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Review on Gastroretentive Drug Delivery System

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Abstract: *In the current days, gastro retentive drug delivery system receives great attention because they increase the performance of control release dosage forms, which can take orally. The main purpose of gastro retentive drug delivery system is to improve bioavailability of drug. Gastric Retention along with oral control drug delivery is advantageous to many drugs having low absorption window hence poor bioavailability. The concept of novel drug delivery system arose to overcome certain aspects related to physicochemical properties of drug molecules and the related formulation. Gastro retentive drug delivery system is one of such novel approaches to prolong gastric resident time, there by targeting site specific drug release in the stomach for local or systemic effect. Gastro retentive drug delivery systems are promising systems that float immediately upon contact with gastric fluids which may increases the bio availability of encapsulated drug along with absorption in the intestine. The present review addresses briefly about the classification, formulation consideration for GRDDS, factors controlling gastric retention, merits, demerits and applications of gastro retentive drug delivery system.*

Keywords: Gastroretentive, Flotation, Mucoadhesion, Drug delivery system, Current approaches in GRDDS

I. INTRODUCTION

The goal of any delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. The oral drug delivery system is the oldest and most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Oral dosage forms are intended for systemic effects resulting from drug absorption through gastrointestinal tract. Gastro retentive Drug Delivery System is an approach to prolong the gastric residence time, thereby targeting site-specific drugs release in upper Gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of drug. Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include floating systems, bioadhesive systems, swelling, expanding systems, delayed gastric emptying systems and low density super porous systems. The strategies for delaying drug transit through the GIT fall into the following categories.

- Pharmacological approach
- Physiological approach
- Pharmaceutical approach

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

Advantages of GRDDS: -

1. Improves the bioavailability of drug and which is metabolized in the upper part of the GIT.
2. Reduces dosing frequency for the drug with a relative short duration half – life, thereby, improving patient's compliances.
3. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects.
4. A longer stay in the stomach may be beneficial for local actions in the upper small intestine, such as the treatment of peptic ulcer disease.
5. Greater effectiveness of treatments.
6. Enhanced bioavailability.
7. Enhanced first pass biotransformation.

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8. Sustained drug delivery/ reduced frequency of dosing.
9. Targeted therapy for local ailments in the upper GIT.
10. Reduced fluctuations of drug concentration.
11. Minimized adverse activity at the colon. Its specific drug delivery.

Disadvantages of GRDDS:

1. Floating system has limitation that it requires high fluid level in stomach for floating and absorption efficiently.
2. The swelling formulation can be swelled in the system before reaching the site of the stomach.
3. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin
4. Unsuitable for drugs that are unstable in acidic environment. E.g. Erythromycin
5. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin & NSAID's.
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9. Drugs that absorb selectively in colon. Eg. Corticosteroid.

Factors affecting the gastric retention time

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 administration of gastric-emptying delaying drugs, Raft forming System. While using these approaches GRDDS affected by various factors like –

1. **Density**: - Gastric retention time is a function of dosage form that depends on the density. The density of the dosage form should be less than that of gastric contents.
2. **Size:** - Size must to be higher than 7.5 mm in thickness.
3. **Shape of the dosage form:-** Either in circles or sphere-shaped formulation exhibit Improved property associated to other shapes.
4. **Fed or unfed state :-** Under fasting conditions, the GI motility is characterized by periods of strong motor activity that occur every 1.5 – 2 hours. The MMC (Migrating Motor Complex) sweeps undigested material from the stomach and if the timing of formulation coincides with that of MMC, the GRT of the units can be very short, however in the fast state MMC is delayed and GRT is longer.
5. **Nature of Meal:** - Feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying, rate and prolonging drug released.
6. **Caloric content:** - If the meals content high proteins and fats GRT can be increased by 4 – 10 hours. 7. Frequency of Meals: - 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.
7. **Gender**: - Mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.
8. **Age**: - People with age more than 70 have a significantly longer GRT.

Concomitant drug administration:

Floating time is affected by anticholinergic drug like atropine and propantheline, opiates like codeine can prolong.

Conditions for GRDDS :

- Drugs that act locally in the stomach (antacids and drugs for pyloric viz.,Misoprostol)
- Drugs those are primarily absorbed in the stomach (Amoxicillin)
- Drugs that are poorly soluble at intestinal fluids (Furosemide, Diazepam, Verapamil)
- Drugs which show a narrow window (Cyclosporine, Methotrexate,)
- Drugs that are absorbed rapidly in the GI tract (Metronidazole, Tetracycline)
- Drugs that usually degrade in the colon (Ranitidine, Metformin HCL)

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- Drugs that disorganize normal colonic microbes (Antibiotics against helicobacter pylori)
- Drug that are absorbed from the proximal part of the gastrointestinal tract(GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain condition.
- Treatment of peptic ulcers caused by H.pylori infection.

Floating drug delivery system

- Effervescent system
- Non-effervescent system

Non floating system

- High density system
- Swelling system
- Bio/mucoadhesive system
- Magnetic system

Floating drug delivery system

The management of illness through medication is entering a new era in which growing number of novel drug delivery systems are being employed and are available for therapeutic use. Oral sustained release gastro-retentive dosage forms (GRDFs) offer many advantages for drugs with absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach, improving the bioavailability of the medication. Floating Drug Delivery Systems (FDDS) is one amongst the GRDFs used to achieve prolonged gastric residence time. The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in-vitro techniques, invivo studies to evaluate the performance and application of floating systems, and applications of these systems.

Effervescent system

Effervescent floating drug delivery systems release gas CO2, thus reduce the density of the system and remain buoyant in the stomach 2 for a prolonged period of time and released the drug slowly at a desired rate so it can be used to prolong the gastric residence time in order to improve the bioavailability of drug. In the present article we will discuss in detail about effervescent agent and mechanism of effervescent floating drug delivery system. Oral sustained release gastro-retentive dosage forms offer many advantages for drugs with the absorption from upper parts of the gastro intestinal tract. Gastric emptying is a complex process and it is highly variable. The floating drug delivery systems are useful methods to avoid this variability which increases the retention time of the drug delivery systems for more than 12 hours. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, classification, advantages, in vitro and in vivo evaluation parameters, and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form and the future potential of FDDS. At attempt has been made in this review article to introduce the readers to current development in floating drug delivery system.

Gas generating System

The main mechanism is involved in this System is the production of CO2 gas due To reaction between sodium bicarbonate, Citric acid and tartaric acid. The gas Produced results in the reduction of Density of the system, thereby making it Float on the gastric fluids. Salts and Citric/tartaric acid release CO2, which Entrapped in the jellified hydrocolloid layer Of the system which decrease its specific Gravity and making it float over chime24The system

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consist of a sustain release Pill as seed surrounded by double layer. The inner layer is an effervescent layer Containing sodium bi carbonate and Tartaric acid. The outer layer is of a Swellable membrane layer containing PVA shellac .

Volatile liquid containing system

These have an inflatable chamber which Contains a liquid e.g. ether, cyclopentane, That gasify at body temperature to cause The inflation of the chamber in the Stomach. These systems osmotically Control floating system containing a Hollow definable unit. These are two Chambers in the system first contain the Drug and the second chamber containing The volatile system.

Non effervescent

Microballoons is a novel technology of pharmaceutical field in the floating drug delivery for achieving gastric retention. Microballoons are gastro retentive drug delivery systems that are based on the non-effervescent approach. Generally microballoons are in spherical shape without a core. These Microballoons are free flowing powder which consists of protein and synthetic polymers and the size ranges from 200 µm. These Microballoons are low density systems which have sufficient buoyancy to float over the gastric fluid for prolonged period of time without any irritation to gastrointestinal tract. Microballoons are prepared by using different techniques such as simple solvent evaporation method, double emulsion method, phase separation coacervation method, polymerization method, spray drying method, spray congealing method and hot melt encapsulation methodi. Hydrodynamically balanced system-It Is a formulation of a drug with gel Forming hydrocolloids meant to remain Buoyant in the stomach contents .Drug Delivery Systems have a bulk density Lower than gastric fluids and thus remain Buoyant in the stomach for a prolonged Period of time, without affecting the gastric Emptying rate. While the system is floating On the gastric contents, the drug is Released slowly at a desired rate from the System. After the release slowly at Desired rate from the system. After the Release of the drug, the residual system is Emptified from the stomach. The results in An increase in the GRT and a better Control of fluctuations in the plasma drug Concentrations.

Micro balloons-Micro balloons (Hollow microsphere) are In the strict sense, empty particles of Spherical shape without core. These Microspheres are characteristically free Flowing powders comprising of proteins or Synthetic polymers, ideally having a size Less than 200 micrometres. Micro balloonsLoaded with drug in their outer polymer Shell are prepared by a novel methods Such as solvent evaporation to create a Hollow inner core. The drug and an enteric Acrylic polymer mixture are dissolved in Ethanol /dichloromethane solution.

Non – Floating Drug Delivery System

In non – floating drug delivery system the dosage form of gastro retentive drug delivery System does not float in the stomach but stays remain in the stomach by different mechanism. The drug may settle down in stomach showing bioadhesive and mucoadhesive properties, In this system dosage form release drug in sustain manner it also releases it drug at targeted site. It is also a pH dependent drug delivery system it gets dissolved at a certain pH.

A. High density or sinking systems – In this approach, the density of formulation must be superior to the density of normal gastric content. These formulations are developed by coating drug on a heavy core or mixed with inert substances such as iron powder, barium sulfate, Zinc oxide, and titanium oxide. This system has its disadvantage that the size of dosage form is increased to achieve the high density. But the effectiveness of this system in human beings was not observed and no formulation has been marketed.

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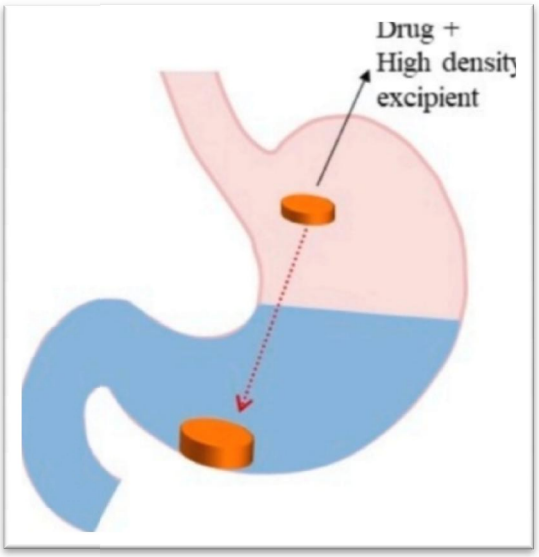

Swelling system

These are the dosage forms, which after swallowing swells to such an extent that their exit from the pylorus is prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. These systems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter. Controlled and Sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release. On coming in contact with gastric fluid the polymer imbibes water and swells**)**

Bio/mucoadhesive systems

Bio/mucoadhesive systems bind to the gastric Epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact Between the dosage form and the biological Membrane. A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive Polymer) or the mucus lining of the GIT (mucoadhesive polymer

Magnetic Systems

Dosage forms contain a small internal magnet and a magnet is placed in abdomen over the position of stomach that retains dosage form in gastric region.

Disadvantage

External magnet need to be positioned with a degree of precision.
Patient noncompliance
Not very used

Challenges involved in GRDDS

The GRDDS are stomach specific and required to retain in the stomach only. Therefore, the retention of the dosage form in the stomach or in the upper part of the small intestine for a long period of time until all drug from the system is released at pre-determined rate is the biggest challenge in formulating GRDDS. The gastric emptying process is highly variable and depends on various factors. However, the main factor is dosage form and fasted or fed state of the stomach. The gastric emptying time is also influenced by the factors such as food, caloric content, gender, and age. The process of gastric emptying is also prolonged by high fat and high calories containing food. The GRT is varying and related to the patients age, gender, size and shape of dosage forms, individual disease state and body mass index. The GRT is also affected by the pylorus. Another fact is the animals (dog or rabbit) that have different size of the pylorus

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and its peristaltic movement than that of human beings. Indigestible polymers and fatty acid salts also alter the motility pattern of the stomach under fed conditions and assist in decreasing gastric emptying rate. Therefore, it is necessary to conclude the results carefully.

EVALUATION

Floating lag time (FLT), Total floating Time (TFT) floating strengthFor low-density system, raft-forming SystemThe test was carried out in a simulated Fluid (SGF) at 370C. The time between Introduction of dosage form and its Buoyancy on the SGF (FLT) and the time During which the dosage form remains Buoyant (TFT) were measured. The Floating strength is measured using Specifically designed basket holder Connected with analytical balance. The Reduction of weight on the analytical Balance over time determines the floating betweenStrength.

Swelling studies-For super porous hydrogel system, Expandable system.The test is carried out by placing the Weighed amount of dosage form into the Swelling medium (0.01N HCl) and weight, Diameter, and length of swollen samples Are measured at predetermined time Point.

Determination of drug content:-

A precise 10 ml of In-situ gel from various batches was measured and transferred into a 100 ml volumetric flask, which already contained 50-70 ml of 0.1 N HCl. The mixture was sonicated for 30 minutes, and the volume was adjusted to 100 ml. The contents were visually confirmed to be completely dispersed and subsequently filtered using Whatman filter paper. From this solution, 10 ml was extracted and diluted to 100 ml with 0.1 N HCl. The concentration of metoclopramide HCl was then determined using a double beam UV-visible spectrophotometer at the reference wavelength.

Invitro Drug Release

The in vitro release rate of Levetiracetam from a sustained-release gel was assessed using USP equipment equipped with a paddle over disk at a temperature of 37±0.5°C. A dissolution medium of 500cc of 0.1 N HCl was used. The speed of the test was deliberately kept low to prevent the gelled formulation from breaking, simulating the gentle agitation conditions present in vivo. At predetermined intervals, 5cc samples were withdrawn, filtered, diluted, and analyzed at a specified wavelength using an 1800 double beam UV spectrophotometer. The cumulative drug release was calculated using an equation derived from a standardization curve.

Application of GRDDS

1. Enhanced bioavailability:

Increased bioavailability of riboflavin GRDF as compared to non-GRDF formulations.

Increases drug absorption by several processes.

2. Sustained drug delivery/Reduced frequency of dosing:

Drugs with short biological half life can, sustained and slow input from GRDF result in improved pharmacokinetics and patient compliance.

Reduced dosing frequency.

3.Targeted therapy for local ailments in the upper GIT:

Prolonged and sustained release from GRDF may advantageous for local therapy in stomach and small intestine.

4. Reduced fluctuation of drug concentration:

Continuous release of the drug from GRDF Produces blood drug concentration in a narrow range.

Fluctuation in the drug effect can be minimized and adverse effect due to concentration can be prevented. Good for drugs with narrow therapeutic index.

II. CONCLUSION

Based on the different literature survey, GRDDS has a specific scope in the pharmaceutical field, the market of GRDDS product would be vast will more patient compliance. Gastro retention drug delivery system is good beginning in oral drug delivery system it offers various potential advantage to enhance bioavailability, absorption etc. GRDDS approaches Increase the bioavailability of the drug. Due to their maximum retention in gastric region, these

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formulations has majorly used in treatment of gastrointestinal diseases like gastritis and peptic ulcer. Commercially it is emerging slowly as an important novel drug delivery system with numerous potential benefits.

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