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STOMACH SPECIFIC DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

The purpose of writing this review on gastroretentive drug delivery systems is to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels we have summarized important factors controlling gastric retention. Incorporation of the drug in a controlled release gastroretentive dosage forms which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. High density (sinking), floating, bio- or Mucoadhesive, expandable, magnetic systems. Finally, advantages of gastroretentive drug delivery systems and the evaluation parameter were covered in detail.

Keywords Gastroretentive, Floating, Mucoadhesive, Expandable, etc.

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INTRODUCTION

Drug delivery systems that can precisely control the release rates or targets drugs to a specific body site have had an enormous impact on health care system.^[1]

The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms. Although tremendous advances have been seen in oral controlled drug delivery system during last two decades, this system has been of limited success. This approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.^[2]

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

Hydrophilic polymer matrix system are widely used for designing oral sustained release delivery systems because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance.^[4]

Gastric emptying:

The process of gastric emptying occurs during both fasted state and fed state however, the pattern of motility differs markedly in these two states. In the fasted state, it is characterized by an interdigestive series of electrical events, which

propagate both through stomach as well as small intestine every 2-3 hours. This activity is called as interdigestive myoelectric complex (IMC), and is often divided into four consecutive phases.

Phase I: It is a quiet period lasting from 30-60 min. with rare contractions.

Phase II: It is a period of similar duration consisting of intermittent action potentials gradually increases an intensity and frequency as phase progresses.

Phase III : It is a short period of intense, large regular contractions lasting from 10-20 min. as it serves to sweep undigested materials out of stomach and down in small intestine, it is termed as 'housekeeper waves'. As the phase III of one cycle reaches the distal part of small intestine, the phase III of next cycle begins in duodenum.

Phase IV: It is brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of IMC is delayed. In other words, feeding results in a lag time prior to onset of gastric emptying (Figure-1)^[5].

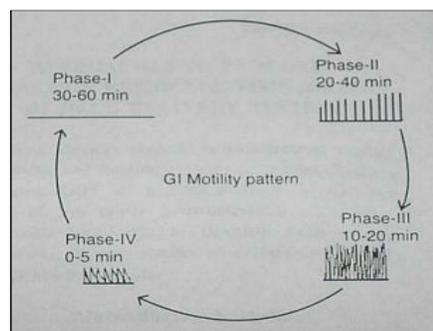


Figure-1: Pictorial representation of the typical GI motility pattern in fasting state.

Factors controlling gastric retention of dosage forms:

The gastric retention time (GRT) of dosage form is controlled by several factors^[6,7,8], that affect their efficacy as a gastroretentive system.

- **Density –**

GRT is a function of dosage form buoyancy that is dependent on the density.

- **Size –**
Dosage form units with a diameter of more than 9.5 mm are reported to have an increased GRT.
 - **Shape of dosage form –**
Tetrahedron and ring-shaped devices with a flexural 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.
 - **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.
 - **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.
 - **Nature 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.
 - **Caloric content –**
GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.
 - **Frequency of feed –**
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.
 - **Gender –**
Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.
 - **Age –**
Elderly people, especially those over 70, have a significantly longer GRT.
 - **Posture –**
GRT can vary between supine and upright ambulatory states of the patient.
 - **Concomitant drug administration–**
Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.
 - **Biological factors –**
Diabetes and Crohn's disease.
- Advantages of gastroretentive drug delivery systems:**
- **Enhanced bioavailability:**
The bioavailability of riboflavin CR-GRDF (Control Release Gastro Retentive Dosage Form) is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.
 - **Sustained drug delivery/reduced frequency of dosing:**
For drugs with relatively short biological half life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency.
 - **Targeted therapy for local ailments in the upper GIT:**
The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine.
 - **Reduced fluctuations of drug concentration:**
Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range

compared to the immediate release dosage forms.

- **Improved selectivity in receptor activation:**

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

- **Reduced counter-activity of the body:**

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity.

- **Extended time over critical (effective) concentration:**

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration.

- **Minimized adverse activity at the colon:**

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon.^[8]

Limitations:

1. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
2. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
3. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
4. Not suitable for drugs that have solubility or stability problem in GIT.
5. Drugs which are irritant to gastric mucosa are also not desirable or suitable.
6. The dosage form should be administered with a full glass of water (200-250 ml).

7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout GIT.^[1]

Potential Drug Candidates for GRDDS:

Atenolol^[9]
 Acyclovir^[9,10]
 Metoprolol^[9]
 Valacyclovir^[9]
 Propranolol HCl^[11]
 Glipizide^[12,13]
 Dipyridamol^[14]
 Ofloxacin^[15]
 Dextromethorphan HBr^[16]
 Ranitidine HCl^[17,18]

Approaches to achieve gastric retention:

1. **High density (sinking) system or non-floating drug delivery system:**
2. **Floating drug delivery systems:**
 - a) Non-effervescent system-
 - i) Colloidal gel barrier system
 - ii) Microporous compartment system
 - iii) Alginate beads
 - iv) Hollow microspheres / Microballons
 - b) Gas-generating (Effervescent) systems-
3. **Expandable systems**
4. **Bio/Muco-adhesive systems**
5. **Magnetic Systems**

1. High density (sinking) system or non- floating drug delivery system:

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm³). Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm³) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on

density than on diameter of the pellets, although many conflicting reports stating otherwise also abound in literature. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm³. However, no successful high density system has made it to the market^[1].

2. Floating drug delivery systems:

a) Non-effervescent system:

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment^[19]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates^[20]. This system can be further divided into the sub-types:

i) Colloidal gel barrier systems:

Sheth and Tossounian first designated this hydrodynamically balanced system^[21]. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact

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with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around its surface^[7].

ii) Microporous compartment system:

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls^[22]. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content^[23]. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

iii) Alginate beads:

Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues^[2]. Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours^[24,25].

Shimpi *et al* formulated a multi unit floating granules of diltiazem hydrochloride using gelucire 43/01^[26]. Patel *et al* were developed and optimized a controlled-release multiunit floating system of a highly water soluble drug, ranitidine HCl, using Compritol, Gelucire50/13, and Gelucire 43/01 as lipid carriers^[27].

iv) Hollow microspheres / Microballons:

Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere^[2]. Microballoons were floatable *in vitro* for 12 hrs, when immersed in aqueous media. Radio graphical studies proved that microballoons orally administered to human were dispersed in the upper part of stomach and retained there for 3 hrs against peristaltic movements^[8]. Kamila *et al* prepared a multiunit floating drug delivery system of rosiglitazone maleate by encapsulating the drug into Eudragit® RS100 through nonaqueous emulsification/solvent evaporation method & is evaluated *in vitro* & *in vivo*^[28].

Hascicek *et al* studied the clindamycin release kinetics from floating delivery systems consisting of two modules assembled in void configuration, according to the modified release technology platform known as Dome Matrix^[29]. Strusi *et al* studied the floating Dome Matrix® modules assembled in void configuration for the administration of drugs that can have a therapeutic advantage from prolonged gastric residence time. The system is strong enough to remain assembled *in vivo* for at least 5 hr^[30].

Chawdhary *et al* had developed and characterized mucoadhesive microcapsules of glipizide employing various mucoadhesive polymers for prolonged gastrointestinal absorption^[11].

Sustained release floating microspheres using polycarbonate were developed by Thanoo *et al*, employing the solvent evaporation technique and aspirin, griseofulvin and p-nitroaniline were used as model drugs^[31].

Kaishima *et al* described hollow microspheres (microballoons) with drug in their outer polymer shells, prepared by a novel emulsion solvent diffusion method^[32].

b) Effervescent (gas generating) systems:

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as

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polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid)^[23]. Tadros MI has developed a gastroretentive controlled-release drug delivery system with swelling, floating, and adhesive properties^[33]. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1^[34]. In this system carbon dioxide is released and causes the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc^[20]. Kumar *et al* formulated the floating matrix tablets of acyclovir using swellable polymers like HPMC K4M, HPMC K15M & sodium alginate with NaHCO₃ as effervescent agent.^[35] Mallikarjune *et al* developed floating tablets of Glipizide employing two different grades of HPMCK4 and HPMC K15 polymers by effervescent technique; these grades of polymers were evaluated for their gel forming properties. Sodium bicarbonate is incorporated as a gas-generating agent^[36]. Bilayer or multilayer system has also been designed^[37,38]. Yadav *et al* has developed a bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach using propranolol hydrochloride as a model drug^[39]. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers.

Ray *et al* has formulated gastric floating tablets of tramadol hydrochloride^[40].

Khemariya *et al* formulated floating tablets of ranitidine, combination of sodium bicarbonate (70mg) and citric acid (15mg) is found to achieve optimum in vitro buoyancy. The tablets with methocel K100 were found to float for longer duration of time as compared to formulations containing methocel K15M^[41].

Meka *et al* had developed a gastro retentive floating drug delivery system with multiple-unit minitabs based on gas formation technique in order to prolong the gastric residence time and to increase the overall bioavailability of the drug (Captopril)^[42].

Following is the table of patents on FDDS for different drugs^[43]:

Sr. No.	Type of formulation	Patent no
1	Gastro retentive dosage form	U.S-7,413,752
2	Multiple unit floating dosage form	European patent (EP) 10697
3	Bilayer tablet	EP-002445
4	Floating Tablet	U.S-66,352279
5	Microspheres	U.S-6207197
6	3-layer table	U.S-5780057
7	Foams (or) hollow bodies	U.S-5626876
8	Floating Tablet	U.S-5169639
9	Granule	U.S-4844905
10	Floating capsules	U.S-4814178,-79
11	Tiny pills	U.S-4434153
12	Floating capsule	U.S-4126672
13	Floating device	U.S-4055178
14	Empty globular shells	U.S-3976164

Table 1: Patents on FDDS

3. Expandable systems:

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT)^[8]:

- 1) a small configuration for oral intake,
- 2) an expanded gastroretentive form, and
- 3) a final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high

rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Jamzad *et al* developed a matrix monolithic tablet of glipizide using different swellable polymers^[44].

4. Bio/Muco-adhesive systems:

Bioadhesive drug delivery systems (BDDS) are used to localise a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Sanap had formulated the gastroretentive mucoadhesive beads of Glipizide using different polymers like sodium alginates, carbapol 974P and sodium carboxy methyl cellulose^[45]. Gastric mucoadhesion

does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seems to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin. Some investigators have tried out a synergistic approach between floating and bioadhesion systems. Other approaches reported include use of a novel adhesive material derived from the *fimbriae* (especially Type 1) of bacteria or synthetic analogues combined with a drug to provide for attachment to the gut, thereby prolonging the transit time, a composition comprising an active ingredient and a material that acts as a viscogenic agent (for example curdlan and/or a low-substituted hydroxypropylcellulose), etc.

Patel *et al* had formulated floating-bioadhesive tablets to lengthen the stay of glipizide in its absorption area. Effervescent tablets were made using chitosan (CH), hydroxypropyl methylcellulose (HPMC), carbopol P934 (CP), polymethacrylic acid (PMA), citric acid, and sodium bicarbonate. Tablets with 5% effervescent base had longer lag time than 10%^[46].

Madgulkar *et al* were formulated the trilayer gastric mucoadhesive tablets of poorly insoluble drug Itraconazole with the middle drug releasing layer sandwiched between upper and lower mucoadhesive layers^[47].

Shishoo *et al* had formulated an oral multi-particulate formulation with site specific sustained delivery of rifampicin. The oral gastroretentive rifampicin formulation consisted of rifampicin pellets for immediate release as the loading dose and a bio/mucoadhesive rifampicin tablet for extended release^[48].

5. Magnetic Systems:

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about 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^[49].

Gastric Retention Technologies:

There are a few companies that have focused efforts on the design of gastric retention technologies. DepoMed, Inc. has developed technology that consists of a swellable tablet. DepoMed is also working with Elan Corporation and is considering licensing its technology. Alza Corporation has developed a Gastroretentive platform for the OROS[®] system, which showed prolonged gastric residence time in a dog model as the product remained in the canine stomach at 12 hours post dose and is frequently present at 24 hours. Pfizer Pharmaceuticals has patents for gastric retention technology that uses extendable arms, but has no product. Merck & Co., Inc., has patents describing technologies using various unfolding shapes to encourage gastric retention. Madopar[®] is an HBS floating system not available in the US, and contains 200mg levodopa and 50mg benserazide. Kos Pharmaceuticals, Inc., technology is based on superporous, superabsorbent hydrogels. Superporous hydrogels contain densely concentrated small pores that produce capillary channels that absorb water quickly. This rapid absorption results in dramatic swelling that is much faster than a conventional hydrogel^[50].

EVALUATION OF GRDDS:

Floating systems:

1) Floating/buoyancy 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. These parameters can be measured as a part of the dissolution test^[52].

2) Floating Time:

Test for buoyancy 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 floating time^[52].

3) Specific gravity:

The specific gravity of floating systems can be determined by the displacement method, using benzene as a displacing medium^[52].

4) Resultant weight:

An in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid.^[53] This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F_{buoy}) and gravity (F_{grav}) forces acting on the object as shown in the equation:

$$F = F_{\text{buoy}} - F_{\text{grav}}$$

$$F = d_f gV - d_s gV = (d_f - d_s) gV$$

$$F = (d_f - M / V) gV$$

in which F is the total vertical force (resultant weight of the object), g is acceleration due to gravity, d_f is the fluid density, d_s is the object density, M is the object mass, and V is the volume of the object. By convention, a positive resultant weight signifies that the force F is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force F acts downward and that the object sinks^[2].

Bio/mucoadhesion systems:

1) Mucoadhesive strength and mucoadhesion time:

These are measured by modified balance method. Briefly, a balance is taken and its left pan is replaced with a weight to the bottom of which a tablet is attached. Both sides are balanced with weight. Porcine gastric mucosa having a thick layer of mucus is fixed to a rubber cork, which is already attached to the bottom of the beaker containing corresponding medium with a level slightly above the mucosa. The weight, which is attached to the tablet, is brought into contact with the porcine mucosa & is kept undisturbed for 5 minutes and then the pan is raised. Weights are continuously added on the right side pan in small increments and the weight at which the tablet detached from the mucosa is recorded as the mucoadhesive strength. For measuring mucoadhesion time a 10-gram weight is put on right side pan after raising it and the detachment time is noted. The time period throughout which the tablet remained attached to the mucosa is mucoadhesion time^[51].

2) Swelling index:

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^[52].

$$\text{Water uptake} = WU = (W_t - W_o) \times 100 / W_o$$

Where,

W_t = weight of dosage form

at time t

W_o = initial weight of dosage

form

Dissolution/drug release:

Standard USP or IP dissolution apparatus have been used to study in vitro release profile using both basket and rotating paddle.

In vitro release rate study of mucoadhesive tablet is carried out using the Apparatus 2 (Paddle apparatus) method. Place the tablet in a dry basket at the beginning of each test. Lower the paddle

before rotation operates the apparatus immediately at 50 rpm. Medium used for release rate study is 900ml 0.1 N HCl during the course of study whole assembly is maintained at 37 ± 0.5 °C. Withdraw a sample at specific time interval and replaced with equal amount of fresh dissolution medium.

The withdrawn samples are diluted with dissolution medium and then filtered with whattman filter paper and assayed^[53].

Gastroretention:

1) GI Transit using Radio-Opaque Tablets:

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in mucoadhesive tablets to determine the effects of mucoadhesive polymers on GI transit time. Feces collection (using an automated feces collection machine) and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesives labeled with Cr-51, Tc-99m, In-113m, or I-123 has been used to study the transit of the tablets in the GI tract^[54].

2) Gamma Scintigraphy Technique:

Distribution and retention time of the mucoadhesive tablets can be studied using the gamma scintigraphy technique. A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium-labeled HYAFF tablets. Dimensions of the stomach part of the sheep can be outlined and imaged using labeled gellan gum, and the data collected are subsequently used to compare the distribution of radiolabeled HYAFF formulations. The retention of mucoadhesive-radiolabeled tablets based on HYAFF polymer is found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to stomach epithelium. The combination of the sheep model and the gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomach mucoadhesive tablets^[54].

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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^[52].

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^[52].

5) Ultrasonography:

Used sometimes, not used generally because it is not traceable at intestine^[52].

6) ¹³C Octanoic Acid Breath Test:

¹³C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO₂ gas which comes out in breath. The important Carbon atom which will come in CO₂ is replaced with ¹³C isotope. So time up to which ¹³CO₂ 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 CO₂ release. So this method is cheaper than other^[52].

Conclusion:

GRDDS, comprised mainly of floating, bioadhesive, and swellable systems, have emerged as an efficient means of enhancing the bioavailability and controlled delivery of drugs that exhibit an absorption window. Gastroretentive dosage forms provide an additional advantage for drugs that are absorbed primarily in the upper segments of gastrointestinal tract, i.e., stomach, duodenum and jejunum. Designing GRDDS requires a thorough understanding of the physicochemical properties of the drug, the physiological events of the GIT, and formulation strategies. A careful consideration of the interplay of these parameters can help in

designing a successful GRDDS. Growth in the understanding of the effect of GI physiology on drug delivery and the increasing sophistication of delivery technology will ensure the development of

an increasing number of GRDDS to optimize delivery of drug molecules that exhibit regional variability in intestinal absorption.

Name	Type and drug	Remarks	References
MadoparHBS (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules	55
Valrelease	Floating capsule, Diazepam	Floating Capsules	56
Amalgate Float Coat	Floating antacid Floating gel	Floating dosage form	57
Topalkan	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation	58
Convion	Ferrous sulphate	Colloidal gel forming FDDS	58
Cifran OD	Ciprofloxacin	Gas generating floating form	58
Cytotech	Misoprostol	Bilayer floating capsule	59
Liquid Gaviscon	Mixture of alginate	Suppress gastro esophageal reflux and alleviate the heart burn	59

Table 2: Commercial stomach specific floating formulations.

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