GASTRORETENTIVE DRUG DELIVERY SYSTEM (GRDDS): TO GET SITE SPECIFIC & CONTROLL RELEASE OF DRUG- A COMPREHENSIVE REVIEW

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ABSTRACT

In the previous few year, lots of attempt have been made to enhance the gastro retentive time, bioavailability of drug, therapeutic effectiveness and prolong action of the drug for the oral dosage form. So GRDDS (gastro retentive drug delivery system) suitable to fulfill the above need of the oral dosage form and also enhance the therapeutic efficacy of the drug which have narrow absorption window, the drug which are soluble in acidic environment, and also the drug which are unstable at alkaline pH. Now in this review article we discuss the need of GRDDS, physiology of the stomach, factors affecting GRDDS, suitable and non-suitable for GRDDS, merits and demerits of GRDDS. So this technology I very much useful to improve the gastric emptying rate in both the fasted and the speed state.

KEYWORDS: Gastro retentive drug delivery system, Gastric emptying time, Floating and non floating system, narrow absorption window.
INTRODUCTION
As we know that, the oral route is the most predominant and widely accepted route compare to other route of administration. However, there are many problems that were faced by oral drug delivery system like low bioavailability, low gastric retention time, surface area, enzymatic activity etc, so that GRDDS is a perfect technology to overcome such problems.\([1]\)

After many attempt researcher develop a drug delivery system which provide a therapeutically effective plasma drug concentration for a sufficient period of time so that the fluctuation of the drug concentration and the dosage frequency decreases.\([2]\) The GRDDS help to prolong the release of the drug before it reach the absorption site in the stomach.\([3]\) GRDDS are very useful for the drugs by improving their.\([4]\)

- Reduce the gastric retention time
- Increase the bioavailability
- Reduce the toxicity
- Increase the therapeutic effect
- Lower the drug wastage
- Provide uniform release of drug for prolong period
- Reduce the fluctuations.

PHYSIOLOGY OF STOMACH
For the GRDDS, the most Imp thing is to understand the anatomy & physiology of stomach so to develop the successful form of GRDDS. As we all know that stomach is anatomically divided into four major region:
(1) Cardia,
(2) Fundus,
(3) Body, &
(4) Pylorus(Shown in Figure 1)
The undigested food in the stomach store in the fundus & body, whereas the cardiac contain cardiac sphincter which prevent the food of the stomach from going back to oesophagus and function of pylorus is to prevent the reentering the food in the stomach from large intestine.

The interdigestive myoelectric cycle of the stomach involves 4 phases:

- **Phase 1 (Basal phase)** - last from 30 to 60 min but contain lack of contractile and secretory activity.
- **Phase 2 (Preburst phase)** - last from 20 to 40 min having increase in contractile frequency.
- **Phase 3 (Burst phase)** - last from 10 to 20 min with very short contraction time and passed forward the undigested food.
- **Phase 4** - last from 0 to 5 min and it is the transition period between the 1 and 3 phase.\(^{[5,6]}\)

**Advantages of GRDDS\(^{[7]}\)**

1. Enhance the bioavailability and efficiency of drugs and economic usage of dosage form.
2. It also help to reduced the risk of resistance to antibiotic & also reduced the fluctuation of release of the drug.
3. Due to the less counter activity of body, the GRDDS system provide the release of drug with high efficiency.
4. To overcome the Gastric emptying time and Gastric retention time the GRDDS manufactured the drug with low density so that it become buoyant in the stomach.

5. The GRDDS provides a systematic and controlled drug delivery system which minimize the chances of drug over exposure at the diseased site.

6. Optimized release in case of short half-life drugs, causes flip flop pharmacokinetics and also make sure patient compliance with minimize the dosage frequency.

**Disadvantages of GRDDS**\(^8\)

1. Unsuitable for the drug which are unstable at acidic environment.

2. Drugs that are equally absorb nicely through GIT. E.g. Nifidipine, Isosorbide.

3. The release of drug is selective in the colon.

4. For the perfect acting of the drug of GRDDS, the FDDS require high level of fluid in stomach.

5. Some drugs give irritation at slow release. E.g. Aspirin and NSAID’s.

**Factor controlling GRDDS**\(^9,10,11\)

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**Figure 2: Factor controlling GRDDS.**
1. **Density:** The drug with the high density is settled down at the bottom, whereas the drug with low density is floated on the surface. Suitable density required for floating property is less than 1.0 gm/cm³.

2. **Size:** The diameter should be more than 7.5mm size.

3. **Shape:** The spherical & round shaped drug is best for GRDDS as compare to the other shapes.

4. **Single or multiple unit formulation:** Multiple units are desirable due to foretell release profile.

5. **Fed or Unfed State:** During unfed state, the gastric retention time is less due to the increase in gastric motility.

6. **Nature of Meal:** The compound that containing high amount of fatty acid and other indigestible polymers generally slower the gastric retention time due to variation ingastric motility.

7. **Frequency of Feed:** Low occurrence of migrating myoelectric complex (MMC) contributes to GRT up to 400 times, which in turn depends on the frequency of food intake.

8. **Gender:** The Gastric Emptying Time is different in males & females, and the GET is more in males as compared to females.

9. **Age:** GRT is high in geriatric patients and less in neonates and children. Age above 70 (>70) exhibit longer GRT.

10. **Posture:** GRT become vary between supine andupright position of the patient.

11. **Disease State:** Gastric disease such as diabetes, chron’s disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc, fluctuates the GRT.
Classification of GRDDS\[12,13\]

![Classification of GRDDS](image)

**Gastroretentive Approach Mechanism**

**Low-density systems/ floating systems**

The floating system was first introduced by the Davis in 1968. System causes buoyancy in gastric fluid. Density of pellets/tablets is lower than the density of stomach fluid. So here the drug is buoyant upon the surface for prolonged period of time and give the controlled released of drug during gastric retention time. The Low density system consist of two system:

1. Effervescent Systems
2. Non Effervescent Systems\[1,14,15,16,17\]
(1) Effervescent Systems
The effervescent system is use in both the single and multiple unit system because it contain an volatile liquid and a gas generating agent (Sodium carbonate, Citric acid, Calcium carbonate and Tartaric acid). The gas generating agent are generally used with the hydrophilic polymers because the device is getting direct contact with the GI acid and also control the release of the drug.\textsuperscript{[18,19]} Here, when the drug comes in contact with the GI fluid then the CO2 is released and entrapped in the hydrophilic polymer which provide the drug buoyancy and extend the drug release.\textsuperscript{[20]}

Generally, the effervescent system used in both the single & multiple unit system, so in the preparation of the single unit system the drug, hydrophilic polymer, gas generating agent and the other excipients are used whereas, in the preparation of multiple or bilayer unit system it consist of two layers i.e. one layer is of drug, hydrophilic polymer and the gas generating agent and the another layer is of quick releasing drug and excipients but without any polymer so to get the quick action also.\textsuperscript{[14,21]}

(2) Non effervescent Systems
The Non effervescent system was first developed by the Sheth & Tossounian in 1984.\textsuperscript{[22]} The Non effervescent system is a system where the gas generating agents are not required, but here the swellable & gel forming derivatives and polymers are used.\textsuperscript{[23]} Here the drug is not coated by the polymer but it is mix with the polymer. The non effervescent system also used in both the single & multiple unit system in the floating system and in the microballons microsphere.

The polymers used are HPMC, sodium carboxymethyl cellulose, polyethylene oxide, agar, alginic acid, etc and this are mixed with the polymer and perfectly fill in the capsules.\textsuperscript{[14,24]} Due to the mixing of the drug with the polymer when the capsules comes in contact with the GI fluid and it swells up and the drug start releasing and give its effect.\textsuperscript{[25]}

High density systems
High density system is a system in which the density of the drug is greater than that of gastric fluid.\textsuperscript{[14]} Hoelzel, in 1930 first discovered the effect of high density on GRT. Generally, the drug with high density had slower gastric retention time as compared to that of light density system. The High Density system improves the gastric retention time, but the drug with high density and high dose are very important.\textsuperscript{[26]}
Figure 4: GRDDS based on (a) low-density systems and (b) high-density systems.

**Expandable systems**

The expandable system is also known as “plug type system”, because of its ability to block the pyloric sphincter. The main purpose of using this type of system is to increase the gastric retention system (GRT). The swelling & the release of the drug is because of the diffusion. Here, also the hydrophilic polymers are used such as HPMC, carbopol, etc which act by absorbing the fluid in the body and swells up and then diffuse the layer and give release of the drug and in the same manner in unfolding system the polymers are mixed with the drug in the compressed form in the gelatin capsule so that in the fluid gelatin will dissolve and the drug will release. The swellable system give release upto 16 hr and with good floating property. Also to improve the floating property some hydrophilic polymers like sodium carbonate are used but with that the swelling of the drug decrease because of the low viscosity grade of chitosan. There are some drawbacks of the expandable system such as its biodegradable polymer, while storing it become hydrolysed, then it is difficult to manufacture such system, etc.
Bioadhesive/Mucoadhesive systems

The mucoadhesive/bioadhesive system was first developed by the Park & Robinson in 1984(31). Here the drug with this system act by adsorb or bind to the gastric epithelial cell surface so that it increase the gastric retention time (GRT) of the drug in the stomach.(14, 32) In this system the drug is incorporated in the polymer which we called as mucoadhesive agent and it may be synthetic or natural polymers. Generally, the drug is released when there is an bonding between the mucosal surface and the polymer so that due to this interaction the drug release.(33) This system act by two ways: The Interaction phase & Consolidation phase.(34) Common polymers used in the mucoadhesive system are chitosan, carbopol, polyethylene glycol, HPMC, polyacrylic acid, etc(14, 28). After the administration of the drug when the drug reach at the application site there it make a bond between the polymer & the mucosal layer and prolong the gastric residence time and the main advantage of the mucoadhesive agent is it is non irritant, non toxic, having site specific activity and bind to the mucin through hydrogen, electrostatic, hydrophobic & disulfide bond.

The mucoadhesion system when used in the combination with the floating system then it form the Mucoadhesion floating drug delivery system (MFDDS) and improve the gastric retention time.\(^{30,35,36,37}\) The major disadvantage of the mucoadhesion drug delivery system is that there is a chance that the drug may have connection with the oesophagus which may lead to the collateral lesions.\(^{12,45}\)

![Figure 5: Mucoadhesion System.](image-url)
Raft forming systems
The raft forming system is a type of system where the excipients of effervescent & the gel forming polymers are used to sustained the released of the drug at the targeted site. The drug with this system give action after comes in contact with the body fluid. After that the device swells up and form an viscous cohesive gel and the formation of this continuous gel layer is known as Raft.\textsuperscript{[14,39]} Here, the polymers (gel forming polymer) used are sodium alginate and few gas generating agent, so that the CO2 is liberated so that the raft is float on the fluid because of decrease in the bulk density. The CO2 is obtained when the gas generating agent (sodium carbonate)comes in contact with the GI fluid and the formed raft are float on the fluid which present in the stomach for more than a fewhours so that it should give the sustained or prolong release and such system is mainly used in the antacid drug.\textsuperscript{[28,39]}

Figure 6: Raft Forming System.

Magnetic systems
This system of drug delivery give action depend upon the magnet. The dosage form with this system consist of an drug(active pharmaceutical ingredient), excipient and the magnet. The magnet used in the drug which is later placed in the stomach are extracorporeal magnet so that the drug give an site specific activity & also improve the gastric retention time.\textsuperscript{[14,40]} But if the exact position of the magnet is fixed then there may be a chance of patient compliance, but yet the therapeutic activity of the magnetic system is not described.
**Ion-exchange resin systems**

In the ion exchange system, the resin (cross linked polymer) are used instead of simple polymer and the resin used may be anionic or cationic. Here the resin help to give the sustained release of the drug. At maximum time the drug release from the device is in the stomach so that the resin used are cationic. The manufacturing of the dosage form with system is by homogenously mixing the resin with the drug or API for definite period of time, so that the ions that are present in the drug are absorbed by the resin and remove the cation from the resin. Such resin with the drug are called as resinates. Now when anybody administered this drug, the drug comes in contact with the GI fluid or the acidic environment after that the drug ions that are bind to the resin are replaced by the hydrogen ions and when all the drug ions are replaced then the resin are eliminated out by the body.\cite{41}

The release of the drug is also depend upon some factors such as the particle size of the drug, cross linking density, etc. The disadvantage of this system is that it is difficult to take the assessment of the drug bind to the resin and it is important for the safety purpose.

**Evaluation Parameters of GRDDS**

The evaluation parameters of the GRDDS consist of two types: In Vivo Parameter & In Vitro Parameters.

**Evaluation parameter**

- **In vivo parameter**
  - In this parameter, the animal & human models are required to check the bio-availability of the drug & GRT.

- **In vitro parameter**
  - In this parameter, the weight, tensile strength, friability, drug content, content-uniformity, etc of the drug.
**Future Perspective of GRDDS**

The main problem face by the oral route of administration is gastric retention time (GRT) and gastric emptying time and it is problematic for the drug which are absorbed in the upper part of intestine. To overcomesuch problems, the GRDDS is used which improve the gastric retention time (GRT) and bioavailability of the drug.

The system that are involved in the GRDDS are low density system, high density system, expandable system, magnetic system, ion exchange resin system, etc. As the GRT is different for the fed & fasted state, so that there is no system which is best for that. For getting the proper action of the drug, all the system of GRDDS should follow the quality attributes so to understand the working and formulation of the drug. The quality attributes of the drug include its swelling property floating behavior, mucoadhesive strength, mucoadhesion time, etc whereas, the invitro study include the tensile strength, friability, drug content, etc. By applying the QbD the understanding of the manufacturing process become very easy and also very important to minimize the risk of failure. As we know that the all system of the GRDDS are very beneficial, but still the therapeutic studies of the magnetic system is not explained.

**CONCLUSION**

As discussed above that the GRDDS is very much useful to improve the bio availability, gastric retention time, gastric emptying problem face by the drug that are absorb in the upper intestine of the stomach. The GRDDS contain low & high density system, mucoadhesion system, expandable system, etc. Before applying such system it is compulsory to have an proper knowledge about the anatomy of the stomach. Presently, the GRDDS is very much beneficial for the single dosage form, whereas for the future it is very much important for the GRDDS to focus on the combinational dosage form. And lastly as we know that the GRDDS is very important and useful but by applying the QbD to GRDDS the understanding of the process and formulation become also easy.

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