Gastroretentive Floating and Mucoadhesive Drug Delivery Systems- Insights and Current Applications

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Abstract: *Gastro retentive drug delivery system (GRDDS) is one of the novel approaches in the area of oral sustained release dosage forms. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation require frequent dosing to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained release GRDDS is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would-be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT. The present review highlights the features of GRDDS specifically from a practical and industrial viewpoint.*
Keywords: *Bioadhesive, floating drug delivery, gastroretentive, mucoadhesive, polymeric nanoparticles*

I.   Introduction

Poor absorption of many drugs in the lower GIT necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and upper small intestine. These drug delivery systems suffer from mainly two diversities: the short gastric retention time(GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine)leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolonged gastric residence time by the drug delivery. [1]

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bioadhesive system, swelling system and expanding system and floating system. Unfortunately floating devices administered in a single unit form Hydrodynamically balanced system (HBS) are unreliable in prolonging the GRT owing to their 'all- or- nothing' emptying process and, thus they may causes high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract. [2, 3]

Certain types of drugs can benefit from using gastric retentive devices. These include:
- Acting locally in the stomach.
- Primarily absorbed in the stomach.
- Poorly soluble at an alkaline pH.
- Narrow window of absorption.
- Absorbed rapidly from the GI tract.
- Degrade in the colon.
- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounters at the   lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal Small intestine to treat   certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.

II.   Different Techniques Of Gastric Retention [4]

Various techniques were used to encourage gastric retention of an oral dosage form are retention mentioned below: See Fig. 1.

A. Floating/Low Density delivery systems   B. Bioadhesive or mucoadhesive systems
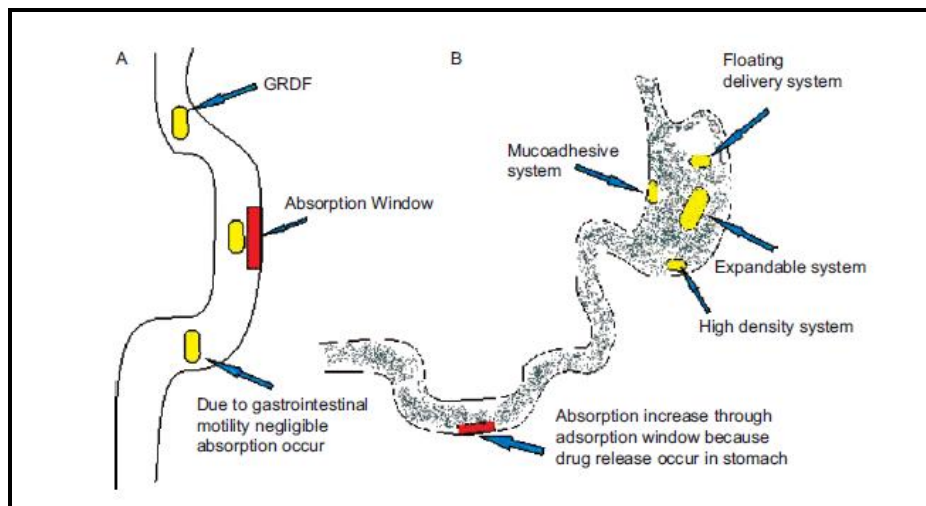C. Expandable systems   D. High density systems

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Fig. 1: Approaches to Gastro Retention [5]

2.1 Floating/Low Density delivery systems

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically 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 the gastric contents. [6, 7] Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropyl methylcelluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy. [8, 9]

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric 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 GI 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 meal 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. [10]

2.1.1 Effervescent systems

These buoyant systems utilized matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion exchange resin technology, etc. [11]

2.1.2 Non Effervescent systems

These systems incorporate one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethylcellulose, hydroxypropylcellulose, HPMC, and sodium carboxymethylcellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into the dosage forms. The drug is thoroughly mixed with gel-forming hydrocolloid, which swells in contact with gastric fluid and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the

exterior surface of the dosage form dissolves, the integrity of gel layer is maintained by the hydration of adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage forms. Non effervescent systems are commonly formulated as hollow microspheres, alginate beads, porous systems and hydrodynamically balanced system. [12]

2.1.2.1 Hollow microspheres

Multiparticulates such as hollow microspheres have been widely exploited in the avenue of gastroretention. Several research endeavours have been carried out globally on these potential systems. Recently, **Rane** *et al*[51] prepared hollow microspheres of rosiglitazone maleate by O/W emulsionsolvent diffusion technique using biodegradable anionic acrylic resin as a polymer. Eudragit S100 based formulation demonstrated favourable *in vitro* floating and sustained release profile for longer period of time.

2.1.2.2 Alginate beads

Alginates have gained importance primarily due to their high biocompatibility and non-toxic nature in oral administration. They also exhibit a protective effect on the mucous membranes of the upper GIT. These significant advantages have prompted researchers to investigate alginates mediated floating dosage forms. [13]

2.1.2.3 Porous systems

Porous materials are emerging as a new category of host/guest systems. Various types of pores allow them to adsorb drugs and release them in a more reproducible and predictable manner. Low density porous carriers such as porous adsorbents include silica, calcium silicate, magnesium aluminometa silicate, porous ceramic, propylene foam powder, zeolites, activated carbon, silicon dioxide, ceramics, calcium carbonate, iron oxides, titanium dioxide, bauxite and zirconium oxide have achieved popularity in the development of FDDS. [14] These materials in porous dosage forms allow the inclusion of drugs inside a porous compartment that possess a relatively lower density than the gastric juice and remain buoyant in the stomach.

When porous systems are brought into contact with intestinal fluid, drug release must be preceded by the drug dissolution in the water filled pores or from surface and by diffusion through the water filled channels. Because of the great surface area drug solubility is strongly improved in the GI-fluid. Adsorption and entrapment of drug molecules in porous systems can also lead to enhanced physicochemical drug stability. Due to small pore sizes the formation of crystalline material is restricted by the confined space of the pores, thus retaining the drug in its amorphous form guaranteeing in most cases higher dissolution rates than the crystalline form. In addition, the presence of hydroxyl groups forming inter- and intra-molecular hydrogen bonds were identified as a factor for enhancing dissolution. [15]

TABLE 1: Drugs Reported to be used in the Formulation of Floating Dosage Forms

Floating Dosage Forms	Effervescent systems	Non Effervescent systems
Floating Microspheres	Itopride hydrochloride, pamabrom and carbimazole, diltiazem hydrochloride	Rifampicin, glipizide, rosiglitazone maleate, indomethacin, 5-fluorouracil, ranitidine hydrochloride, piroxicam
Floating beads	Metronidazole, 5-fluorouracil, riboflavin	Famotidine, pantoprazole, metronidazole
Floating Tablets	Propranolol hydrochloride, norfloxacin, acyclovir, ciprofloxacin, zinc acetate dihydrate, nimodipine, silymarin, theophylline, verapamil hydrochloride, metoclopramide hydrochloride	Verapamil hydrochloride, captopril, nimodipine, theophylline
Floating pellets	Ofloxacin, tetracycline hydrochloride and theophylline, riboflavin	Metronidazole, lansoprazole
Floating Capsules	Nicardipine hydrochloride, verapamil	Ofloxacin, propranolol hydrochloride, L-dopa and benserazide

2.1.3 Role of Polymers in Floating drug delivery

The currently available polymer-mediated noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper segments of GI tract, i.e., the stomach, duodenum and jejunum. Some of the unresolved, critical issues related to the rational development of FDDS include (1) the quantitative efficiency of FDDSs in the fasted and fed states; (2) the role of buoyancy in enhancing GRT of FDDS; and (3) the correlation between prolonged GRT and SR/PK characteristics. [16]

TABLE 2: Polymers used for the development of Floating Drug Delivery

Delivery system	Polymer Type	
	Cellulosic hydrocolloids	Gel-forming hydrocolloids and matrix former
Microspheres/ Microparticles	Ethyl cellulose	Eudragit, Polycarbonate, Polyacrylate, Polymethacrylate, Polystyrene, Chitosan, Gelatin, Alginate, Gelucir
Tablets	HPMC, HPC, HEC, MC, NaCMC	Carbopol, Carrageenan, Gum guar, Gum Arabic, Sodium alginate, Polyethylene oxide, Polyvinyl lactam, Polyarcylates,, Polyvinyl acetate
Capsules	HPMC, HPC, HEC, NaCMC	Sodium alginate, Carbopol, Agar

2.2 Bioadhesive or mucoadhesive systems

This approach involves the use of bioadhesive or mucoadhesive polymers, which can adhere to the epithelial surface in the stomach as shown in Fig. 2. [17] The original concept of bioadhesive polymers as platforms for oral controlled drug delivery was to use these polymers to control and to prolong the GI transit of oral controlled delivery systems for all kinds of drugs. Whereas bioadhesion has found interesting applications for other routes of administration (buccal, nasal, rectal and vaginal), it now seems that the controlling approach of GI transit has been abandoned before having shown any significant clinical outcome. [18] According to in vivo results obtained in animals and in humans, it does not seem that mucoadhesive polymers are able to control and slow down significantly the GI transit of solid delivery systems. Attention should be paid to possible occurrence of local ulcerous side effects due to the intimate contact of the system with mucosa for prolonged periods of time. 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 seem to limit the potential of mucoadhesion as a gastroretentive force. [19, 20]
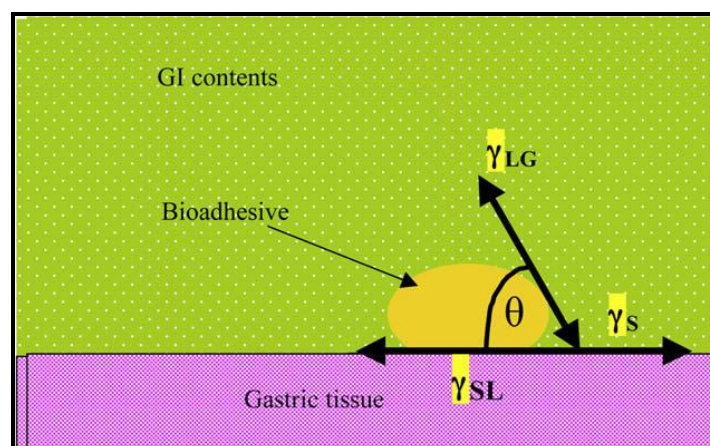

Fig. 2: The interfacial forces involved in polymer spreading, where Ɵ is angle of contact, γ_{LG} is liquid–gas surface tension, γ_{SL} is solid–liquid surface tension, γ_{SG} is solid–gas surface tension.

2.2.1 Bioadhesive/Mucoadhesive polymeric systems

Most orally administered particles are not retained and undergo direct transit through the GI tract. Mucoadhesion has been commonly employed in attempting to improve the residence time of particles in the GI tract. Non-specific mucoadhesion of micro or nanoparticles in the GI tract is a well-known phenomenon; in 1962, Florey observed in cats that particles of India ink become coated with intestinal mucus such that they do not come into contact with the intestinal epithelium. [21, 22] Consequently, mucoadhesive micro or nanoparticles could have limitations for oral delivery, including the possibility of adhering nonspecifically to unintended surfaces. It is likely that rather than reaching the more slowly cleared firmly adherent mucus layer, mucoadhesive nanoparticles will become trapped in the loosely adherent mucus layer and become vulnerable to rapid clearance. Significant work has been undertaken in attempt to overcome these limitations in vivo, including the use of specialized polymeric, pH-responsive, and lipid-based formulations.

2.2.1.1 Polymers Used for Mucoadhesive Nanoparticles

The properties of the mucoadhesive nanoparticles, e.g. their surface characteristics, force of bioadhesion, release pattern of the drug, and clearance, are influenced by the type of polymers used to prepare them[60]. Suitable polymers that can be used to form mucoadhesive nanoparticles include soluble and insoluble, nonbiodegradable and biodegradable polymers. These can be hydrogels or thermoplastics, homopolymers, copolymers or blends, natural or synthetic polymers.

Characteristics of an ideal mucoadhesive polymer: [23]
  i.   The polymer and its degradation products should be nontoxic and should be no absorbable from the GI tract.
 ii.   It should be nonirritant to the mucus membrane.
iii.   It should preferably form a strong no covalent bond with the mucin-epithelial cell surfaces.
 iv.   It should adhere quickly to most tissue and should possess some site specificity.
  v.   It should allow easy incorporation of the drug and should offer no hindrance to its release.
 vi.   The polymers must not decompose on storage or during the shelf life of the dosage form.
vii.   The cost of polymer should not be high so that the prepared dosage form remains competitive.
The examples of some mucoadhesive polymers are given in TABLE 3

TABLE 3: Some Mucoadhesive Polymers

Natural	Synthetic	Biocompatible	Biodegradable
Sodium alginate	Polyvinyl alcohol, Polyamides, Polycarbonates, Polyalkylene glycols, Polyvinyl ethers,	Esters of haluronic acid,	Polulactides,
Pectin	Esters and halides, polymethacrylic acid, Polymethylmethacrylic acid,	Polyvinyl acetate,	Ployglycolides,
Tragacanth	Methyl cellulose, ethyl cellulose, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose,	Ethylene glycol	Poly(lactide-co-glycolides), Polycaprolactones,
Gelatin	Sodium carboxymethylcellulose	-	Polyalkyl cyanoacrylates, Polyorthoesters, Polyphosphoesters, Polyanhydrides,
Carageenan	-	-	Polyphosphazenes, Chitosan, Poly ethylene oxide

Robinson and his group using the fluorescence technique concluded that:
  i.   Cationic and anionic polymers bind more effectively than neutral polymers.
 ii.   Polyanions are better than polycations in terms of binding/potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.
iii.   Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
 iv.   Degree of binding is proportional to the charge density on the polymer.
  v.   Highly binding polymers include carboxy methyl cellulose, gelatine, hyaluronic acid, carbopol, and polycarbophyl.

Molecular characteristics:
    Investigations into polymers with various molecular characteristics have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion. The properties exhibited by a good mucoadhesive may be summarized as follows:
  i.   Strong hydrogen-bonding groups [-OH, -COOH]
 ii.   Strong anionic charges
iii.   Sufficient flexibility to penetrate the mucus network or tissue crevices
 iv.   Surface tension characteristics suitable for wetting mucus/mucosal tissue surface
  v.   High molecular weight

2.2.2   Evaluation of mucoadhesion
2.2.2.1 *In vitro* techniques
        The best approach to evaluate mucoadhesive microspheres is to evaluate the effectiveness of the mucoadhesive polymer to prolong the residence time of drug at the site of absorption, there by increasing absorption and bioavailability of the drug. The quantification of the mucoadhesive forces between polymeric microspheres and the mucosal tissue is a useful indicator for evaluating the mucoadhesive strength of microspheres. *In vitro* techniques have been used to test the polymeric microspheres against a variety of synthetic and biological tissue samples, such as synthetic and natural mucus, frozen and freshly excised tissue, etc. [24] The different *in vitro* methods include the following.

i. Tensile stress measurement using Wilhelmy plate technique:
        The Wilhelmy plate technique is traditionally used for the measurement of dynamic contact angles and involves the use of a microtensiometer or a microbalance. The CAHN dynamic contact angle analyzer (model DCA 322, CAHN instruments, Cerritos) has been modified to perform adhesive microforce measurements. By using the CAHN software system, three essential mucoadhesive parameters can be analyzed. These include the fracture strength, deformation to failure, and work of adhesion. [25]

ii. Novel electromagnetic force transducer:

The electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer mamoparticle/microsphere from a tissue sample. It has the unique ability to record remotely and simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the mucoadhesive force. The primary advantage of the EMFT is that no physical attachment is required between the force transducer and the particle. This makes it possible to perform accurate mucoadhesive measurements on the small nanoparticles/microspheres, which have been implanted *in vivo* and then excised (along with the host tissue) for measurement. This technique can also be used to evaluate the bioadhesion of polymers to specific cell types and hence can be used to develop BDDS to target-specific tissues.

iii. Shear stress measurement:

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. Adhesion tests based on the shear stress measurement involve two glass slides coated with a polymer and a film of mucus. Mucus forms a thin film between the two polymer-coated slides, and the test measures the force required to separate the two surfaces. [26]

Mikos and Peppas designed the *in vitro* method of the flow chamber. The flow chamber made of plexiglass is surrounded by a water jacket to maintain a constant temperature. A polymeric nanoparticles/microsphere placed on the surface of a layer of natural mucus is placed in a chamber. A simulated physiologic flow of fluid is introduced in the chamber and movement of nanoparticles/microsphere is monitored using video equipment attached to a goniometer, which also monitors the static and dynamic behavior of the nanoparticles/microparticle.

iv. Miscellaneous methods:

Other techniques for evaluation of mucoadhesive strength include adhesion number, *in vitro* wash-off test for microspheres, falling liquid film method, [27] everted sac technique, [28] novel rheological approach [29] and flow - through approach. [30]

2.2.2.2 *In vivo* techniques (Measurement of the residence time)

Measurements of the residence time of mucoadhesives at the application site provide quantitative information on their mucoadhesive properties. The GI transit times of many mucoadhesive preparations have been examined using radioisotopes and the fluorescent labeling techniques.

i. GI Transit using radio-opaque nanoparticles/microspheres:

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in mucoadhesive nanoparticles/microspheres 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 have been used to study the transit of the nanoparticles/microspheres in the GI tract.[31]

ii. Gamma scintigraphy technique:

Distribution and retention time of the mucoadhesive nanoparticles/microspheres 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 microspheres. 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 microspheres based on HYAFF polymer was 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 nanoparticles/microspheres. [32]

III. Grdds- The Industrial Perspective

Pharmacotherapy of various disease states can be amended by drug repurposing through GRDDS. Assessment of the effect of the fed and fasted condition on product performance should be necessary during initial development phases. Dual working technology would be a possible way to overcome drawbacks associated with different GRDDS. Before development of a drug product, the principles of scale up and process validation must be considered to improve the quality and market availability of GRDDS. Knowledge of all

regulatory aspects will help to deliver a product to the market within a reasonable timeframe and in a cost-effective manner. [33]

Varieties of investigations have been done that lead to development of various GRDDS. However, only few can make way to market. These technologies show excellent in vitro results but fail to give desirable in vivo performance. Mucoadhesive and floating technologies are getting substantial attention and most of the drug products available in the market are based on the principle of these technologies. In consequence, dual working systems based on mucoadhesive and floating principles have more potential to increase industrial implementation of GRDDS and can improve the in vivo performance of the active moiety. Furthermore, combination of mucoadhesion technology with floating technology can ameliorate loopholes associated with floating technology like floating lag time. In future, some more gastroretentive technologies can be combined to improve the gastric retention and to reduce the associated drawbacks[GIP]. Thus, market appearance of GRDDS can be improved by opting an appropriate drug and delivery system with incorporating all the relevant quality attributes. TABLE 4 below gives an overview of technologies adopted by pharmaceutical companies to formulate GRDDS.

TABLE 4: Technologies adopted for GRDDS

Technology	Company	Product	Active pharmaceutical ingredient
Bioadhesive tablets	Lupin, India	Xifaxan	Rifaximin
Effervescent floating system Colloidal gel forming floating system Gas-generating floating system	Ranbaxy, India	Zanocin OD Conviron Cifran OD	Ofloxacin Ferrous sulphate Ciprofloxacin
Foam-based floating system Effervescent and swelling-based floating system	Sato Pharma, Japan	Inon Ace Tablets Prazopress XL	Sime´thicone Prazosin hydrochloride
Coated multi-layer floating and swelling system	Sun Pharma, India	Baclofen GRS	Baclofen
Polymer-based swelling technology: AcuForm_	Depomed, Inc., USA	Gabapentin GR	Gabapentin
Floating liquid alginate preparation	Pierre Fabre Medicament, France	Topalkan	Aluminium magnesium antacid
Erodible matrix-based system	Bayer, USA	Cipro XR	Ciprofloxacin hydrochloride and betaine
Floating capsule Floating, CR capsule	Roche, UK	Valrelease Madopar	Diazepam Levodopa and benserazide
Expandable film filled in capsule	Intec Pharma	Accordion Pill TM	-
Gastroretention with osmotic system	GlaxoSmithKline	Coreg CR	Carvedilol
Bilayer floating capsule	Pharmacia Ltd., UK	Cytotec	Misoprostol (100/200 μg)

IV. Conclusion

he present review showcases the salient features particularly attributed to floating and Mucoadhesive type of gastro retentive drug delivery systems with emphasis on the novel delivery systems employing polymers, characterization methods and suitable examples. Despite the numerous advantages offered by these delivery systems, a thorough insight and understanding of the factors influencing the fate of the drug *in vivo* needs to be explored.

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