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Review on Gastro Retentive Drug Delivery System.

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ABSTRACT

The Gastro Retentive Drug Administration System (GRDDS) is ideal for extending drug residence duration in the stomach and achieving site-specific drug delivery in the upper gastrointestinal tract. GRDDS is a medication that is released locally to treat GI illnesses. This will result in a high concentration of medication at the gastric mucosa, allowing for long-term drug release. GRDDS allows for the drug's release to be prolonged and continuous in the upper GI tract.

It is a frequently used method of keeping the dosage form in the stomach for a long time and slowly releasing the medicine, which can address many of the problems associated with traditional oral delivery, such as inadequate bioavailability.

Keywords: Swelling system, Gastroretentive drug delivery system, Floating system, Gastric residence time, Mucoad-hesive system.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. 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 gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.

After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).

These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), 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. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions:

- Fundus,
- Body, and
- Antrum pylorus.

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC).

DIFFERENT APPROACHES OF GRDDS:

- **Floating Drug Delivery System (Low Density System):**

Floating drug delivery system (FDDS) possess bulk density lower than the gastric fluid and because of this reason it remains buoyant in the stomach without affecting gastric emptying time for an extended period of time. While the system is floating on the gastric content, the drug released slowly at a desired rate from system, which results in increase in gastric retention time and better control in fluctuation of plasma drug concentration. After complete release of the drug, the residual system is emptied from the stomach.

✓ **Advantages of floating drug delivery system:**

1. Simple and conventional technique for formulation.
2. Site-specific drug delivery.
3. Controlled delivery of drugs.
4. Delivery of drugs for residual action at a specific site in the stomach.

✓ **Disadvantages of floating drug delivery system:**

1. The major disadvantage of a floating system is due to the necessity of a sufficient level of gastric fluids to float without a sink. However, this limitation can be overcome by coating the dosage form with bio adhesive polymers that easily adhere to gastric mucosa.
2. The drugs those get significantly absorbed throughout gastrointestinal tract, with significant first-pass metabolism, are desirable candidate predominantly.

✓ **Application of floating drug delivery system:**

1. FDDS are claimed for the increased efficacy of drugs as recent studies show that the administration of Diltiazem floating tablets twice a day would be more effective compared to normal tablets in hypertensive patients.

2. In case of Parkinson patient, FDDS is effective in absorption of the drug over a period of 6-8 h and maintained substantial plasma concentration.

❖ **Mucoadhesive / Bioadhesive System:**

Mucoadhesion means attachment of the drug to the mucus coat. This approach helps to increase the gastric residence time of the dosage form by binding them to the gastric mucosa. The adhesion is favored by rapid hydration. This mucoadhesive system is not that much feasible as the bond formation for mucoadhesion is prevented by the acidic environment and presence of thick mucus in the stomach. Polymers used for this purpose may include polycarbophil, carbopol, CMC, chitosan, lectin etc.

Since from the last 40 years, the concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. He use of various mucoadhesive polymers have achieved the significant interest in formulating the sustained release, extended release as well as prolonged release dosage forms. He mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities. He delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora. For the desired mucoadhesive strength of the mucoadhesive dosage forms, there are various mucoadhesive polymers that can be used. Hence polymers are either natural or synthetic macromolecules which are capable of adhering to the mucosal surfaces. From last three decades, the use of various mucoadhesive polymers has achieved a great interest in the field of pharmaceutical technology. Nowadays, the use of mucoadhesive polymers has been accepted as an important strategy to prolong the residence time and to improve the localized effects of drug delivery systems on various mucus membranes of a biological system.

❖ **Raft Forming System**

This system focus more for delivery of antacid and delivery of drugs used to treat gastrointestinal infection and disorders. The basic mechanism involves formation of viscous cohesive gel when the system comes in contact with gastric fluid. In this each portion of liquid swells and forms a continuous layer of gel known as raft. The raft floats because of buoyancy created by formation of CO2. This raft acts as a physical barrier to prevent the reflex of gastric content into the esophagus. Figure 5 represents raft forming system's mechanism.

✓ **Advantages of Raft Forming System**

1. It does not interfere with activity of anti-secretory agent e.g., cimetidine.

2. It may not interfere with the function of pyloric sphincter.

❖ **Expandable System:**

This system may be of two types:

1) Unfoldable system and 2) swellable polymer.

1) Unfoldable systems uses biodegradable polymer. This concept uses carrier such as capsule in which compressed system is incorporated which extends in the stomach.

2) Swellable systems are retained due to their mechanical property. The swelling is resulted from absorption of water.

❖ **Superporous Hydrogel:**

Super porous hydrogels (SPHs) are recent advancement in **gastro retentive drug delivery system** (GRDDS) which also includes intragastric floating system (low density system), mucoadhesive system, high density system and swellable system.

Conventional hydrogel have pore size ranging from 10 mm to 10μm. This hydrogel possesses very slow process of water absorption and require several hours to attain equilibrium state.

In contrast to conventional hydrogel, superporous hydrogel have average pore size >100μm. Superporous hydrogel swells to equilibrium size within minute. This occurs because of rapid water uptake by capillary wetting through numerous interconnected open pores. Superporous hydrogel swells to large size and have sufficient mechanical strength to withstand the pressure created by gastric contraction.

This approach is based on the principle that encapsulation of drug within the microporous compartment which having pores on the top and on the bottom wall. Peripheral walls are completely sealed to prevent any direct contact of gastric fluid to the undissolved drug.

As delivery system contains entrapped air chamber, when it reaches into the stomach, floating of the system on the gastric fluid takes place. Gastric fluid enters into the pores and dissolves the drug which causes release of dissolved drug.

❖ **Magnetic System:**

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. This approach of increased gastric retention time is based on the principle that dosage form contains a small internal magnet. A magnet is placed in abdomen over the position of stomach that retains dosage form in the gastric region.

❖ **High Density System:**

This system possesses a density of about 3 g/cm3 which are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements.

This system is prepared by coating a drug on a heavy core or mixed with the inert material such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. Figure represents high density system in stomach.

The major drawback with such system is that it is technically difficult to manufacture formulation with high amount of drug and to achieve density of about 2.8 g/cm3.

Factors Affecting Efficacy of GRDDS

- **Particle size: -** It should be in the range of 1 – 2 mm to pass through the pyloric valve into the small intestine.
- **Density: -**Density of the dosage form affects the gastric emptying rate. A buoyant dosage form has density less than the gastric fluid to float.
- **Size: -** Size of the system should be in greater than 7.5 mm in diameter.
- **Shape: -** Ring and tetrahedron shaped system shows better gastric retention compared with the other shapes.
- **Single or multiple unit formulation: -**Multiple unit formulation shows more predictable release profile. It also allows co-administration of the units with different release profile or containing incompatible substances. It also permit large margin of safety as compared to single unit formulation.
- **Nature of the meal and caloric content: -**Indigestible polymers, increased caloric content, fatty acid salt, increased acidity, fat and protein meal increase gastric retention time.
- **Food intake: -**Gastric retention time is increased in fed state.
- **Posture: -**Gastric retention time is different for inactive and active state of the patient.
- **Gender: -**Mean gastric retention time in male is less as compared to female regardless of weight, height and body surface.
- **Age: -**Age greater than 70 shows longer residence time.
- **Biological factor: -** Disease like gastroenteritis, gastric ulcer, diabetes, hypothyroidism retard gastric emptying rate while partial or total gastrectomy, duodenal ulcer promote gastric emptying rate.
- **Single unit/multiple unit: -**Multiple units are preferable because of predictable release profile, coadministration of different units, larger safety margins.

- **Food intake: -** GRT is longer in fed states.
- **Nature, calorie content: -** Indigestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, Fat and protein meal increases GRT.
- **Frequency of intake: -**GRT increases 400 times due to low frequency of **MMC.**
- **Nature of drug: -** Drugs with impact on gastro intestinal transit time e.g., Codeine and Pharmacokinetic agents e.g., metclopramide, cisapride increases GRT.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

1. Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

2. Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

- **DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS**

1. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin
2. Unsuitable for drugs that are unstable in acidic environment. E.g. Erythromycin

- **APPLICATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS:**

1. Bioavailability
2. Site Specific Drug Delivery System

CONCLUSION

Based on the literature survey, it can be concluded that GRDDs offers various potential advantages for drugs with poor bioavailability. Drug absorption in the gastro intestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. The control of gastro intestinal transit of orally administered dosage forms using GRDD systems can improve the bioavailability of drugs that exhibit site specific absorption. GRDFs also provide an additional advantage for drugs that are absorbed primarily in the upper segment of GIT, i.e., stomach, duodenum and jejunum. Different approaches for GRDD are studied each having their own advantages and disadvantages. Due to unpredictability of human GIT development of efficient GRDFs is a real challenge to pharmaceutical technology as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology.

In the future it is can be easily assumed that GRDD systems will become more popular in terms of delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy's.

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