to control the GI transit of the dosage form.The concept of magnetic drug delivery systems has been evaluated in human. By using amagnetic model dosage form which consists of small magnets attached to a pH-telemetringcapsule (Heidelberg capsule), it was demonstrated that due to an external magnet the GRTof the model dosage form could be significantly extended. In addition, magnetic depot tablets have been analyzed. They were retained in the stomach region for a prolonged period of

time; hence, an extension of the acyclovir absorption after peroral administration of a sustained-release magnetic drug delivery platform was achieved [40].

Despite the promising results of the in vivo studies, the magnetic drug delivery systems exhibit a major shortcoming: the external magnet needs to be placed with a high degree of precision; therefore, a good patient compliance is required.

e) High-density systems

Orally-administered pharmaceutical dosage forms with a density higher than the density of the gastric contents (1.004-1.01 g/cm3) sink down to the bottom of the greater curvature of the stomach, in case the patient is in an upright position, and get entrapped in the folds of the antrum. The devices are located on a level lower than the pylorus away from the antral mixing. Consequently, the gastric emptying is supposed to be delayed. High-density systems are prepared by the incorporation of heavy inert material, such as barium sulfate, iron powder, titanium dioxide, and zinc oxide [41]. Contradictory results were obtained regarding the influence of density on the GI passage time of dosage forms. The in vivo gastric emptying rates of pellets with densities of 0.94 g/cm3 and 1.96 g/cm3 did not differ significantly in scintigraphy studies. The observation is supported by the finding that pellets with densities of 1.29 g/cm3 and 1.92 g/cm3 did not vary in gastric emptying times. In contrast, Bechgaard and Ladefoged have reported prolonged average GI transit times in ileostomy subjects after increasing the density of a multiparticulate formulation from 1 g/cm3 to 1.6 g/cm3 [42]. The clinical study of Simoni et al. showed that the administration of an enteric-coated sinking ursodeoxycholic acid tablet formulation (density>1 g/cm3) to healthy subjects resulted in a better bioavailability of ursodeoxycholic acid compared to an enteric-coated floating tablet and a hard gelatin capsule. Above a threshold value of 2.4-2.8 g/cm3, the high-density delivery systems are reported to be retained in the rugae at the bottom of the stomach [43].

A significantly prolonged stomach residence time was found for pellets with a density of 2.6 g/cm3 and 2.8 g/cm3 in comparison to control pellets with a density of 1.5 g/cm3. Up to now, there is no high-density GRDDS available on the market. A drawback of the dosage forms is the limited drug loading capacity. High amounts of heavy inert material need to be added to the formulations in order to achieve and maintain a sufficiently high density. The porosity of high-density devices is low, resulting in a slow drug release speed and in difficulties controlling the drug release kinetics.

f) Floating systems

The concept of tablets which have a density less than unity was first described in 1968 by Davis. His invention was aimed to solve the problem of gagging and choking experienced by some people when swallowing a pharmaceutical dosage form. Due to a density less than unity, the medicinal pill floats on liquid surfaces. The intake with a certain volume of water is supposed to facilitate swallowing of the dosage form. FDDS are pharmaceutical dosage forms exhibiting a density lower than the gastric fluids (1.004-1.01 g/cm3). Due to its density less than unity, the dosage form floats on the gastric contents and is retained in the stomach while releasing the API. FDDS offer the advantage that they do not influence the gastric emptying process. But, the filling state of the stomach is important; a certain amount of liquid is required for floating delivery platforms. Single-unit FDDS (e.g. tablets, capsules) are associated with the problem of “all-or-nothing” gastric emptying. Therefore, high inter-subject and intra-subject variability in GI transit time and in bioavailability are observed. However, most floating devices described in literature are single-unit dosage forms. The design of multiple-unit FDDS offers the possibility to overcome the shortcomings of single-unit devices. Multiple-unit floating dosage forms spread over the gastric contents and they are gradually emptied from the stomach. The drug release profiles are supposed to be more predictable and inter-individual as well as intra individual differences in bioavailability are claimed to be reduced [44].

Different mechanisms are known to achieve flotation: floating systems due to swelling of excipients, non-effervescent systems with an inherently low density, and effervescent systems which float due to the generation and entrapment of gas.

(i) Non-effervescent drug delivery systems with flotation due to swelling

One of the first floating GRDDS described in literature is the so-called hydrodynamically balanced system (HBSTM). It is a single-unit floating gelatin capsule which contains a mixture of drug substance and one (or more) gel-forming hydrophilic polymers. For example, agar, alginic acid, carrageenans, hydroxyethylcellulose, HPMC, hydroxypropylcellulose, and sodium carboxymethylcellulose have been studied as gelation-layer-forming excipients [45]. Upon contact with the gastric fluids, the gelatin capsule shell dissolves; hydration and swelling of the polymers occur. A buoyant mucus body with a density of less than unity is formed. At the surface, the gelatinous barrier erodes constantly and a new hydrated layer is generated. The API release is controlled by diffusion and by erosion of the hydrated gel barrier. The principle of HBSTM is also applied for the preparation of floating gastroretentive tablets and mini-tablets.

Kumar et al. has studied the use of glycerol mono oleate (GMO) matrices for the manufacture of floating, swelling GRDDS. The API was added to molten GMO under stirring. Then, the molten mass was transferred into cylindrical molds and frozen. The swelling and flotation performance of the devices has been evaluated in vitro. The authors concluded that GMO matrices are suitable for oral controlled-release floating GRDDS [46].

(ii) Non-effervescent floating drug delivery systems with inherently low density

The preparation of FDDS featuring an inherently low density (i.e. the devices are immediately floating on the gastric contents) is favored. The systems have a reduced risk of

unpredictable, premature gastric emptying because the flotation mechanism does not need to be activated in the stomach. Long floating lag times increase the possibility of premature gastric emptying of the dosage forms by the "housekeeper waves" before flotation starts. An inherently low density may be achieved by the entrapment of air and/or the incorporation of low-density material. Such kind of low-density material includes, for example, fatty components or oils, porous material, and foamed powders [47].

Krögel and Bodmeier proposed HPMC tablets in combination with a hollow, impermeable cylinder. Each HPMC tablet closes one of the ends of the cylinder in a way that an air-filled compartment is created providing an inherently low density to the delivery system. But, the flotation of the device is terminated as soon as at least one of the tablets has dissolved [48].

A delivery platform (Dome Matrix®) based on hydrophilic matrices which are prepared by "release modules assemblage" technology has been presented by Losi et al. The device is constructed of units having the shape of a disc with one convex and one concave base. For FDDS, two different base-shaped matrices (i.e. "male" and "female" module) are interlocked in "void configuration". The internal void space provides an inherently low density to the dosage form [48, 49]. Strusi et al. evaluated the in vivo performance of a FDDS based on the Dome matrix® technology in humans. The scintigraphy proofed a significantly-prolonged GRT for the floating device compared to the non-floating control system [49].

A single-unit floating delivery device with an inherently low density was developed by Watananbe et al. The system consists of a hollow core (e.g. empty hard gelatin capsule, polystyrene foam, pop rice grain) coated subsequently with two layers: a subcoat of cellulose acetate phthalate and an outer API-containing coating of ethylcellulose/HPMC [50]. FDDS based on highly porous foamed powder, which provides an inherently low density, have been proposed. Tablets were compacted of propylene foamed powder, matrix-forming polymers, API, and optional a filler material [51]. The highly porous foamed powder was also used for the preparation of multiparticulate FDDS [52, 53].

Multiple-unit hollow microspheres (microballoons; size ranging from 1 up to 1000 μm) consisting of enteric polymers, combined optionally with hydrophilic or hydrophobic polymers, and containing the API in the outer polymeric shell were prepared by emulsion solvent diffusion method. Lee et al. introduced a non-volatile oil as core material to optimize the drug release kinetics from the devices [54]. The drug delivery platform has been investigated following oral administration of riboflavin-containing microballoons and non-floating controls to healthy human volunteers. The GI behavior was studied by scintigraphy and by urinary excretion of riboflavin. In the fed state, the floating microspheres were dispersed in the upper part of the stomach and were retained for a prolonged period of time (up to 5 h) compared to the non-floating reference formulation. Based on the in vivo results, the authors concluded that floating microballons are suitable for improving the drug bioavailability and for sustaining the pharmacological action [55].

An alternative technique for the design of multiple-unit FDDS featuring an inherently low density was proposed. The individual units with a size of 4-7 mm consist of a calcium alginate core and a calcium alginate (or calcium alginate/polyvinyl alcohol) membrane with an air compartment between core and outer layer. The authors reported excellent in vitro buoyancy properties of the FDDS. The behavior of the air-compartment multiple-unit GRDDS was also investigated in human subjects. In the fasted state, the floating and non-floating dosage forms did not differ in their gastric emptying time. In contrast, the GI passage time was found to vary under fed conditions: the FDDS were retained in the stomach for a prolonged time period. The findings were supported by the study results of Whitehead et al. In the case of floating calcium alginate beads, the scintigraphic evaluation in humans in the fed state showed extended gastric transit times compared to the non-floating controls [56].

(iii) Effervescent drug delivery systems with flotation due to gas generation and entrapment

The flotation of dosage forms may be achieved by gas generation, upon contact with body fluids, and entrapment of the gas bubbles in a swollen matrix. For example, carbon dioxide is generated by carbonates or bicarbonates reacting with acidic components (i.e. gastric acid, citric or tartaric acid added to the formulation). Effervescent floating devices have been prepared by intermixing carbon-dioxide-producing excipients with matrix components and compacting the mixture into tablets [57].

As they offer the possibility to formulate and optimize the API and the flotation-promoting excipients individually, bilayer and multilayer floating tablets have been proposed. The gas-generating layer contains effervescent substances and, maybe in addition, acidic excipients. Upon contact with the acidic gastric fluids, carbon dioxide is generated and gets entrapped within a gelling hydrocolloid; thus, providing buoyancy to the dosage form. Additionally, capsules that are based on the same flotation mechanism were evaluated. For example, Umezawa et al. patented floating mini-capsules with a diameter in the range of 0.1-2.0 mm. The mini-capsules consisted of a sodium bicarbonate core coated with an inner HPMC layer and an outer pepstatin layer [58].

A balloon-like, multiple-unit dosage form which floated due to carbon dioxide generation was developed and evaluated by Ichikawa et al. The system is constructed of a core-shell structure, i.e. the sustained-release core is coated with two subsequent layers: an inner effervescent (e.g. sodium bicarbonate and tartaric acid) layer and an outer swell able membrane containing polyvinyl acetate and shellac [59].

The applicability of ion-exchange resin beads for the preparation of effervescent FDDS was studied in vitro and in vivo by Atyabi et al. The resin beads are loaded with bicarbonate which, upon exposure to acidic gastric fluids, releases carbon dioxide. The delivery system floats due to entrapment of the gas within a semipermeable membrane that surrounds the resin beads. The scintigraphic evaluation in human volunteers showed a significantly prolonged GRT of the coated resin beads compared to non-coated controls [60, 61].

An alternative approach to provide flotation to dosage forms by gas formation is the use of matrices containing a gas with a boiling point below 37oC (e.g. cyclopentane, diethyl ether). The gas is incorporated in the device in solid or liquid form at ambient temperature. It evaporates at physiological temperature and inflates the dosage form. Several drug delivery systems have been patented using this floating mechanism (**Fig. 4**). Though, the approach is mainly interesting from scientific point of view as the manufacture of the complex devices is expected to be challenging [47].

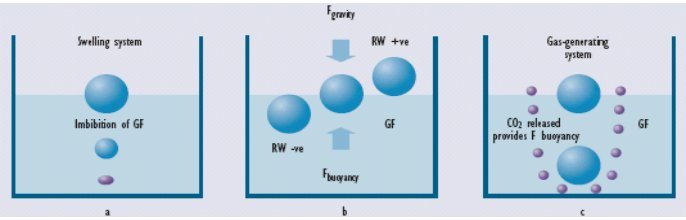

Fig. 4: The mechanism of floating systems

Buoyancy due to gas generation and entrapment is associated with the disadvantage of floating lag times because the gas needs to be produced first. Therefore, the delivery device may undergo a premature stomach emptying before it starts floating on the gastric contents.

g) Raft forming systems

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. Floating Rafts have been used in the treatment of Gastric esophageal reflux disease (GERD). 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. This raft floats on gastric fluids because of low bulk density created by the formation of CO2. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO2 to make the system less dense and float on the gastric fluids . Jorgen et al described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus [15, 16].

h) Combination systems

This kind of system combines different gastro retentive approaches to extend the GRT of drug delivery platforms; thus, is allows to overcome the drawbacks of the individual concepts. It is common to combine the working principles of flotation and bio/mucoadhesion. The joint application of swelling and bio/mucoadhesion for gastro retentive drug delivery was also investigated [62].

The introduction section illustrates that various techniques have been invented to prolong the GI transit time of drug delivery systems. But, the summary reveals that the manufacturability of GRDDS is challenging and some of the gastro retentive approaches cannot be generally considered as “safe” for administration to humans.

Applications of Floating Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability[63, 64].

1. Sustained Release Drug Delivery System 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 e.g. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated *in vivo*.

The formulation compared with commercially available Micard 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) [65].

2. 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, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets[66].

3. Absorption Enhancement 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 e.g. 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%) [67, 68].

4. Enhanced Bioavailability The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non CR-GRDF 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[69].

5. 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 betalac-tam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance[70, 71, 72].

6. Reduced Fluctuation 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[71, 73, 74].

There are some examples of market available product with increased GRT (**Table 1**).

Tab. 1: List of Market available products

S.No.	Brand Name	Drug	Dosage Form including drug delivery system	Polymer Used	Manufacturers
1	Cifran O.D	Ciprofloxacin	Gas-generating floating tablet	Xanthan gum and sodium alginate	Ranbaxy
2	Conviron	Ferrous Sulphate	Gas-generating floating tablet	----	Ranbaxy
3	Liquid Gavison	Mixture of Alginates	Raft-forming liquid alginate preparation	Alginates	GlaxoSmith Kline
4	Madopar HBS	Levodopa and Benserazide	Floating controlled release capsule	HPMC	Roche
5	Oflin OD®	Ofloxacin	Gas-generating floating tablet	Hydroxy propyl cellulose	Ranbaxy, India
6	Topalkan	Al-MG antacid	Floating liquid alginate preparation	----	Pierre farbe drug, France
7	Cytotec®	Misoprostol	Gas-generating floating tablet	----	Pharmacia, US
8	Valrelease	Diazepam	Floating Capsule	-----	Hoffmann La Roche, USA
9	Glumetza	Metformin Hydrochloride	extended release tablet	HPMC	Depomed
10	Almagate flot coat	Al-MG antacid	Floating Antacid Formulation	sodium alginate and aluminum hydroxide	Pierre farbe drug, France

CONCLUSION

The purpose of writing this review was to compile recent literature on pharmaceutical approaches used in enhancing the Gastric Residence Time (GRT). Enhancing the GRT may explore new potentials of stomach as drug-absorbing organ. Several approaches are currently used including Floating Drug Delivery System (FDDS), swelling and expanding system, polymeric bioadhesive systems, modified-shape systems, high density system and other delayed gastric emptying devices. The drugs having absorption window in the upper part of Gastro Intestinal Tract (GIT) have enhanced bioavailability when formulated through these techniques. The recent technological development for enhancing GRT including the physiological and formulation variables affecting gastric retention, patented delivery systems, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. In addition this review also summarizes the Applications of Floating Drug Delivery System.

CONFLICT OF INTERESTS

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ABBREVIATIONS

GRDDS:- Gastroretentive Drug Delivery Systems
GRT:- Gastric Residence Time
CRDDS:- Controlled-Release Drug Delivery Systems
FDDS:- Floating Drug Delivery System
MMC:- Migratingmotor Complex
HBSTM:- Hydrodynamically Balanced System
GERD:- Gastric Esophageal Reflux Disease
CR-GRDF:- Controlled Release Gastroretentive Dosage Forms
HBS:- Hydrodynamically Balance

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