CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Review article

Fundamentals and Therapeutic Applications of Gastro-Retentive Drug Delivery Systems

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ARTICLE INFO:
Received: 09 Jan 2023
Accepted: 15 Feb 2023
Published: 28 Feb 2023

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ABSTRACT:
Oral drug delivery system is the most often used drug delivery system, although in some circumstances oral administration of a drug might be difficult, such as when the drug has low bioavailability or a short half-life, necessitating regular dosage to maintain therapeutic effect. Gastroretentive drug delivery system (GRDDS) is one method utilized to increase the drug's residence period within the body. These dosage forms will remain in the body or GIT for a longer period of time, resulting in prolonged gastric retention. Candidates for this GRDDS include drugs with low solubility or unstable in the colon and intestine. Numerous methods are employed in the formulation of GRRDS dosage forms, including the high density system, the low density system (floating system), the magnetic system, and the Raft system, among others. Floating system is one of the systems that are utilized more frequently than others. These GRDDS can be assessed using in-vitro and in-vivo measures. There are numerous advantages of GRDDS, such as the fact that the bioavailability of drugs that are metabolized in the upper part of the GIT can be increased using this method, and because GRDDS have sustained release properties, they can be used to treat certain disorders of the stomach and small intestine. GRRDS is capable of providing site-specific medication delivery.

Keywords: Gastro retentive, retention, floating, sustained.

1. INTRODUCTION

Oral drug delivery system is the most commonly used drug delivery system in comparison with other routes of drug administration as it has certain advantages over others like easy administration of drug, easy transportation as well as patient compliance. But in certain cases, oral administration of a drug becomes a challenge. For example, sometimes drugs have low bioavailability and sometimes drugs with short life gets eliminated out from body quickly, due to which frequent dosing is required to maintain the therapeutic effect of drug. So, to overcome these types of problems many approaches are done like sustained or controlled release of drug, which will allow the drug to deliver or release the drug slowly in control or sustain manner in GIT and will be there in systemic circulation for comparatively longer period of time. In these types of cases the drug will be present in GIT and release drug in control manner to its absorption sites [1]. In the case of oral drug delivery, drugs mainly advertise two types of things; it can be either short gastric retention time (GRT) or short/ unpredictable gastric emptying time (GET). In case of GET there will be incomplete release of drug from the particular dosage form to its absorption site [2]. For the formulation of site-specificdrugs, it is important that drug should have high or prolong gastric residence time which will also leads to increase in drug release duration, enhance bioavailability, improves the solubility of drugs and reduction in wastage of drug [3]. In case of local administration of drug GRT is found to be advantageous [4].

Gastroretentive drug delivery system (GRDDS) is one of the approaches that is used to increase the residence time of drug inside the body. In the case for both local as well as systemic release of drug target specific drug delivery is the best approach which can be successful with the help GRDDS. As these type of dosage forms will remain in body or GIT for longer period of time which will lead to prolong gastric retention of the drugs. There are many approaches for GRDDS like high density also known as sinking type of dosage forms which will retain in the bottom of GIT and other one is low density type which is also known as floating type drug delivery system in which drug will float over the gastric fluid due to buoyancy [5]. Others are like mucoadhesive that will stick to mucous layer, swellable type, unfoldable type, magnetic systems etc [6].

Physiology of the Stomach

In GRDDS, stomach plays anessential role. So, for the successful formulation of GRDDS it is required that one should understand the anatomy as well as physiology of stomach. The stomach is mainly divided into two parts: the proximal stomach and the distal stomach. Fundus and body

are there in proximal stomach whereas antrum and pylorus are present in distal stomach. To store the food and then to crush it and then slowly release that grinded food to duodenum is the main function that is done by stomach [7]. For undigested food fundus and body acts as reservoir. In case of antrum, it primarily acts as pump which will assist gastric emptying by propelling action. Migrating Myoelectric/Motor Complex (MMC) is the term that is used for themobility pattern of the stomach. There are different phases of MMC. Gastric emptying can be occurred at fed state as well fasting state but the thing is that the pattern of emptying of gastric will be drastically different in both of the cases. In every 90-120 min sequence of electric will be there in inter digestive system in cyclic manner which will be through stomach and intestine [8]. The diameter of the pylorus increases up to 19mm during the inter-digestive state [9]. Due to which the particles which are having size less than 19mm will pass through the pylorus duodenum. In case of fed state, after ingestion of meal motor activity will get generated in 5-10 min and will continue the time food remains in the stomach, which will result in delaying of gastric emptying time [10].

Phases of MMC: Phases of MMC is represented in Table 1.

Table 1: Phases of MMC

Phase	Comments	Duration (min)
1	Quiescent period with unusual contractions	30-60
2	Intermittent Contractions	20-40
3	Strong, large regular contractions. Phase 3 is also known as "housekeeper wave"	10-20
4	Transition phase between phase III and phase I	0-5

2. FACTORS AFFECTING GRDDS

The factors that are to be considered and are important for controlling GRT are: density of drug, type and size of dosage form, fast or fed state, type of meal, food intake, age, gender, posture, physical state, diseased state etc.

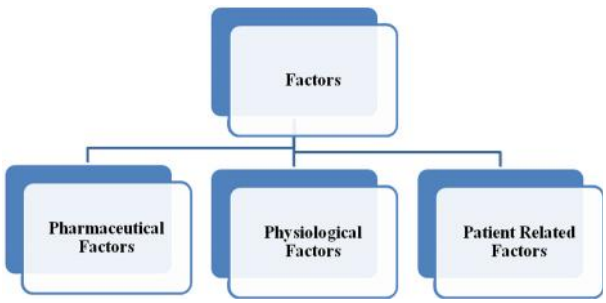

Fig 1: Factors affecting GRDDS

2.1. Pharmaceutical Factors: In the formulation of GRDDS the most important thing is selection of excipients and polymers [11]**.** For example, in case of mucoadhesion type dosage form polymers that are high muco-adhesive properties are use like HPMC, in case of expandable type, polymers having higher swelling properties are used.

Moreover, GET also get affected by the density of dosage form. If the dosage form will have density than gastric fluid then it will sink to the bottom of stomach whereas if the dosage form will have low density then it will float over the gastric fluid.

In designing of indigestible single unit dosage form, shape and size of dosage form are of great importance [12]. Mostly, if dosage form will have larger size then it will have larger GRT the dosage forms that are having diameter of 7.5mm are showing better GRT than that of one who are having 9.9 mm. Based the shape, the tablets that are of ring-shaped and tetrahedron shaped, they show better GRT [13].

2.2. Physiological Factors: Various extensive factors like type of meal, caloric content, posture, physical state, diseased state etc. can also affects the GRT [14]. If food is having high caloric and density and high viscosity then GRT will also increases. Posture of the person also affects the GRT. If a person sleep at left side then GRT will increase.

2.3. Patient related Factors: Different patient related can also influence the GRDDS. These can be age, gender, emotional state etc. It has been found that females generally have low gastric emptying time as compared to males and this is may be due to hormonal influences. Younger patients have comparatively low GRT as compared to elder patients [15]. Same is the case in diseased state as it also affects GRT. For example, if a person is suffering from depression then he will have increased rate of GRT as compared to persons who are suffering from anxiety.

3. DRUGS HAVING POTENTIAL FOR GRDDS

- Drugs having slow solubility at high pH like diazepam, verapamil HCl.
- Drugs that is unstable in intestinal or colon like metronidazole, ranitidine HCl.
- Drugs which are locally active in stomach like antacids.
- Drugs which have narrow absorption window in GIT like L-Dopa, PABA, riboflavin etc.
- Drugs which are able to disturb normal microbes of colon like Helicobacter pylori.

Drugs unsuitable for GRDDS

- Drugs which are having limited solubility in acid like phenytoin.
- Drugs those are intended to release selectively in colon like 5-amino salicylic acid.
- Drugs instable in gastric environment like erythromycin

4. APPROACHES TO ACHIEVE GRDDS

4.1. High Density Systems: Those formulations that are having density larger than that of gastric fluid, they are known as high density (sinking). As in this formulation sink to the bottom of the stomach. Their density is more than 1.004 gm/cm^3. In this formulation is prepared by either coating the drug with heavy core or by mixing the drug material with inert materials like zinc oxide, iron

powder, titanium dioxide, barium sulphate etc. By this approach density of the formulation increases to 1.5-2.4 gm/cm^3. To increase or prolong the GRT of the formulation it is necessary that formulation should have density close to 2.4gm/cm^3 [16].

4.2. Low Density Systems: Low density systems are also known as floating drug delivery system, in which formulation has density less than that of gastric fluid and hence it floats over the gastric fluid [25]. This low-density system/floating system is the most important and most extensively used system for gastro-retentive drug delivery system [17]. In this drug will have buoyancy effect and hence it will remain buoyant over gastric fluid and drug will release slowly from dosage form at a desired rate. On the basis of mechanism of buoyancy, this system is further classified into two types: Non-effervescent floating system and Effervescent floating system. The major requirements of floating drug delivery are [18]:

- Formulation is supposed to slowly liberate content so as to act as a reservoir.
- Should have density 1.004-1.01gm/cm^3.
- Should cohesive type gel barrier.

4.2.1. Non-Effervescent floating system: With use of highly swellable polymers, polysaccharides, polycarbonate, polystyrene, polymethyl acrylate, poly acrylate, polymethyl acrylate etc.these non-effervescent floating systems can be prepared. There are different excipients that are used in this system like HPMC, sodium alginate, calcium chloride, agar, carbopol, polyvinyl acetate, polyethylene oxide and polycarbonates. This system is further divided into following:

Hydrodynamically balanced system (HBS): These HBS was firstly designed by Sheth and Tossounian [19]. In this system drug has to be mixed with gel forming hydrocolloids to make it buoyant so that it can float over the gastric fluid. In this system, formulations are single unit dosage forms that contain one or more gel forming polymers that are hydrophilic in nature. Polymers that are mainly used for making these kinds of systems are HPMC, hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polyacrylate, polystyrene, agar, alginic acid and polycarbophil [20]. In this polymer has to be mixed with drug and after that it is administered in HBS capsule. When capsule shell comes in contact with water, it will dissolve and the mixture that is inside the shell will swell and form gelatinous barrier, which will result in providing buoyancy to the dosage form for long period of time in gastric juice [21]. Delivery of drug effectively depends on the stability of drug loading and polymer effectively and will depend on its release profile.

Micro balloons/ hollow spheres: Till now this system is the most promising technique of floating system as it has advantage of both multi-unit system as well as good floating property. To prolong the GRT of a dosage form micro balloons/ hollow spheres are to be filled with drug in their polymer shelf and then prepare by simple solvent evaporation or solvent diffusion method [22]. The polymers that are commonly used in this system are agar, cellulose acetate, calcium alginate, Eudragit S and low methoxylated pectin etc. Buoyancy effect as well as the release of drug from dosage form is mainly depend on plasticizer polymer ratio, quantity of polymers, and the type of solvent used for the formulation. This system can float for >12 hours over the acidic dissolution media.

Alginate beads: Alginate beads improve GRT for more than 5.5 hours. Based on cross-linked beads this multi floating system has been developed [18]. These formulations were prepared by either Calcium and low methoxylated pectin and sodium alginate or by calcium low methoxylated pectin and sodium alginate. In this calcium solution has to be prepared and then in that solution sodium alginate bead is dropped which will cause the precipitation of calcium alginate. Then these precipitated beads will get alienated out and then dried by air convection and freeze drying which will lead to formulation of porous system. Due to which it can maintain floating force over 12 hours [23].

Micro-porous compartment system: In a microporous compartment there will be encapsulation of drug reservoir and compartment will have pores along with its top and bottom wall. To prevent the direct contact of gastric surface with un-dissolved drug the walls of peripheral device are completely dissolved. The floatation chamber in the stomach containing entrapped air causes the formulation to float over the gastric fluid. Through aperture, gastric fluid enters and dissolves the drug and then it will cause dissolved drug for continuous transport for absorption of drug across the intestine.

4.2.2. Effervescent floating system: By the generation of gas, floatability of dosage form can be achieved. In these materials that have to be buoyant will utilize matrices and are prepared with swellable polymers like polysaccharides (chitosan), effervescent components (like sodium carbonate, citric acid) [24]. For generation of gas the optimal stoichiometric ratio of citric acid and sodium bicarbonate is 0.76:1. In this system, formulation floats over gastric fluid due to release of carbon dioxide. In this bilayer or multilayer system can also be designed [25]. In this firstly gas and the other excipients can be formed or formulated independently and then the gas forming agent can be incorporated into the layers that are on the dosage form. In this system, the main requirement is that in this high level of fluids are required to float the formulation to work in effective way. That's why the drugs which show irritant effect on gastric mucosa those are not suitable for this system.

4.3. Super-porous hydrogel system: Due to its elevated mechanical force and flexible properties this system is mostly used for controlled release formulation. As this system has a pore size greater than 100 micrometers, through these numerous pores water uptake will be there by capillary

wetting action and due to which it will swells rapidly. In the case of conventional hydrogel system, they work very slowly and due to which they take many hours to reach equilibrium. In this system, it swells up to 100 times and then they will have enough mechanical strength and are able to withstand the pressure produced by gastric contraction which will lead to increase in GRT. In this system basically highly swellable polymers are used. But the disadvantage of this system is that they are highly sensitive to pH as swelling can be reversible due to change in pH and mechanical strength will be poor for the structure.

4.4. Expandable system: In this there will be either increase in volume or in shape of the formulation which will lead to increase in GRT. Before, they were used only for veterinary purposes but now this system has its application in humans also. This system is also known as "Plug type system" as this system is able to block the pyloric sphincter. In this the three things that are mainly required are: small size of drug, ability of drug to expand in gastric fluid to prevent passage from pyloric sphincter and then in the end reduction in the size of sphincter after complete release of drug so that it can evacuate out from the body. In this expansion of the drug can be occurring by two ways either by swelling or unfolding. For swelling and release of the drug the main mechanism is diffusion. In the case of unfolding polymer and drug both are compressed inside the gelatin capsule. The mechanism followed in this is expanded configuration as when the dosage form comes in contact with gastric fluid gelatin will get dissolve and then release the drug. There are few limitations of this system like sometimes the polymers used in this system may cause bowel obstruction, intestinal adhesion and gastropathy [2].

4.5. Mucoadhesive/ Bioadhesive system: In this system the formulation will prolong the GRT of drug by adhering to the gastric epithelial cells. In this system the drug that is integrated in mucoadhesive agent will be either synthetic or natural polymer. In this there will be bonding between the polymer and mucosal surface which will be responsible for mucoadhesion process. In this there will be involvement of basically two steps: contact stage and consolidation stage. By the use of mucoadhesion various types of dosage forms can be prepared like tablets, capsules, microspheres, beads etc. and the polymers that are used for their mucoadhesive property are HPMC, sodium alginate, chitosan, polyethylene glycol etc. These polymers should be non-toxic, inert, non-irritant to the mucosal layer. It is basically use for its site-specific property. The property of mucoadhesion of polymer mainly depends on the molecular weight, structure, cross-linking density, charge, and concentration and hydration degree of the polymer [26].

There are various theories related to mucoadhesion.

Table 2: Theories related to mucoadhesion

Theories	Mechanism of mucoadhesion
Wettability	Penetration of mucoadhesive polymer and it will make close touch with mucous layer.
Diffusion	The flexible polymer chains are strand by physical embarrassment of mucin.
Adsorption	Due to secondary forces like Vander wall forces and hydrogen bonding, there will be bioadhesion
Fracture	To separate mucus and polymer detachment force is required which will reflect adhesion
Electronic	Between glycoprotein mucin and bioadhesive material, there will be attractive electrostatic force

4.6. Raft forming system: In this the effervescent polymers are formulated with polymers that form gel in order to achieve the sustained release of the drug. In these floating rafts will be acting as blockade between esophagus and stomach and due to which local effect can be achieved. Due to which it can be used for esophageal reflux disease. When formulation comes in touch with gastric fluid, formulation will swell and there will be a formation of cohesive gel due to which continuous layer will form over the gastric fluid and this continuous layer is known as Raft [14].

4.7. Magnetic system: In this GRT can be increased as in this case dosage form that is intended to use will contain small internal magnet and then magnet will have to be placed on the stomach In this patient compliance may be a problem as magnetic system seem to wok, and the outer magnet should be placed in a accurate way [27].

5. EVALUATION PARAMETERS OF GRDDS

GRDDS formulation can be evaluated by two ways: In-vitro parameters, In-vivo parameters.

5.1. In-vitro evaluation parameters: In vitro evaluation parameters of GRDDS are done by different ways for different type of dosage forms. In case of tablets different parameters like weight variation, content uniformity, drug content, friability and in-vitro drug release can be determined. In case of floating type dosage forms parameter like floating lag time and floating duration can be determined. Apart from this swelling rate, water uptake capacity, gel strength etc. can also be determined.

5.2. In-vivo evaluation parameters: Through in-vivo studies one can understand the bioavailability and GRT of the drug. For in-vivo evaluation of drug, main requirement is of animal or human model.

Various diagnostic techniques are used in evaluation of in-vivo response of the drug. These imagining techniques include MRI, gamma scintigraphy, radiology, ultrasonography, and gastroscopy. To find out the position as well as level of GRDDS and its transit time gamma scintigraphy has been done. It is also used to determine the dissolution and disintegration profile of the drug [28]. In this minute amount of stable isotopes are to be added in the

preparation of the formulation and then that isotope will convert into gamma emitting material and then gamma rays will released and that will be captured as an image. Major advantage of this technique is that it has good safety profile.

For preclinical evaluation, disintegration rate, and esophageal transit of GRDDS, X-Ray technique is used. In this barium sulphate (radio opaque material) is mixed with the formulation and then radiographs will be taken after the intake of formulation. Major advantage of using it is that it is cost effective and simple. Safety issues are there in this case as rhythmic contact to X-Ray will result in different health hazard [29].

6. ADVANTAGES OF GRDDS [30]

- The drugs that get metabolized in the upper part of GIT, the bioavailability of those drugs can be enhanced by this method
- Sustained release of drugs having short life can be achieved and may result into flip flop mechanism and it also increase patient compliance by reducing the dose frequency.
- These formulations are having buoyant tendency over the gastric fluid so it is able to overcome the adversities of GRT and GET.
- Due to it's sustaining release property, GRDDS are also able to treat disorders related to stomach and small intestine.
- GRDDS is able to provide site specific property due to which it will reduce the undesirable side effects.
- Improved selectivity in receptor activation can be achieved by reducing the drug concentration fluctuations.

7. APPLICATIONS

There are many applications of GRDDS. These can be understood in table which will describe the suitable drug candidate for GRDDS whereas the table will represent GRDDS products that are present in market.

Table 3: GRDDS products available in market

Delivery system	Brand Name	Active Ingredient	Manufacturer
Bio adhesive tablets	Xifaxan	Rifampicin	Lupin, India
Bilayer floating capsule	Cytotec	Misoprostol	Pfizer, UK
Coated multi-layer and swelling system	Baclofen GRS	Baclofen	Sun Pharma, India
Effervescent floating liquid alginate preparation	Liquid Gavison	Alginic acid and sodium bicarbonate	Reckitt Benckiser Healthcare, UK
Effervescent and swelling based floating system	Prazopress XL	Prazosin hydrochloride	Sun pharma, Japan
Erodible matrix-based system	Cipro XR	Ciprofloxacin HCL and betaine	Bayer, USA
Expandable System	Accordion pill	Carbidopa/Levodopa	Intec pharma, Israel
Raft forming system	Topalkan	Aluminium Magnesium	Pierre Fabre medicament, France
Gastro retention with osmotic system	Coreg CR	Carvedilol	GSK, UK

8. CONCLUSION

Gastro-retentive drug delivery is one of the methods utilised to increase the drug's residence time within the body. GRDDS are able to persist in body or gastric fluid for an extended period of time, allowing for sustained drug release. GRDDS is able to deliver site-specific properties, hence reducing unwanted side effects. There are numerous methods for creating GRDDS, such as the floating drug delivery system, the high density system, and the magnetic system. These approaches that are processed in the upper GIT can increase the bioavailability of these drugs.

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ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: Not applicable.