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An Insight on the Strategical Approach of Gastro-retentive Drug Delivery System

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ABSTRACT

Gastro-intestinal tract (GIT) is one of the major parts of the body, which helps in the absorptionof the drugs, based on the pKa value drug gets absorbed in the different part of GIT tract. Drugswith the acidic pH is in its un ionizable form and readily gets absorbed in the stomach. The main aim of this article is to understand the different novel strategical approach used to improvethe retention time of the drug in the stomach and enhance the absorption of the drug into the systemic circulation. The strategies in GRDDS are Effervescent system, floatation system, highdensity system, magnetic system, ion exchange system, swellable system. The article also focus on the Physiology of Stomach

Conclusion: *This article investigate, complies and present the recent and past literatures whichfocus on the suitable drug candidates for GRDDS, merits, demerits, challenges, Novel GRDDS strategies, applications, marketed GRDDS formulation, patents on GRDDS formulation*

Keyword: *Gastro-retention drug delivery system, Patents, Physiology of Stomach, Strategies in GRDDS, Drug candidates for GRDDS.*

INTRODUCTION (74)

The oral route for the delivery of the medication is considered as one of the oldest and most convenient method. With the new innovations and novelty in this method has made it possible to deliver the medication in a more sustained and controlled manner. GRDDS is the desirable approach for the optimized therapeutic benefit for a drug with narrow absorption window. Drugs get absorbed within the initial parts of Gastro intestinal tract and protect them from getting degraded in the presence of intestinal pH. An increased gastro-retentive enhances the bioavailability, solubility of the BCS class II drugs. To create an effective GRDDS several strategies are used such as high density, low density.

A wide range of drug candidates can benefit from GRDDS in various ways (69, 70, 71)

1) Drugs which act on the stomach cells for the local and the better action such as misoprostol, H2 blockers in order to reduce the gastric secretion
2) Drugs which are readily get absorbed in the acidic pH in an un ionizable form
3) Drugs with limited oral Bioavailability such as dipyridamole (pH- 6.4) and others, whose solubility reduces at the alkaline pH
4) Drugs that exhibit the absorption window either follow active transport mechanism or pH dependent solubility for absorption
5) Drugs having high affinity in the stomach area but has the less gastric retention time and limited absorption

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6) Drugs with high plasma fluctuations such as ciprofloxacin, clarithromycin
7) Drugs with low solubility in the alkaline pH such as ofloxacin, cinnarizine
8) Drugs degrade in colon
9) For the drugs with shorter half-life, dosing frequency can be reduced for a better patient compliance
10) Control and prolong release of the medicament from the dosage form can be achieved
11) Maintaining concentrations consistently above the minimal inhibitory concentration, mainly for the antibiotics, like b-lactams and tetracyclines, to reduce the development of antibiotic resistance (Gupta et al., 2002) *30*
12) Effective for spatial and temporal distribution of API with a narrow absorption window at a predetermined location and at a predetermined time. (Chine, 1990; Kawatra et al., 2012) *31*,*32*
13) Establishing flip-flop pharmacokinetics, particularly for medications with a short half-life, providing control over the kinetics of drug disposition, minimizing negative effects
14) Overcomes GET and GRT physiological constraints without harming normal physiology

Limitations of GRDDS

A. The drug which easily gets degraded in the stomach or the acidic medium are not a suitable candidate for the GRDDS
B. Drugs which have a gastric irritation are not suitable for this kind of system e.g.- NSAID's
C. Drugs having a high affinity to colon and has a better absorption in colon are not suitable candidates for GRDDS
D. The drugs which have limited stability in the acidic pH cannot be used for the GRDDS formulation

Physiology of GRDDS (75)

Stomach plays a very important role in the GRDDS system as the main aim is to enhance the gastric retentive time period of formulation and its very crucial to understand the stomach physiology and anatomy.

The stomach is split into 2 parts anatomically, the first part is the proximal stomach- fundus, body part and other; distal stomach –pylorus and antrum. Major mechanism of stomach is temporarily storage and grinding of the food and pass it to duodenum. Proximal stomach act as the reservoir for undigested and the distal stomach act as pump to help in the gastric emptying process, the gastric emptying rate in the fed state is different from fasted state.

In case of fasted state, in every 120 min, electrical events of myloelectric cycle runs in a cyclic manner through the stomach and the small intestine. During this phase the diameter of the pylorus increases up to 19mm and particle smaller than that of the 19mm can easily exit from pylorus and enter into duodenum.

However, there is a completely different process in the fed state, the activity is generated at 5-10 min after the ingestion of the meal and is a continuous process until the food remain in stomach, which increases gastric retention time. This cycle is considered as the migrating myloelectric cycle or interdigestive myloelectric cycle.

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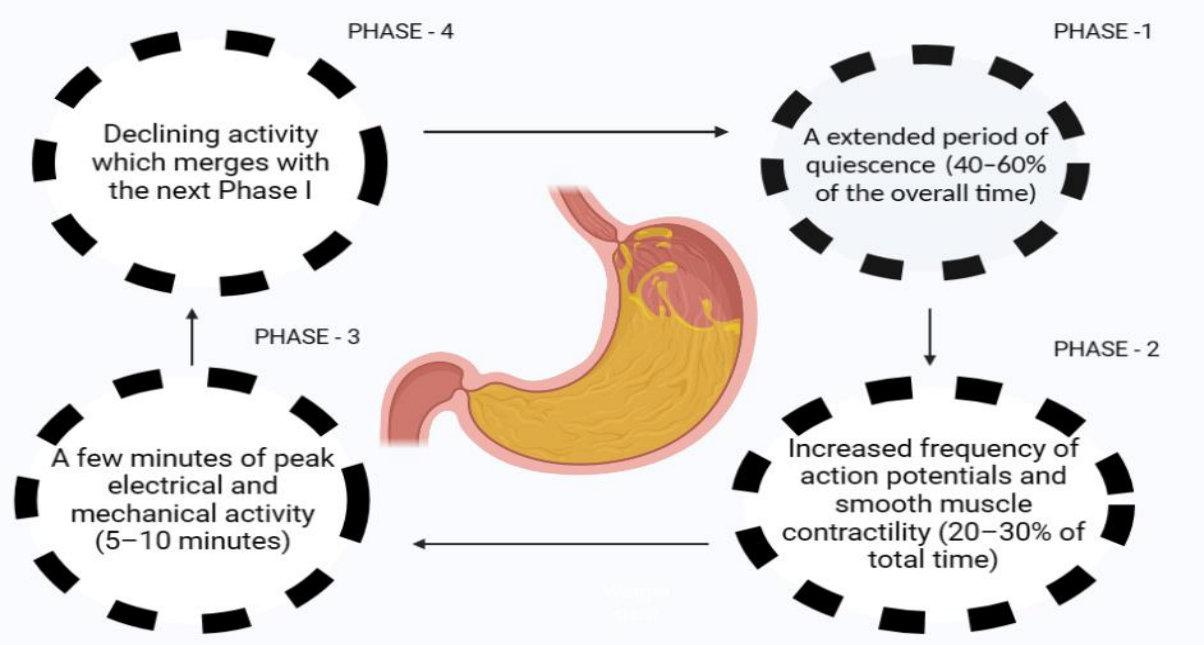

Factors affecting GRDDS efficacy (68)

1) Density- Incase of floating tablet the density has to be below 1.004g/ml. whereas, for high density it should be around 2.00g/ml
2) Size of dosage form- the dosage form with the diameter of higher than 7.5mm has increased gastric resident time
3) Dosage form shape – Tetrahedron shape stays in stomach region for a longer period of time with increased gastro-resident, when compare to the other shape.
4) Unfed and fed state- In unfed/fasting state the migrating myloelectric cycle is faster when compare to the fed state
5) Calories present – higher the protein or fats, higher gastric resident time
6) Frequency of ingestion of food- higher the frequency of feed, higher is the gastric resident time
7) Age – Elderly or aged people has high GRT (4.6 ±1.2 hours), when compare to the Young and the adult people (3.4±0.6 hours)
8) Type of food- food with indigestible fatty acid, polymers can alter the GRT
9) Pathological factors – Crohn's disease or Diabetes can also alter the GRT

Challenges in the GRDDS formulation (36,38)

One of the main challenges in GRDDS is to maintain the drug inside the stomach for a longer time period by maintaining the predetermined drug release. The gastric emptying time is varied from patient to patient and a lot more factor also has an influence on the drug release and the stay of dosage form in the stomach. *36* Drugs with solubility problems in the gastric juice cannot be formulated in the GRRDS Formulation. The position of the body also has a major impact on the formulation. Especially in case of the Floating drug delivery system and amount of the gastric fluid present in the stomach makes an important impact on the formulation success. In case of mucoadhesive formulation, if there is an increased mucus secretion then the formulation can be a failure. Patients with achlorhydria the formulation can be a complete failure because of the fast gastric emptying rate when compare to normal. Whereas, when we look into the unfolding type the problem arise if the unfolding of the formulation from the carrier is not a success or the ability of the formulation to regains its

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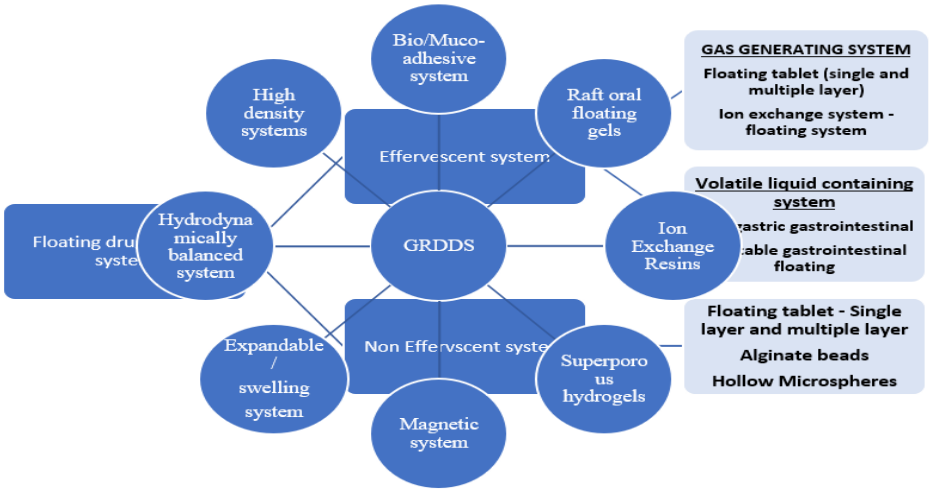
original form fails. Super porous hydrogel can face stability problems due to the highly unstable polymers. Mucoadhesive system can bind to the oesophagus as they have the ability to bind to mucin which leads to choking and can be of threat if there is a major incident. *38* Some of the factors which affects GRDDS are food intake, gender, calorie content, stage of life, type of food also has an effect on the gastro retention of the formulation **36**

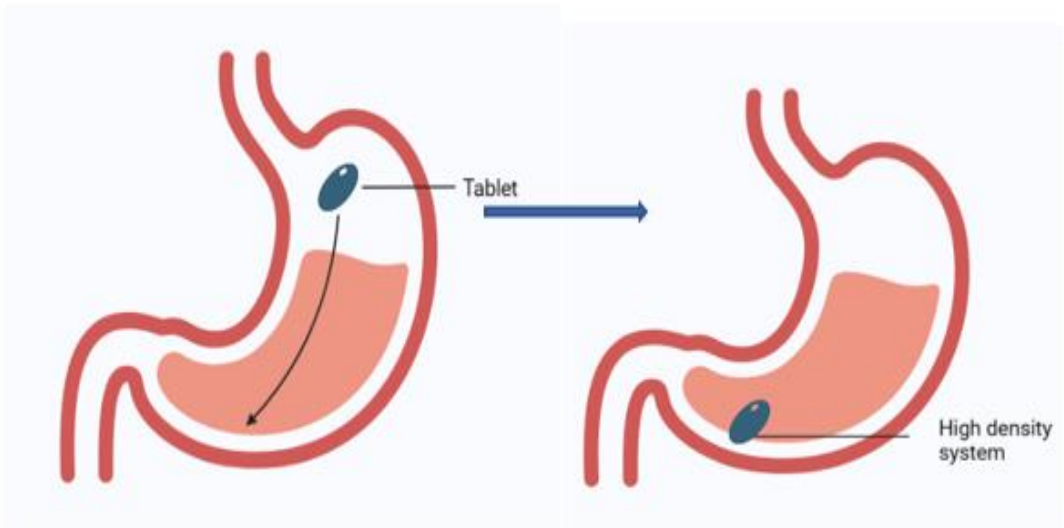
Strategies involved in the Gastroretentive Drug Delivery System



A. High density system (13)

The gastric fluid has a density of 1.004g/ml, this system has a density close to 2.5gcm^{-1}, Such system can retain for a longer time in the lower part of the stomach, which also help the formulation to with stand the peristaltic movement in the stomach as the system gets entrapped within the folds of the antrum of the stomach. Normally these formulations are prepared by the addition of the heavy inert materials like iron powder, titanium dioxide, barium sulphate in order to increase the density and the gastro retentive also depends upon the density of the formulation

Disadvantage – it is a challenging task to manufacture with a large amount of drug (>50%) and also to achieve the required density.



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B. Floating system/ hydrodynamically balanced system (1,2,6,76)

It was Davis in 1968 who described about the floating system in this method the density of the formulation is less than that of the gastric fluid, the material floats which prolongs the gastric resident time, there is a formation of the cohesive gel barrier and the content should be released slowly to serve as a reservoir. once there is a compete release of the drug, the residual s completely removed from the stomach

I. **EFFERVESCENT SYSTEM-**

It is made up of an effervescent agent that release carbon dioxide gas when they come into contact with Stomach fluid. This gas is trapped in the developed formulation and alters the buoyancy property which has a major effect on the drug releasing property, these systems normally use the sodium bicarbonate and citric acid to achieve the floatability by effervescences. The stoichiometric ratio of sodium bicarbonate and citric acid for production of gas is 1:0.76

Volatile liquid containing system- Volatilization of an organic solvent can also be applied in order to produce the gas which helps in floating. it contains two chambers which is separated by an impermeable, pressure-responsive, movable bladder. 1st chamber has drug and the other has the volatile liquid. The enhanced gastric retention can be achieved by addition of an inflatable chamber, containing liquid such as cyclopentane and ether which convert into gas at body temperature, which leads to the inflatation of the chamber, there is a continuous release of the drug from the reservoir

Non effervescent System

The polysaccharides/polymer involved has a tendency to swell when in come in contact with water and have a property of gel formation. Polymers involved are polyacrylate, polystyrene, polycarbonate, polymethacrylate.

Appropriate mixing of the drug with the polymer, which has the tendency to form a gel result in the enhanced gastro-resident time and also help to maintain the integrity of the density, shape, size of the formulation in the gastric fluid. There are few commonly used excipients such as sodium alginate, calcium chloride, Carbopol, Hypromellose, polyethylene oxide, HPMC.

- Major drawback is the release of the drug depends upon the floating of the dosage form
- This system is divided into the subtypes such as – Colloidal gel barrier system
- Alginate beads and Hollow Microspheres.

i. **Hydrodynamically balanced microspheres/ colloidal gel barrier system-**

These systems include medications that have hydro-colloids that gel and are designed to float on stomach contents. By doing this, the dose of medicine that reaches the absorption sites is increased and the stomach retention duration is prolonged. Useful materials include alginic acid, agar, sodium carboxy methylcellulose, polyacrylate hydroxyethyl cellulose, and HPMC. API and polymer are combined, in a capsule which is hydrodynamically balanced is typically used for administration.

The capsule cover subsequently disintegrates when it comes into touch with water, and the resulting combination expands to form a gelatinous barrier that gives gastric fluid prolonged buoyancy. Because of ongoing surface erosion, water can enter the inner layers

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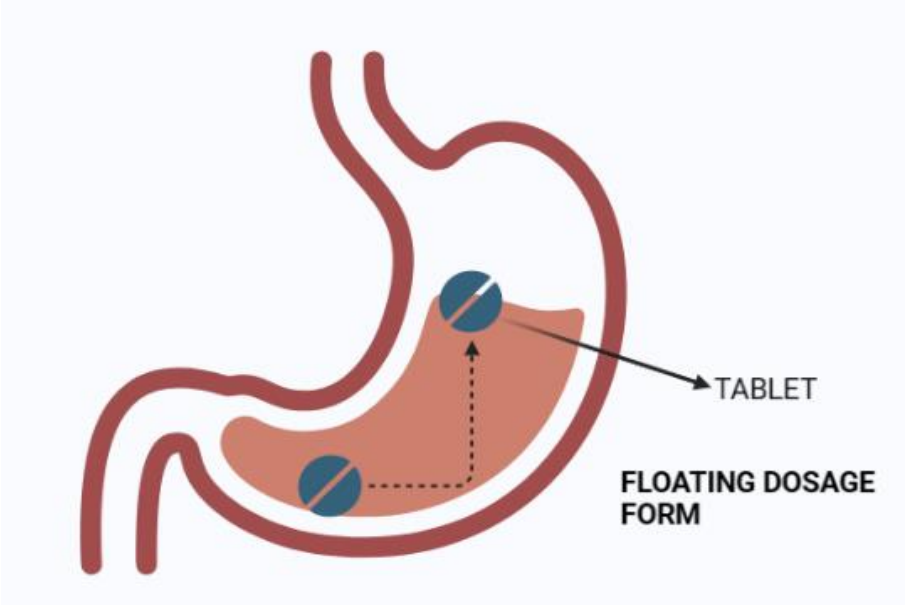
of capsule, keeping the surface hydrated and buoyant. Lipid excipients are used to create formulation having low density that reduce erosion. The Madopar LP formulation, based on this technology, was sold during the 1980s.

ii. **Alginate beads-**

Calcium alginate that has been freeze-dried has been used to create multi-unit floating formulation. sodium alginate is mixed with the calcium chloride and forms calcium alginate which precipitate and form spherical beads with a diameter of around 2.5 mm. Following the separation of the beads, a porous system that can sustain a floating force for more than 12 hours is created by snap-freezing them in the liquid nitrogen and freeze-drying them at -40 ^{o}C for 24 hours. The prolonged residency duration of these beads that floated was exceeds 5.5 hours.

iii. **Hollow Microspheres**

The innovative emulsion-solvent diffusion approach is utilized to create hollow microspheres that contained API in the outer polymeric shells. Ethanol: Dichloromethane solution was prepared with addition of drug and was agitated by the addition of the polyvinyl alcohol solution with the controlled temperature that is 40 ^{o}C, along with an enteric acrylic polymer. the gas is generated which helps in the floating of the microspheres. Polymer used are- cellulose acetate, Eduragit S, calcium alginate, polycarbonate pectin and others. These microspheres float for more than 12 hours.



iv. Micro sponges

These are the highly porous, cross-linked, polymeric microspheres, which entrap the drug within it and release the drug at a predetermined rate and has a particle size of 5-300micrometer, it is used to decrease the drug irritation to the interior part of the stomach without hindering the therapeutic efficiency.*37*

C. Super porous hydrogels (SPH) (9, 10)

SPH with a three-dimensional assembly and a higher affinity for water are shaped through a close interaction with inorganic solvents. Due to the smaller distances between the interconnected pore framework, they can outfit liquid quickly. The SPH has an extraordinary

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amount of surface area, as well as an intra- or inter-porous empty region. Super porous hydrogel have a pore size >100µm.This SPH characteristic aids in the framework's ability to withstand a significant amount of solvent, which ultimately causes the swell and rise in surface area phenomenon. SPHs are robust enough to endure stomach emptying and peristaltic motions. It is advantageous to enhance their use in gastro-retentive drug delivery systems because of this specific quality of longer gastric retention period.

When compare to the conventional hydrogel the absorption is delayed process and required a period of time to establish the requirement, in term of Super porous hydrogel the swelling and absorption ratio is high and also require less time for equilibrium. A polymeric material, Ac-Di-Sol (croscarmellose sodium) is also used

D. Bio adhesive/ mucoadhesive system-(3,4)

The basic phenomenon is that the dosage form adheres to mucosal layer of the stomach. The creation of electrostatic and hydrogen bonds at the polymer-mucus border is considered to be the mechanism of muco-adhesion. Typically, polymers with an affinity for GI mucosa are used to achieve muco-adhesion. Poly (acrylic acid) Carbopol®, Gantrez®, sucralfate, cholestyramine, sodium alginate, Hydroxypropyl methyl cellulose, sephadex, PEG, chitosan, dextran, poly(alkyl-cyanoacrylate), and polylactic acid are frequently used for bio adhesion
The mechanism involved in the bio adhesion is

a) Wetting theory- The basis of this theory depends upon the polymer ability to swell, spread and contact the mucosal layer
b) Absorption theory- involves the bio adhesion due to the weak forces such as Vander Waal force, hydrogen bond etc.
c) Diffusion theory- there is a physical entanglement of mucin chains into the polymer substrate
d) Electronic theory- there is an electrostatic attractive force between the mucin and the polymer

Major drawback- the highly hydrated stomach contents reduce the bio-adhesiveness of polymers, which makes the system to fail

E. Swelling/ Expandable system (35)

The basic phenomenon is the swelling property of the material in use. These systems are based on 3 configurations, the first one is to the smaller configuration which helps in the easy intake of the dosage form orally, the second one is the expandable of the swelling form, in certain way that in blocks its passage through the pyloric sphincter, hence is also known as the plug type system, the last configuration is to come back to this original form that is the smaller one, so that it can easily be evacuated from the body, the swelling is due to the osmosis phenomenon.

F. Magnetic system- (14)

A dosage form for magnetic systems comprises of an internal magnet, additives, and the active pharmaceutical component. To regulate the positioning of the dose form with an internal magnet, an extracorporeal magnet is positioned over the stomach. The GRT can be impacted by the extracorporeal magnet's orientation and magnetic field intensity

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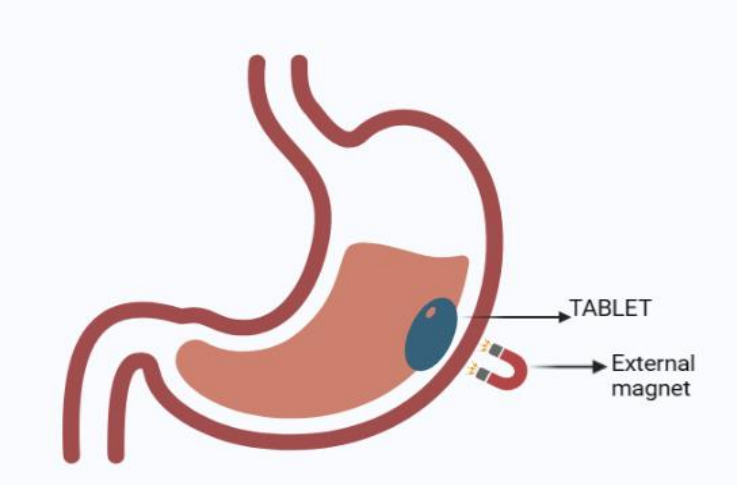

G. Ion Exchange System- (15)
It is the reversible exchange of ions (of like charge) between a liquid and a solid phase without significantly altering the solid's composition or physical characteristics. the solid phases in the IE process, are typically polymers with incorporated ionic moieties. The IE process is referred to as either cation exchange (CE) or anion exchange (AE), depending on the type of ionic species being exchanged. *Atyabi (1995)* Bicarbonate is been added to ion exchange resins and covered with semi permeable membrane. There is a release of carbon dioxide which is trapped inside the coating of the beads, due to this these beads have a longer gastric residence. Theophile was being used for a controlled release and as a gastric retentive system

Limitations- difficulty in the determination of the amount of the drug present and also the safety after the ingestion of the dosage form

H. Raft forming system- (7,8)
When the raft-formulation is in touch with gastric contents, they quickly change from a low viscous, to a viscous, expanded floating form. When in contact with gastric fluid, ion-sensitive polymer solutions like sodium alginate and bicarbonates first become viscous. At the same time, carbon dioxide produced by the bicarbonates is trapped in the viscous gel, causing the raft-forming system to float. As with Liquid Gaviscon (Glaxo smith), these systems have the unusual ability to create a physical layer-like effect on the surface of the gastric contents, which can be used to treat gastroesophageal reflux. Polymers used are- sodium alginate, pectin, HPMC, Carbopol,

Can be of 3 types- Expandable system, swellable system

Expandable system- the formulation is in the form of easily swallowable. Once, it reaches the stomach it expands to a size which is more than the pyloric sphincter. This help in the increased gastric retention time and also the better therapeutic effect. The unfolding and the swelling types are present in the Expandable system

The unfolding system (6)- here these systems are made up of the biodegradable polymers which are folded and is placed inside the capsule to make it more easily swallowable. Once, the capsule gets inside the body the capsule id degraded and the folded polymer will expand.

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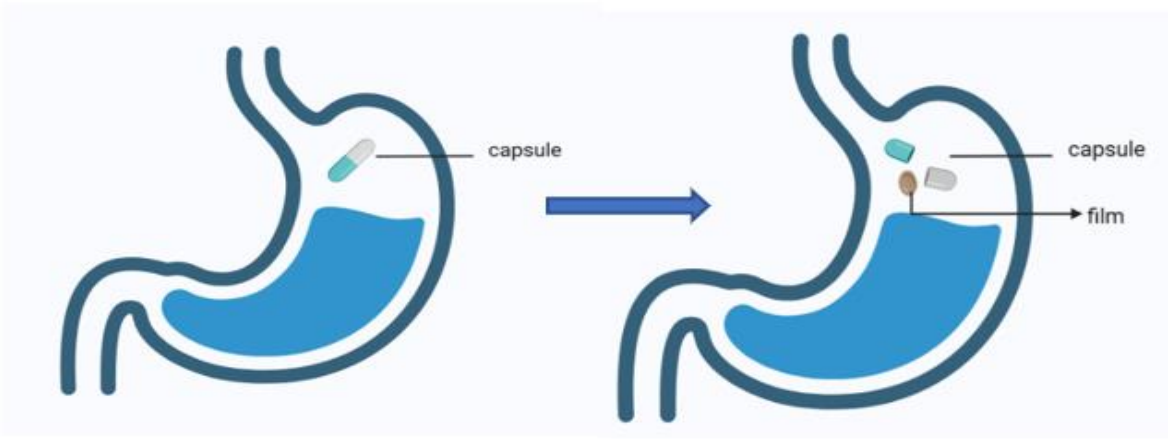
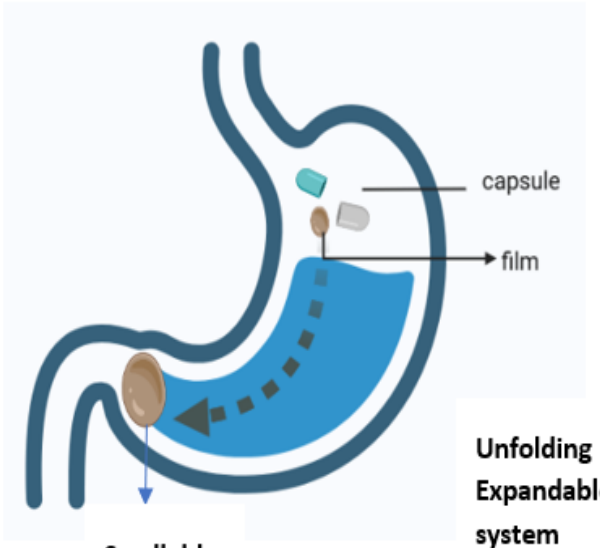
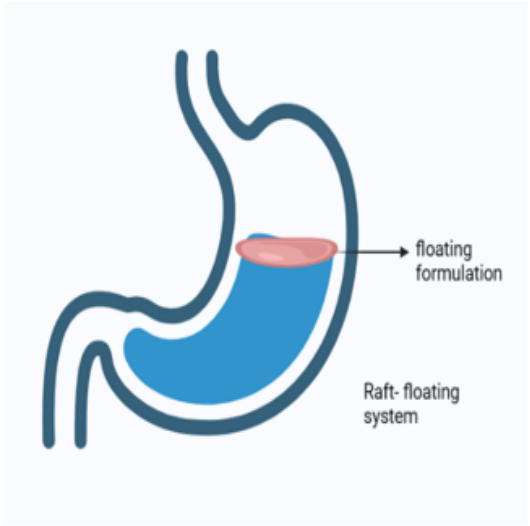
These are present in various forms such as the tetrahedron ring, planar and others.

Swellable system – Retains in the stomach mainly due to its mechanical properties, the swelling occurs due to the osmotic absorption of the water, which increases the size. Hydrophilic polymers are commonly used- HPMC, Carbopol, polyethylene oxide, alginate and even the naturally occurring polymer.





Unfolding Expandable system



PATENTED GRDDS (72, 73,)

Sl.No.	Patent No.	Type of Formulation	Approach	Year	References
1.	US 5769638	Buoyant controlled release powder formulation	In this approach, drugs are released at a controlled pace regardless of the environment's pH due to a floating controlled release powder formulation that is put into capsules.	1992	40
2.	US 5198229	Self-retaining	This method incorporates a drug delivery device with two	1993	41

		GRDDS	densities: one low density for drug delivery while floating in gastric fluids, and one higher density for removal from the stomach.		
3.	US 5232704	Bilayer formulation	The dosage form includes a capsule with a non-compressed bi-layer formulation, one of them is a floating and the other has a controlled-release layer. The dosage form has an initial density of less than 1, a big diameter compared to its size.	1993	42
4.	US 5626876	Floating system	This innovation refers to an oral therapeutic device that can float on gastric fluid	1997	43
5.	US 6207197	GRDDS microspheres with a controlled release	The product has an inner microsphere with a drug and a rate-regulating layer made of a water-insoluble polymer.	2001	44
6.	US 8277843	Controlled buoyant delivery system	The structure in question included a core, one or more layers in which the drug is coated on the core, and a hollow area that was already constructed. This technology offered configurable drug delivery in a controlled manner	2012	45
7.	US 8808669	Floating and swellable system	This method uses a controlled release formulation that has the ability to float and swell at acidic pH and distributes the medication over an extended period of time.	2014	46
8.	US 9314430	Floating system	A dosage form with two cylinder ends those floats because of its unique size and shape.	2016	47
9.	US 9561179	Floating system	the dosage form with a controlled-release microparticles with a drug placed on their surface	2017	48
10.	US 5360793	Raft formulation for antacid	it is an Insitu gel, The Composition included water, preservatives, colorant, xanthan gum, carbonate ions, 0.5-7.0%, 0.1%–1.8%, aluminum hydroxide, and 5–50% bulking agent, water and other additives	2001	18
11.	US 5068109	Raft for	It was claimed that low	1991	22

		pectin	methoxylated pectin, ranging from 1 to 50% by weight, may be formed into an antacid composition. Along with a buffering agent, this mixture also contained 1-30% by weight of a neutralizing agent such magnesium sub carbonate or potassium bicarbonate as a buffering agent		
12.	US 5681827	Raft for Alginate	The development of an oral medication led to suggestions for the treatment of gastritis, peptic ulcer, gastric reflux, esophagitis, and dyspepsia. This preparation was made up of various compositions of sodium alginate, calcium carbonate, potassium bicarbonate, carbomer. Additionally, it contained either sodium saccharin, sodium ethyl Para hydroxybenzoate, sodium butyl Para hydroxybenzoate or sodium hydroxide.	1997	25
13.	US 5456918	Raft for Alginate	It was asserted that the formulation's composition played a key part in the treatment of GORD. This formulation contained 2-15% w/w sodium bicarbonate or potassium bicarbonate, 1.25-10% w/w ranitidine, and 5-35% w/w alginate component. In this composition, an antacid was also chosen to be included from either magnesium trisilicate or aluminum hydroxide.	1995	26
14.	US 4140760	Raft for Alginate	This pharmaceutical dosage form could prevent stomach reflux. it is an *insitu* gel which floats on the gastric contents of the stomach This liquid product contained 1.2-2.0% w/v of calcium carbonate, 0.16–2.6% of sodium bicarbonate, 0.10-1.04% of the calcium carbonate and sodium alginate of low viscosity grade.	1979	
15.	US 4744986	Raft for	Aqueous	1988	24

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		Alginate	antacid Raft formulation was steady throughout a range of viscosity Alginic acid and aluminum salt, were the key ingredients in this product		
16.	US 0119994	Raft formulation	This approach entails the construction of raft formulation that releases medicine in a predictable, regulated way.	2001	49
17.	US 0063980	Raft for pectin	The formulation touches the gastric juices, there is a development of raft floating formulation	2002	50
18.	US 6797283	GRDDS with multiple layers	It is an extended-release dosage form, more specifically, it applies to multilayered active agent dosage forms with a drug layer and a highly expandable layer.	2004	51
19.	US 8586083	GRDDS consist of Hydratable polymer	A medication made by extrusion is part of this technology, which improves stomach retention. Extrusion makes it possible for the product to take on a variety of advantageous forms, such as the usage of a sheet made of a hydratable polymer to stop dosage forms from passing through the stomach.	2013	52
20.	US 9119793	GRDDS of doxycycline	a combination of bio adhesive, floating and swellable, characteristics.	2015	53
21.	US 20150366832	GRDDS FOR Carbidopa	This system uses an enteric polymer that is insoluble in gastric fluid and a hydrophilic swelling polymer to increase gastro-retention	2015	54
22.	US 20150231084	Osmotic Floating tablet	To accomplish gastro-retention, the drug is in Inner core is combined with an outside osmotic core which is a release-delaying polymer, and other components.	2015	56
23.	US 20160338949	GRDDS of pregabalin	The combination consists of a pH modifier and a swellable polymer to create a stabilized, gastroretentive pregabalin dose form.	2016	57
24.	US 4193985	High density	In this technique, a tablet or capsule with many subunits, each	1980	26

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			containing a therapeutically active substance, is used. At least some of these subunits have a higher specific weight than the active agent itself.		
25.	US 4938967	High density	These systems include dosage forms with a minimum subunit density of 2.7 g/ml, which can be achieved by utilizing barium sulphate as a weighing agent, and dosage forms with dimensions of 2 mm	1990	27
26.	US 4767627	Swelling system	This method consists of a swelling dosage form made of an erodible polymer that can release the medication over a long period duration in a regulated manner.	1988	57
27.	US 5443843	Swelling and expandable system with controlled release	This method incorporates a drug dosage form with one or more retention arms connected to a controlled release device that, when expanded, prevents the device from passing through the stomach	1995	58
28.	US 5780057	GRDDS Swellable tablet	This device consists of a 2–3-layer tablet, in which one of the layer when comes in contact with the gastric fluid it swells and increases gastric retention time which also allows the slow release of the drug	1998	59
29.	US 5972389	Gastro retentive oral swellable system for sparingly soluble drug	This method consists of a tablet or capsule that contains many particles made from a combination of the medication and the erodible/swellable polymer. Once consumed, the particles inflate and release the medication gradually as the polymer breaks down.	1999	60
30.	US 6488962	GRDDS tablet	In this method, the oral swellable dose forms are precisely designed to resist stomach transit in order to achieve gastro-retention.	2002	61
31.	US 6548083	Controlled and prolong release of drug delivery	This system consists of a dosage form made from a matrix of polymers that expands when in contact with gastric fluids and	2003	62

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		system	increases the dosage form's retention duration in the stomach.		
32.	US 6723340	Gastro retentive tablets	In this method, poly (ethylene oxide) and HPMC are used in conjunction, allowing for both swelling to aid in gastro-retention and to regulate release of the API from the tablet.	2004	63
33.	US 6776999	Expandable Gastro retentive therapeutical system	This method places more emphasis on drug form than polymer characteristics when determining drug release. A polymer found in the medication delivery device expands when it comes into touch with gastric secretions, making it impossible to remove the device through pylorus.	2004	64
34.	US 7976870	GRDDS oral dosage form	In this approach, an active ingredient is combined with biocompatible, hydrophilic, biodegradable polymer to provide a dosage form. When the polymer comes into touch with gastric juices, it swells, and as the polymer deteriorates, the drug slowly releases. The polymer erosion rate essentially regulates the rate of drug release.	2011	65
35.	US 9393205	Oral tablets	Typically, these systems use monolithic tablets made of a medication combination and one or more swellable polymers. By ingesting gastric secretions, these polymers swell, causing the tablet to float on the stomach's contents and allowing the medicine to be released gradually.	2016	66
36.	US 9801816	GRDDS of Acamprosate	Acamprosate oral dosage for gastric retention with extended release (ER) is dispersed in a polymer that is hydrophilic. The polymer matrix swelled once comes in contact with water to a size that allowed the dosage form to be kept in patient stomach in a fed mode and release acamprosate over an extended	2017	67

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			period of time.		

GRDDS available in the Market

Sl.No.	Delivery system	Name of the Brand	Active Ingredient	Manufacturing company
1.	Bio adhesive tablet	Xifaxan	Rifampicin	Lupin, India
2.	Floating Capsule (Bilayer)	Cytotec	Misoprostol	Pfizer, UK
3.	swelling system (Multi layer)	Baclofen GRS	Baclofen	Sun Pharma, India
4.	Floating system (colloidal forming system)	Conviron	Ferrous sulphate	Ranbaxy, India
5.	Effervescent floating system	Zanocin OD	Ofloxacin	Ranbaxy, India
6.	Floating effervescent formulation	Riomet OD	Metformin hydrochloride	Ranbaxy, India
7.	Floating effervescent formulation	Cifran OD	Ciprofloxacin	Ranbaxy, India
8.	Floating effervescent liquid formulation	Liquid Gaviscon	Alginic acid and sodium bicarbonate	Reckitt Benckiser Healthcare, UK
9.	Floating formulation (swellable and effervescent formulation)	Prazopress XL	Prazosin hydrochloride	Sun Pharma, Japan
10.	matrix system (Erodible)	Cipro XR	Ciprofloxacin hydrochloride and betaine	Bayer, USA
11.	Unfolding expandable system	Accordion Pill	Carbidopa/levodopa	Intec Pharma, Israel
12.	*In-situ* formulation	Topalkan	Aluminum magnesium	Pierre Fabre Medicament, France
13.	controlled release floating capsule	Prolopa HBS	Levodopa and benserzide hydrochloride	Roche, UK
14.	Floating formulation	Cefaclor LP	Cefaclor	Galenix, France
15.	Floating formulation	Tramadol LP	Tramadol	Galenix, France
16.	Polymer based swelling	Gabapentin GR	Gabapentin	Depomed Inc., USA

	technology			
17.	Swelling system	Proquin XR	Ciprofloxacin	Depomed Inc., USA
18.	Floating Capsule	Val release	Diazepam	Roche, UK
19.	Gastro-retentive with osmotic system	Coreg CR	Carvedilol	GlaxoSmithKline
20.	Floating formulation (foam based)	Inon Ace	Simethicone	Sato pharma, Japan
21.	Gas Generating tablets (floating system)	Oflin OD	Ofloxacin	Ranbaxy, India
22.	Controlled release Floating capsule	Madopar	Levodopa and Benserzide	Roche, UK
23.	Swelling system	Glumetza	Metformin hydrochloride	Depomed, USA
24.	Floating system	Almagate Flot-Coat	Aluminum and magnesium mixture	Ranbaxy, India

Evaluation Parameters

S.No.	Method	Evaluation Parameters	Reference
1	Low-density, Raft-forming system	Total Floatation time, floating strength, floatation lag time, density or specific gravity	1, 2
2	Super porous hydrogel system	Swelling index, water retention, drug entrapment efficiency, water uptake capacity	9, 10
3	Mucoadhesion system	Viscosity, Rheology	4, 34
4	Expandable system	In Vitro unfolding study	35
5	Resin system (Ion-exchange)	Size of the particle, moisture content, ion exchange capacity	15, 16
6	*In-vivo studies*	Gamma Scintigraphy, radiology, Gastroscopy, Magnetic marker monitoring (MMM), X- ray, Radiology, Magnetic resonance	35, 36

Example for the GRDDS Research on Various Strategy

S.No.	Name of the drug	Type of system	Polymer used	References No.
1	Levofloxacin hemihydrate	Floating tablet	HPMC K 100 LV	1
2	Moxifloxacin	Floating tablet	HPMC K 100 M	2
3	Moxifloxacin HCl	Bio Adhesive tablet	HPMC K 100 M	3
4	Risedronate	Muco Adhesive	Sodium alginate	4

	Sodium	microspheres		
5	Cinnarizine	Film	Ethyl cellulose and HPMC K 15	5
6	Carbamazepine	Floating tablets	HPMC K4M	6
7	Calcium carbonate	*IN-SITU* gel	Xanthan gum, HPMC K 100 M	7
8	Lafutidine	*IN-SITU* gel	Sodium alginate, HPMCK4M and xanthan gum	8
9	Esomeprazole	Super porous hydrogel	Polyvinyl alcohol, chitosan	9
10	Polymer material	Super porous Hydrogel	Ac-Di-Sol	10
11	Pregabalin	Non-effervescent tablet	HPMC, HPC	11
12	Gabapentin	Swelling	Polyethylene oxide and HPMC K100M	12
13	Famotidine	High density osmotic pump tablet	Polyethylene oxide, iron powder	13
14	Acyclovir	Magnetic system	Magnetic granules	14
15	Theophylline	Ion exchange system	Ion exchange resin beads coated with Eudragit RS	15
16	Domperidone	Ion exchange system	Sodium alginate	16
17	Valsartan	*In-situ* gel	HPMC K 100 M, Sodium alginate Imaging, Ultrasonography	17

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