International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 01-10 www.ijprajournal.com ISSN: 2249-7781

Review on: Gastroretentive Drug Delivery System

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Date of Submission: 20-06-2021 Date of Acceptance: 03-07-2021

ABSTRACT
Gastroretentive drug delivery system (GRDDS) help in treatment of gastritis and peptic ulcer disease. Gastroretentive dosage forms that can be retained in a stomach for prolonged and expected period of time. Recently many new and old drug molecules,either mono or combination product are formulated as gastroretentive drugs delivery system. Thus, this dosage form significantly extend the period of time over which the drug may be released in comparison to controlled release drug delivery system, and maintain therapeutic concentration for prolonged period of time.
KEYWORDS: Gastroretentive, Flotation, Mucoadhesion, Drug delivery system.

I. INTRODUCTION

Controlled and modified release formulation are widely used in modern era to improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Those drugs that are easily absorbed from gastroretentive tract (GIT) and having short half life are quickly eliminated from the systemic circulation. So that frequent dosing of these drugs is mainly required to achieve suitable therapeutic activity. To avoid this limitation, the development of the oral sustained - controlled release formulation is an attempt to release the drug slowly into the Gastrointestinal tract (GIT) and maintain the effective drug concentration in the systemic circulation for a long time. After oral drug delivery would be retained in the stomach and release the drug in controlled manner, so that the drug could be supplied continuously to the absorption sites in the Gastrointestinal tract (GIT). These drug delivery system suffer from the two adversities : the short gastric retention time and unpredictable short gastric emptying time, which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. Prolonged gastric retention improves bioavailability, increase in the duration of drug release, reduce drug waste and improve the solubility of the drugs that are less soluble in pH environment, local action in the upper part of the small intestine e.g. treatment of peptic ulcer.

Gastroretentive Drug Delivery System is an approach to prolonged the gastric residence time, therebytargeting site-specific drugs release in upper Gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of drug.

The strategies for delaying drug transit through the GIT fall into following categories.

1. Pharmacological approach
2. Physiological approach
3. Pharmaceutical approach

The first two approaches are not used commonly because of toxicity problems. The various pharmaceutical approaches are used for gastroretention can be as follows.

1. Low density system/ Floating dosage forms
2. High density systems
3. Modified shape systems
4. Mucoadhesive systems
5. Expandable, unfoldable and swallable systems
6. Magnetic systems

- **Factors Affecting the Gastro retentive system**

Researchers not only using old approaches but also using modified approaches to retain the dosage form in the stomach as a way of increasing the retention time. Like use of floating dosage forms , mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and coadministration of gastric-emptying delaying drugs, Raft forming system . While using these approaches GRDDS affected by various factors like

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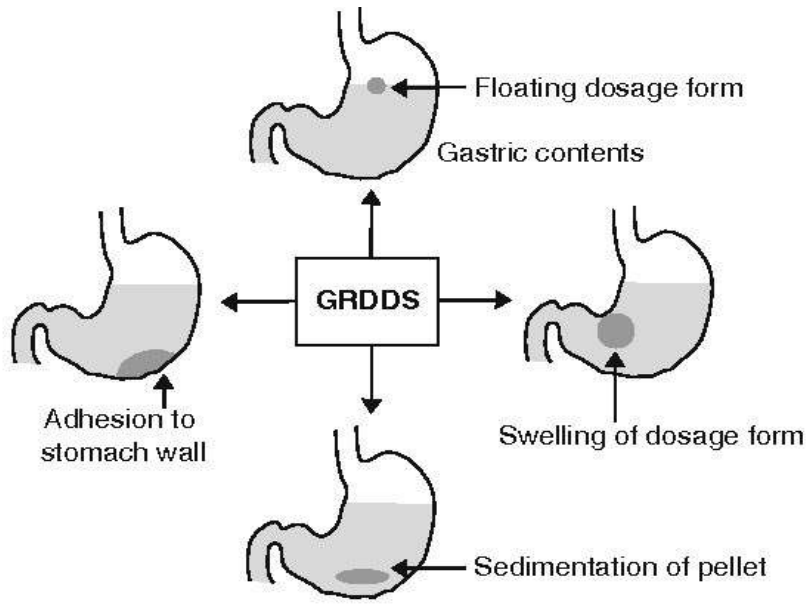
1. Density – Gastric retention time is a function of dosage form buoyancy that is dependent on thedensity.
2. Size – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
3. Shape of dosage form – Tetrahedron and ring 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.
4. Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes that occurs every 1.5 to 2 hours.
5. Nature of meal – Presence of food affect GRDDS 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.
6. Caloric content – If the meal contain high in proteins and fats GRT can be increased by 4 to10hours.
7. 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.
8. Gender – Mean ambulatory GRT in males (3.4±0.6 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.
9. Age – Significantly longer GRT Elderly people, especially those over 70.
10. Posture – GRT can vary between supine and upright ambulatory states of the patient.
11. Biological factors – Diabetes and Crohn's disease, etc.
12. Concomitant drug administration – Floating time is affected by Anticholinergics drugs like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide anditopride.

Classifications



Classification of gastroretentive drug delivery systems (GRI

International Journal of Pharmaceutical Research and Applications
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Table 1. Commonly used drug in formulation of gastro retentive dosages forms

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, pAminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol,Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin,Prednisolone
Powders	Several basic drugs
Films	Cinnerzine

Table 2. Gastroretentive products available in the market

Brand Name	Active Ingredient(s)
Cifran OD	Ciprofloxacin
Madopar	L-DOPA and Benserazide
Valrelease	Diazepam
Topalkan	Aluminum -magnesium antacid
Almagate FlatCoat	Aluminum -magnesium antacid
Liquid Gavison Conviron	Aluminium hydroxide, Ferrous sulfate
Cytotec	Misoprostal

Approch to gastric retention

1. **High-density system**
2. **Expandable system**
3. **Magnetic system**
4. **Bioadhesive system**

1. High-density system :

High-density lipoprotein (HDL) is a comparatively dense and small lipoprotein that can carry lipids as a multifunctional aggregate in plasma. Several studies have shown that increasing the levels or improving the functionality of HDL is a promising target for treating a wide variety of diseases. Among lipoproteins, HDL particles possess unique physicochemical properties, including naturally synthesized physiological components, amphipathic apolipoproteins, lipid-loading and hydrophobic agent-incorporating characteristics, specific protein-protein interactions, heterogeneity, nanoparticles, and smaller size. Recently, the feasibility and superiority of using HDL particles as drug delivery vehicles have been of great interest. In this review, we summarize the structure, constituents, biogenesis, remodeling, and reconstitution of HDL drug delivery systems, focusing on their delivery capability, characteristics, applications, manufacturing, and drug-loading and drug-targeting characteristics. Finally, the future prospects are presented regarding the clinical application and challenges of using HDL as a pharmacodelivery carrier.

Keywords: Drug delivery; HDL; Nanoparticles; Reconstitution.

2. Expandable system :

Oral route has been the most convenient and accepted route of drug delivery. Owing to tremendous curative benefits of the oral controlled release dosage forms are being preferred as the interesting topic in pharmaceutical field to achieved improved therapeutics advantages. Gastroretentive drug delivery system is novel drug delivery systems which has an upper hand owing to its ability of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. Attempt has been made to summarize important factors controlling gastroretentive drug delivery systems. This review covers the advantages, disadvantages, marketed preparation

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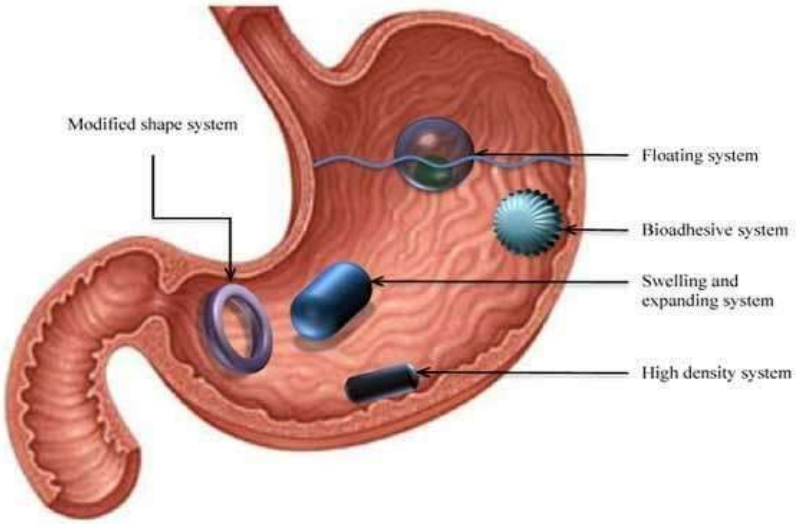
and some patents of gastroretentive drug delivery system and represents the floating and non-floating gastroretentive system and also highlights some of the current gastroretentive approaches. Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive systems, floating systems (low density systems), non-floating systems (high density systems) , magnetic systems, swelling systems, unfoldable and expandable systems, raft forming systems and superporous systems, biodegradable hydrogel systems.

3. Magnetic system :

In these systems, a slight internal magnet in the system and a magnet located on the abdomen above the position of the stomach, is employed. In this system, an extracorporeal magnet is used which enlarges the GRT of the dosage form27 investigated a magnetic system of acetaminophen tablets. Thesetablets were prepared by direct compression process using ultrafine ferrite, microcrystalline cellulose and hydroxypropyl cellulose-H polymers. The authors studied the result of gastric residence of acetaminophen magnetic tablets on drug bioavailability; a stable magnet (neodymium iron-boron magnet) was applied to the stomach of beagle dogs for 8 h after administration of the magnetic tablets.

4. Bioadhesive system :

These methods usually contain a synthetic and natural polymer that are accomplished to tie on the mucus lining, gastric epithelial cell surface, and enlarge the GRT. These systems use the natural and synthetic polymers, i.e., hydrophilic gelling constituents by forming hydrogen bond with various groups, such as sulfate, hydroxyl, carboxyl and amide groups (e.g., cross-linked carrageenan, sodium alginate, Na CMC and polyacrylic acids) that can stick on the epithelial surface of the GIT, fabricated bioadhesive methods of Ofloxacin tablets using hydroxypropyl methyl cellulose (HPMC K100M), crospovidone and psyllium husk polymers. Optimized formulations showed the drug release for 24 h. Fabricated floating mucoadhesive systems of Dipyridamole tablets using HPMC K4M and carbopol 934P. The improved formulations showed 99.92% drug released at 12 h.



Anatomy of the stomach

The gastro intestinal tract can be divided into three main regions

a) Stomach
b) Small intestine- duodenum, jejunum, and ileum
c) Large intestine

The GIT is a muscular tube of about 9m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layercalled oblique muscles and itis situated in the proximal part of the stomach, branching over the fundus and higher regions of the gastric body. The stomach is divided

International Journal of Pharmaceutical Research and Applications
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into fundus, body and pylorus [8]. The stomach is a shaped organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it and releases slowly in to the duodenum. organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it and releases slowly in to the duodenum.

Physiology of the stomach

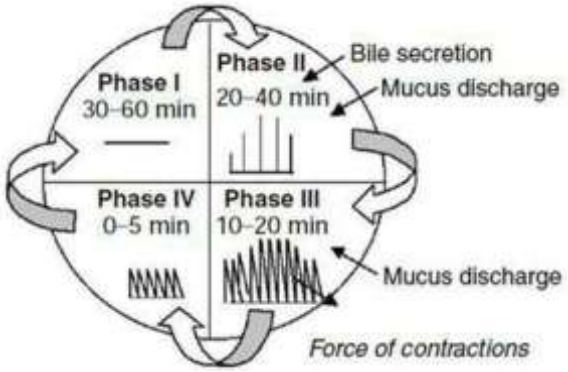
The stomach is an expanded section of the digestive tube between the esophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds calledrugae. There are 4 major types of secretory a epithelial cell that covers the stomach and extends into gastric pits and glands.

1. Mucous cells- secrete alkaline mucus
2. Parietal cells – secrete HCL
3. Chief cells- secrete pepsin
4. G cells- secrete hormone gastrin.

- **Gastric motility and gastric empty rate**

Two distinct patterns of gastrointestinal motility and secretion exist to the fasted and fed state

Figure 2: Phases of Gastic motility and gastric emptying rate



The bioavailability of the orally administered drug depend upon the state of feeding. In the fasted state,it is characterized by an interdigestive series of electric event called inter digestive myoelectric cycle or migratingmotorcomplex. It is divided into 4 phases

a) Phase I (basal phase) it lasts from 40-60 minwith rare contractions
b) Phase II (preburust phase) last from 40-60minwith intermittent potential and contractions.
c) Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions theundigestive food is swept from stomach to intestine. These are known as house keeper waves.
d) Phase IV it lasts for 0-5 min and occurs between phases III and I for two consecutive cycles. After the ingestion of the mixed meal the pattern of contraction changes from fed to that of fasted state, this is known as digestive motility pattern, these contractions reduces the size of the food

particles toless than 1mm after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate.

EVALUATION PARAMETERS OF GASTRORETENTIVE DOSAGEFORMS

A) In- Vitro Evaluation

1) General tests: These tests include appearance, hardness, friability, drug content, weightVariation, uniformity of content.

2) Floating systems

a) Buoyancy Lag Time: Buoyancy lag time is determined to assess the time taken bythe dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time: The time for which the dosage form continuously floats on the dissolution media is termed as floating time. It is usually performed in Simulated Gastric Fluid maintained at 370°C.

c) Specific Gravity / Density: Density can be determined by the displacement method using Benzenes displacement medium.

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3) Swelling systems

a) Swelling Index: After immersion of swelling dosage form into Simulated Gastric Fluid at 370C , dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

B) In-Vivo Evaluation

1) **Radiology:** Barium Sulphate is widely used as Radio Opaque Marker. X-ray is used for examination of internal body systems. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view gastric retention.
2) **Gastroscopy:** Gastroscopy is used to inspect visually the effect of prolongation in stomach.
3) **Scintigraphy:** Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99 Tc.
4) **Ultrasonography:** It is not used generally because it is not traceable at intestine.
5) **Magnetic Marker Monitoring:** This technique is radiation less and so not hazardous. In this technique, dosage form is magnetically marked by incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment.

In vivo evaluation of gastric retention

Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ-scintigraphy and X-ray. 1) In γ-scintigraphy, a small amount of stable isotope is compounded in the dosage forms during its preparation. The inclusion of a γ-emitting radio-nuclide in a formulation allows indirect external observation using a γ-camera or scinti scanner. For x-ray, barium sulfate is used as a contrast medium. It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form. In addition, gastroscopy and ultrasonography studies can be included in the in vivo evaluation of GRDDS. Gastroscopy comprises of per- oral endoscopy, used with a fiber optic and video systems. Ultrasonography is not routinely used in the evaluation of GRDDS. In vivo plasma profile can also be obtained by performing the study in suitable animal model.

Water uptake study: It is done by immersing the dosage form in simulated gastric fluid at 37OC and determining the dimensional changes, such as diameter and thickness, at regular interval of time. After the stipulated time the swollen tablets are weighed and water uptakeis measured in the terms of percentage weight gain, as given:

$WU = (Wt-Wo) \times 100/Wo$

In which, Wt and Wo are the weight of the tablet after time t and initially, respectively. The tablets are also evaluated for hardness, friability, weight variation etc. which are applicable for conventional instant release tablets. For the multiple unit dosage forms like microsphere following tests are also essential apart from the above tests:

1) Morphological and dimensional analysis: It is done with the aid of scanning electron microscopy and optical microscope.
2) Percentage yield of microsphere.
3) Entrapment efficiency: The drug is extracted by suitable method and analyzed to find out theamount of drug present.

Figure : Patents on Grdds

Sr.No	Patents	
1	Gastrorentevive dosage form systems and process of preparation thereof.	US20140271871846
2	Gastrorentevive sustained and pulsatile drug delivery systems	W02013051036 A1
3	GRDDS and their dosage form their method of preparation using calcium carbonate.	W02014057086 A1
4	A novel gastro retentive drug delivery of macrolide.	W02011125075 A3
5	Gastrorentevive controlled release microsphere for improved drug delivery	US6207197 B1
6	Extended release gastro retentive oral drug delivery systems for valsartan	EP2061438 A1
7	GRDDS.	W02009089665 A2
8	GRDDS comprising an extruded hydratable polymer.	US8586083 B2

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Volume 6, Issue 4 July-Aug 2021, pp: 01-10 www.ijprajournal.com ISSN: 2249-7781

Advantages of GRDDS

1. It is used for the treatment of peptic ulcer disease.
2. Commonly used for drugs with narrow absorption window in the small intestine.
3. Minimize dosing frequency.
4. Improved bioavailability of the drugs.
5. Used for drugs which are normally unstable in intestinal fluids.
6. Used to provide sustain the delivery of drug.
7. Used for maintaining maximum therapeutics drug concentration within the therapeutic window.

Disadvantages of GRDDS

1. Floating drug delivery systems has limitation, that they require high level of fluids in stomach for floating and working more efficiently. So more water intake is needed with such dosage form.

2. In sleeping, floating dosage form may swept away (if not of larger size) by contractile waves. So such dosages form should not take just before going to bed.

3. Drugs that are unstable in high acidic environment, very low solubility in acidic environment and causes irritation to gastric mucosa cannot be incorporated into GRDDS.

4. Swellable dosage form must be capable to achieve larger size than pylorus aperture before they exist from stomach.

5. The success rate of bio or mucoadhesive is less because of high turnover rate of mucus layer.

GRDDS

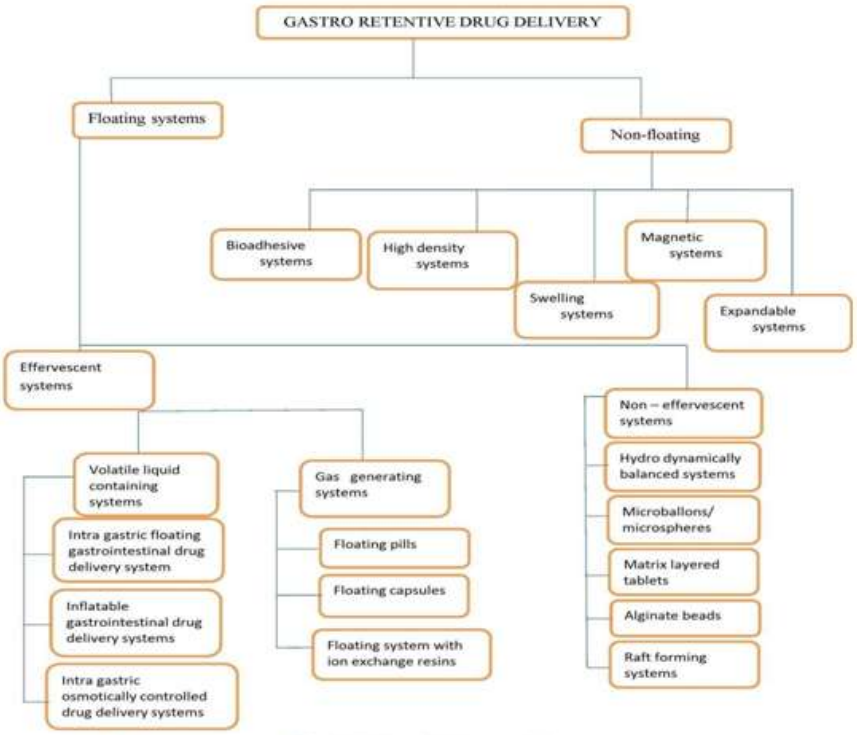

Figure : Flowchart showing different approaches for gastro retentive drug delivery systems

II. CONCLUSION

Gastro retentive drug delivery system offers a potential advantage of enhanced bioavailability and controlled delivery of drug. Gastro retentive drug delivery system showed the potential to increase the gastric retention of drug. Growing understanding of impact of GIT physiology on drug delivery will ensure development of an increasing number of drug delivery system to optimize drug delivery of molecules exhibiting regional variability in drug absorption. The increasing sophistication of delivery technology will ensure the development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and

extensive first pass metabolism. Based on the literature surveyed, we concluded that Gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bio availability . Gastro retentive drug delivery system gives maximum benefit to patient.

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