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A REVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

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ABSTRACT

A Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. The purpose of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention.

Gastroretentive dosage forms release the drug in a controlled manner to their specific site of action. There are several ways to accomplish this, including: Floating systems, Muco-adhesive systems, Magnetic systems, Expandable systems. GRDDS can enhance regulated administration of medication with an absorption window by releasing the medication for a longer period of time prior to it reaching the absorption site. Prolonging a drug's residence duration in the stomach is the aim of a gastro-retentive drug delivery system (GRDDS).

KEYWORDS: Gastroretantive drug delivery system, Bio/Mucoadhesive System, Expanding System Gastrointestinal tract, high density system.

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in Pharmaceutical field to achieve improved therapeutic advantages such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastro intestinal tract (GIT) and have short half life are eliminated quickly from systemic circulation. Frequent dosing of these drugs is required to achieve therapeutic activity. To avoid these limitations, the development of oral sustained controlled release formulation is an attempt to release the drug slowly into the gastro intestinal tract and maintain an effective drug concentration in the systemic circulation for long time. After oral administration, such a drug delivery would be retain in the stomach and release the drug in a controlled manner so that the drug could be supplied continuously to its absorption site in gastro intestinal tract.[1] Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro intestinal tract for local and systemic effect. Gastro retentive dosage form can remain in the gastric region for a longer period and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades several gastro retentive drug delivery approaches been designed and developed, including high density (Sinking) system that is retained in the[2,3,4] mucoadhesive systems that causes bio adhesion to stomach mucosa, unfoldable, extendable or swellable system which limits emptying of the dosage forms through the pyloric sphincter of the stomach, super porous hydrogel system, magnetic system etc. The current review deals with the various gastro retentive approaches that have been recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems. Gastric emptying of dosage form is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which resides in the stomach for prolong period of time than conventional dosage forms. Several difficulties are faced to designing controlled delivery system for better absorption and enhance bioavailability.

Conventional oral drug delivery systems (DDS) is complicated By limited Gastric Residence Time (GRT), Rapid GI Transit can prevent complete drug release in absorption zone & Reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine, Gastro-retentive drug delivery. Gastroretentive drug delivery system has gained immense popularity in the field of oral drug delivery recently. Different innovative approaches like magnetic field assisted gastroretention, plug

type swelling system. These drug delivery system release medication in a predictable and controlled way. GRDDS are suitable for the those drugs which are absorbed from the stomach e.g. albuterol.

To develop GRDDS different materials like ion-exchange resins, mucoadhesive and high-density materials, raft forming substances, magnetic substances, and super porous hydrogels are used. These review provides a concise account of various attributes of recently developed approaches for GRDDS.

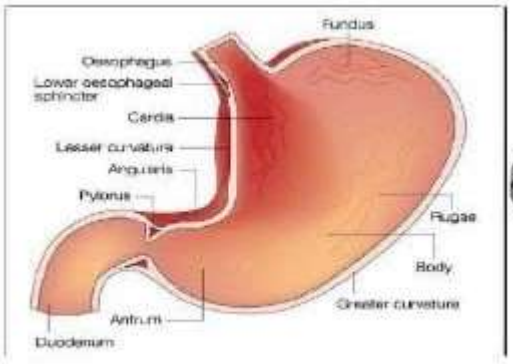


Fig.1 Structure of stomach

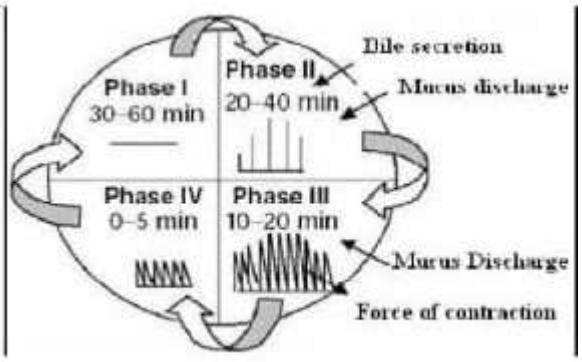


Fig.2 Schematic representation of inter digestive motility

Advantages

1. Bio -availability can be improved.
2. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
3. Treatment of gastrointestinal disorders such as gastro-oesophageal reflux, providing local action.
4. Ease of administration and better patient compliance.
5. Targeted therapy for local ailments in the upper GIT.
6. Sustained drug delivery /reduced frequency of dosing.
7. Controlled delivery of drugs.
8. Enhanced first pass biotransformation.
9. Delivery of drugs for local action in the stomach.
10. Site specific drug delivery.
11. Improved selective receptor activation cv

Disadvantages of GRDDS

1. In patients with achlorhydria can be questionable in case of swellable system.

2. Drugs intended for selective release in the colon.
3. Drugs have limited acid solubility.
4. Retention in stomach is not desirable for drugs that cause gastric irritation e.g. NSAIDS
5. Drugs undergo significant first pass metabolism E.g. Insulin
6. Requires the presence of food to delay gastric emptying.
7. Requriement of high levels of fluids in stomach for the delivery system to float and efficiently.
8. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
9. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
10. These systems do not offer significant over the conventional dosage forms for drugs, which are absorbed throughout GIT.

Drugs suitable for grdds

A GRDDS (Gastro retentive drug delivery system) is designed to prolong the residence time of the drug in the stomach or upper gastrointestinal tract ensuring that it can be released over on extended period. This approach is beneficial for drugs that are poorly soluble in the small intestine or for those that require sustained effect.

Here is a list of drugs suitable for GRDDS

1. Antibiotics

Metronidazole: Used in the treatment of helicobacter pylori infections requiring sustained release to ensure adequate levels in the stomach.

Amoxicillin: Another antibiotic for H-Pylori eradication therapy.

Tetracycline: Used for bacterial infections often formulated in GRDDS to maintain the drugs concentration in the stomach.

2. Non steroidal anti-inflammatory drugs (Nsaids)

Ibuprofen: Prolonged retention can help reduce gastric irritation by releasing the drug over time.

Aspirin: Used in cardiovascular protection, GRDDS can minimize side effect and provide controlled release to improve patient compliance.

Indomethacin: Known for gastric irritability, controlled delivery systems can reduce its side effects while providing continuous release.

3. Anti ulcer drugs

Omeprazole: A proton pump inhibitor used for treating gastric ulcers. GRDDS helps maintain its therapeutic concentration in the stomach for longer periods.

Ranitidine: An H2-receptor antagonist used in the treatment of acid-related disorders. GRDDS can offer extended acid suppression.

Lansoprazole: Another proton pump inhibitor, where GRDDS helps in long-lastin id control.

4. Anti diabetic drugs

Metformin: A widely used drug for type 2 diabetes, GRDDS allows for reduced fluctuations in blood glucose levels.

Glipizide: A sulfonylurea that benefits from controlled release, ensuring sustained action and reducing hypoglycaemia risks.

5. Antihypertensive drugs

Propranolol: A beta-blocker, where GRDDS can ensure continuous plasma levels and reduce dosing frequency.

Lisinopril: An ACE inhibitor, prolonged retention in the stomach improves patient compliance in hypertension management

6. Antifungal drugs

Itraconazole: Poorly soluble in the intestines but highly soluble in the stomach. GRDDS increases bioavailability by retaining the drug in the stomach.

Ketoconazole: Requires acidic pH for absorption, and GRDDS can help retain it in the stomach for effective treatment.

7. Anticancer drugs

Methotrexate: Used for cancer treatment and rheumatoid arthritis, where GRDDS helps in providing a controlled release of the drug.

Paclitaxel: For sustained release, ensuring prolonged therapeutic effects with fewer side effects.

8. Opioids

Morphine: Controlled delivery can help manage chronic pain with reduced risk of side effects like addiction and gastric irritation.

Oxycodone: GRDDS systems can be used to minimize addiction risk by providing extended pain relief**.**

9. Antiepileptic drugs

Phenytoin: A drug with a narrow therapeutic range, where GRDDS can help maintain plasma levels within a therapeutic window.

Carbamazepine: Helps prevent the peaks and highs in plasma levels associated with traditional delivery.

10. Cardiovascular drugs

Digoxin: A narrow therapeutic index drug used for heart failure, where GRDDS allows for more consistent therapeutic plasma levels.

Diltiazem: A calcium channel blocker for hypertension and angina, where controlled delivery improves efficacy and reduces side effects.

Gastroretentive products available in the market

	Brand Name	Active Ingredient(s)
1.	Cifran OD ®	Ciprofloxacin
2.	Madopar ®	L-DOPA and Benserazide
3.	Valrelease ®	Diazepam
4.	Topalkan ®	Aluminum -magnesium antacid
5.	Almagate FlatCoat ®	Aluminum -magnesium antacid
6.	Liquid Gavison ®	Aluminium hydroxide,
7.	Conviron	Ferrous sulfate
8.	Cytotec®	Misoprostal

Factors affecting grdds

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric- emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of

factors that affect their bioavailability and efficacy of the gastro retentive system (Sanjay et al, 2003)

Density

Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.

Size

Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form

Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formations

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state

Under fasting conditions, the Gl motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. (Caldwell et al., 1998; Murthy et al., 2000).

Nature of meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content

GRT can be increased by 4 to10 hours with a meal that is high in proteins and fats (Marvola et al., 1989) (Mojaverian et al., 1988).

Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

Mean ambulatory GRT in males (3.440.6 hours) is less compared with their age and race matched female counterparts (4.6-1.2 hours), regardless of the weight, height and body surface.

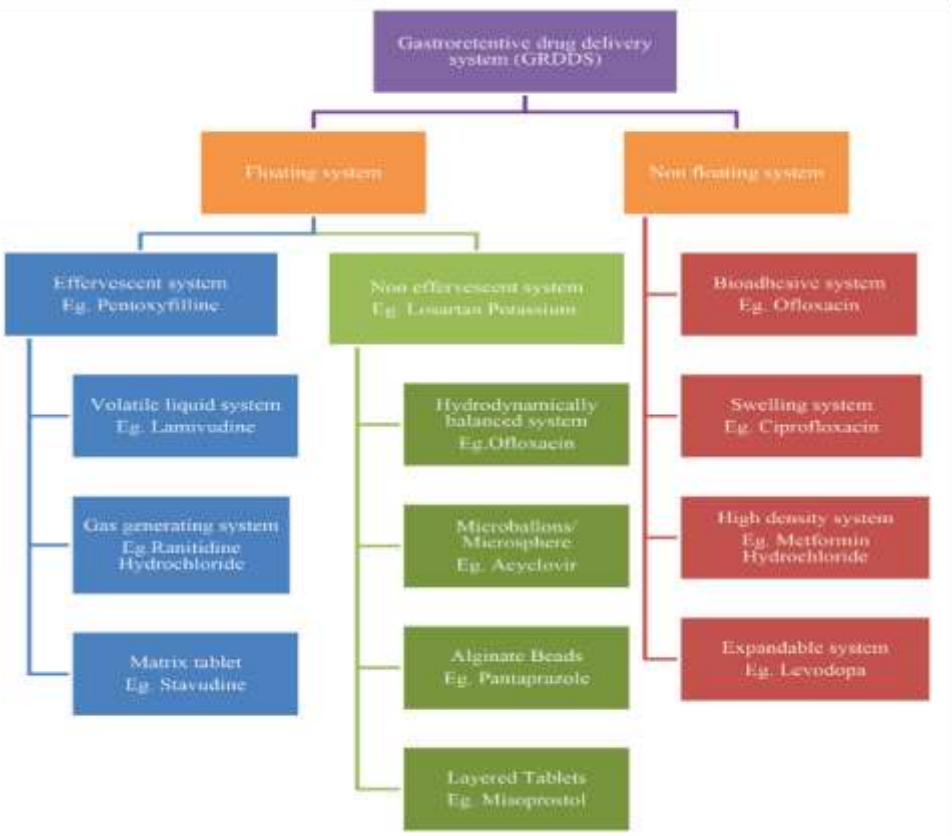
Age

Elderly people, especially those over 70, have a significantly longer GRT

BIOLOGICAL FACTORS

Diabetes and Crohn's disease, ete.

Approaches of grdds



A gastroretentive drug delivery system (GRDDS) is designed to prolong the residence time of a drug in the stomach, improving its bioavailability for drugs that are better absorbed in the stomach or upper small intestine. Below are the main approaches of GRDDS:

1. Floating systems

These systems are designed to float on gastric fluids, thereby maintaining their position in the stomach.

Effervescent systems: Generate gas (e.g., from sodium bicarbonate and citric acid) to maintain buoyancy.

Non-effervescent Systems: Use low-density polymers or materials that swell and stay afloat.

2. Swelling or expanding systems

These systems expand upon contact with gastric fluids, preventing passage through the pylorus. They remain in the stomach until they shrink or dissolve.

Use of hydrophilic polymers that absorb water and swell.

Can revert to their original size for easy excretion.

3. High-Density systems

These systems are denser than gastric fluids (>1.5 g/cm^3) and settle in the stomach.

4. Mucoadhesive systems

These systems adhere to the gastric mucosa using bio adhesive polymers (e.g., chitosan, Carbopol).

Provide prolonged retention by sticking to the stomach lining.

Suitable for drugs with localized effects in the stomach.

5. Magnetic systems

Incorporate magnetic particles that interact with an external magnet to keep the system in the stomach.

Complex and less commonly used due to technological challenges.

6. Super porous hydrogels

These are hydrophilic cross-linked polymers with high water absorption capacity. They swell rapidly to a large size after contact with gastric fluids.

Provide gastric retention by preventing passage through the pylorus.

7. Bio adhesive microspheres

Microparticles that stick to the gastric mucosa and release drugs gradually.

Often used for sustained drug release.

Polymers such as polycarbophil are employed.

8. Raft-Forming systems

These systems form a gel-like structure (raft) that floats on the stomach contents.

Often used for treating gastroesophageal reflux disease (GERD).

Typically composed of alginates, carbonates, or bicarbonates.

Advantages of GRDDS

Prolonged drug release.

Enhanced bioavailability for drugs absorbed in the stomach.

Minimized side effects due to targeted delivery.

Improved patient compliance with reduced dosing frequency.

Each approach has specific applications depending on the drug's physicochemical properties and therapeutic requirements.

Evaluation of grdds

Viscosity measurement: Viscosity can be measured to assess the adhesive strength of the formulation. A higher viscosity often indicates better mucoadhesive properties, as the formulation may be more likely to stick to the mucosal surface.

1. Flow behaviour

The formulation’s flow behaviour in the presence of mucin (a glycoprotein present in mucus) is evaluated to determine how well it interacts with the mucosal environment.

2. Tensile strength test

This method measures the force required to detach the formulation from a mucosal surface, often by using a texture analyser. The higher the force required for detachment, the better the mucoadhesion.

3. Ex vivo mucosal adhesion test

Pig stomach or intestinal tissue: Using ex vivo mucosal tissues (Such as pig stomach or intestinal mucosa), the GRDDS is placed on the tissue, and the adhesive force is evaluated by measuring the force needed to detach the formulation from the tissue.

Mucin-coated slides: A slide coated with mucin is used as a model to evaluate the mucoadhesive properties of the system. The formulation is placed on the slide, and the adhesive force is tested by a force measurement apparatus or using a texture analyzer.

4. Bioadhesion test (In vitro permeation study)

This method tests the ability of the GRDDS to adhere to the mucosal surface while also releasing the drug. The permeation of a model drug through a mucosal membrane (e.g., porcine intestine) can be studied to evaluate both mucoadhesion and drug release characteristics simultaneously.

5. In vitro drug release studies

While primarily focused on release kinetics, drug release studies can also help evaluate mucoadhesion by showing whether the formulation remains in contact with the mucosal surface long enough to deliver the desired dose**.**

Dissolution studies

Dissolution studies of Gastroretentive Drug Delivery Systems (GRDDS) are essential for assessing the drug release profile, which influences the system's efficacy in providing prolonged therapeutic effects. GRDDS are designed to remain in the stomach or upper gastrointestinal tract for extended periods, providing sustained drug release. The dissolution studies help evaluate how the formulation performs under conditions that simulate the physiological environment of the stomach or intestines.

USP Apparatus I (Basket Method): This method is often used for GRDDS that are in a capsule or soft gel form. The GRDDS is placed in a basket, which is rotated in a dissolution medium to simulate gastric conditions. It's particularly useful for testing systems that float or remain buoyant in the stomach.

USP Apparatus II (Paddle Method): This method is commonly used for tablet-based GRDDS. The GRDDS is placed in a dissolution vessel with a paddle stirring the medium at a specified speed. This is typically used for systems that dissolve, swell, or erode to release the drug over time.

USP Apparatus III (Reciprocating Cylinder): This setup is used for floating or bioadhesive GRDDS, where the system is exposed to alternating high and low agitation speeds, mimicking the natural peristalsis of the gastrointestinal tract.

USP Apparatus IV (Flow-through Cell): This is used when the GRDDS is designed to release the drug in a controlled manner (e.g., osmotically controlled systems). It is used for systems that might require continuous flow to simulate the conditions of the gastrointestinal tract.

Marketed formulations

Sr no	Brand name	Drug	Remark	Company
1	Cifran OD®	Ciprofloxacin	Gas generating floating tablet	Ranbaxy
2	Valrelease®	Diazepam	Floating Capsule	Hoffman-LaRoche USA
3	Oflin OD®	Ofloxacin	Gas generating floating tablet	Ranbaxy
4	Cytotec®	Misoprostol	Bilayer Floating Capsule	Pharmacia USA
5	Conviron	Ferrous Sulphate	Colloidal gel forming FDDS	Ranbaxy, India
6	Topalkan	Al- Mg antacid	Floating liquid	Pierre Fabre Drug.

CONCLUSION

According to the review of different published literature and detailed investigations on commercial products, However several advantages of GRDDS for patients have been evidenced in the majority of them**.** Individual drug candidate or a combination of the drugs needs to be assessed case by case regarding the necessary dose and the ease of manufacturing process. Polymer selection remains a critical factor for the formulations that contain high dose. This selection is essential for the compressibility needed to exploit the high doses of the APIs. However, the criteria of ideal polymer should be based on its amount in the dosage form; a minimum quantity that provides a substantial gastric retention.

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