



Gastro Retentive Drug Delivery System

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ABSTRACT

Gastro Retentive Drug Delivery System (GRDDS) is most advantageous for increasing gastric residence time of drug and to achieve site specific drug delivery in upper GIT. GRDDS treats GI diseases by releasing the drug locally. This will leads to high concentration of drug at the gastric mucosa and sustain release of drug can be achieve. GRDDS empowers prolonged and continuous release of the drug to the upper GIT.

Keywords: gastro retentive drug delivery system

INTRODUCTION

Gastro retentive drug delivery system (GRDDS) is a site specific delivery system. It delivers the drug either in stomach or in intestine. The drug delivery is obtained by retention of dosage form in stomach and the drug is released in a controlled manner to the specific site either in stomach, duodenum or in intestine.

Different Approaches of GRDDS¹

Figure 1 represents different approaches of GRDDS

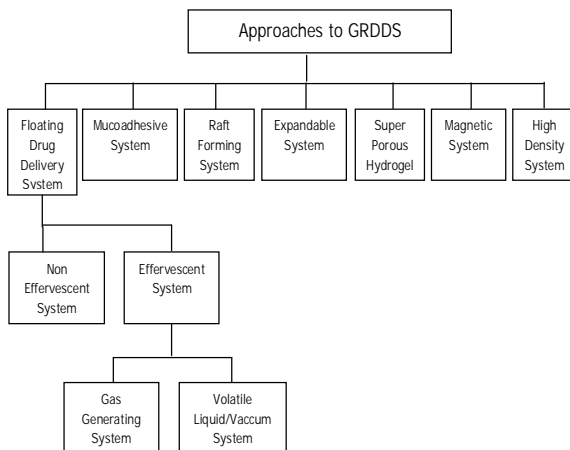


Figure 1: Different approaches for GRDDS

Floating Drug Delivery System (Low Density System)²

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.

Non Effervescent System²

This system is also known as Hydrodynamically Balanced System (HBS). This system remains buoyant by entrapment of air in the swelled polymer. When this system comes in contact with gastric fluid, the hydrocolloid starts to hydrate by first forming the gel at the surface of the dosage form and ultimately control the release of the drug. As the outer surface goes into the solution, the gel barrier is maintained by immediate adjacent hydrocolloid layer. Figure 2 represents overview of mechanism of non effervescent system.

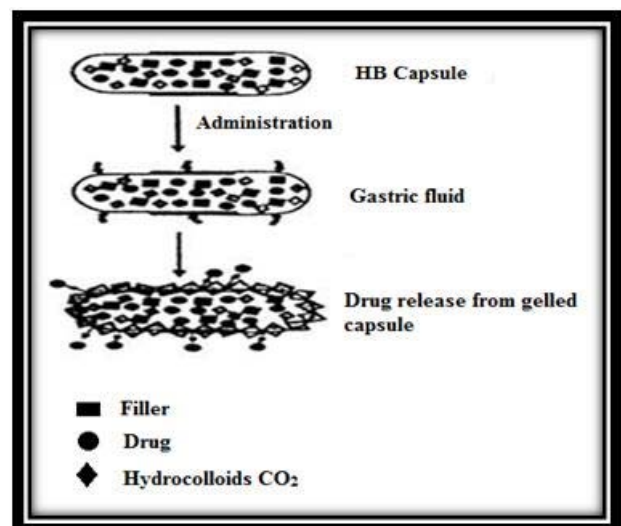


Figure 2: Non Effervescent System

Effervescent System^{2,3}

This system made to float in the stomach by incorporating floating chamber, which may be filled with vacuum, air or inert gas. This system uses matrices prepared with swellable polymer and effervescent components. The matrices are formulated in such a way that when they reach into the stomach carbon dioxide is liberated by acidity of gastric content. This carbon dioxide is entrapped in the hydrocolloid causes the upward

movements of the dosage form and maintain its buoyancy. This system is divided into two classes: 1) volatile liquid containing system and 2) gas generating system.

Volatile Liquid Containing System²

It is osmotically controlled floating system. This system consists of two chambers which are separated by pressure sensitive, impermeable, movable bladder and bio erodible plug which gradually release the gas. The drug and volatile liquid is placed in first and second chamber respectively. Upon administration, the drug is continuously released from the chamber into the gastric fluid. Figure 3 represents Volatile liquid containing system.

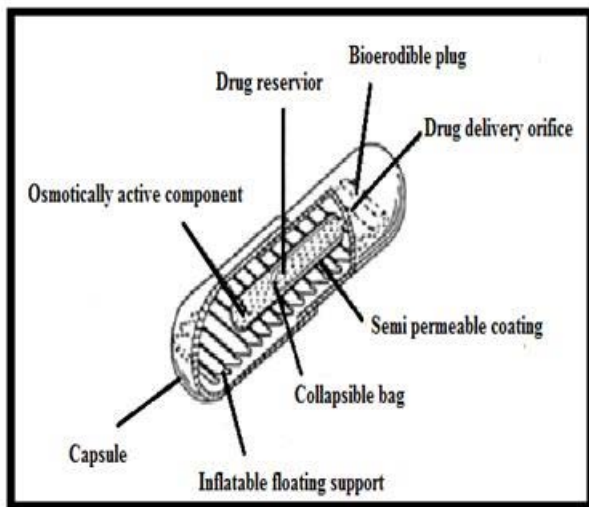


Figure 3: Volatile Liquid containing system

Gas Generating System³

This system uses effervescent reaction between carbonate/bicarbonate salt and citric/tartaric acid which liberate carbon dioxide. This carbon dioxide gets entrapped in the hydrocolloid layer of the system and thus decreases the specific gravity of the system which makes it to float over the gastric fluid. Figure 4 represents general mechanism of Gas generating system.

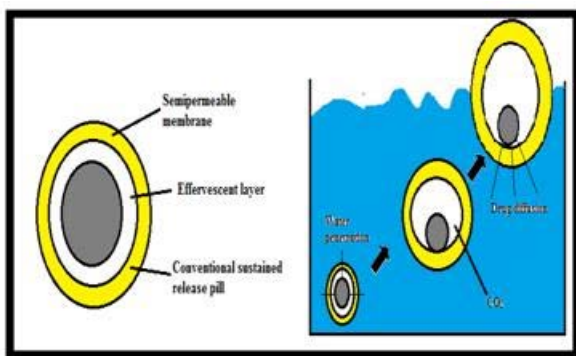


Figure 4: Gas Generating System

Mucoadhesive System^{3,4}

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 polycarboxophil, carbopol, CMC, chitosan, lectin etc.

Raft Forming System^{1,3,4,5}

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 reflux of gastric content into the esophagus. This system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for making the system less dense than the gastric fluid and to float on the gastric fluid. Figure 5 represents raft forming system's mechanism.

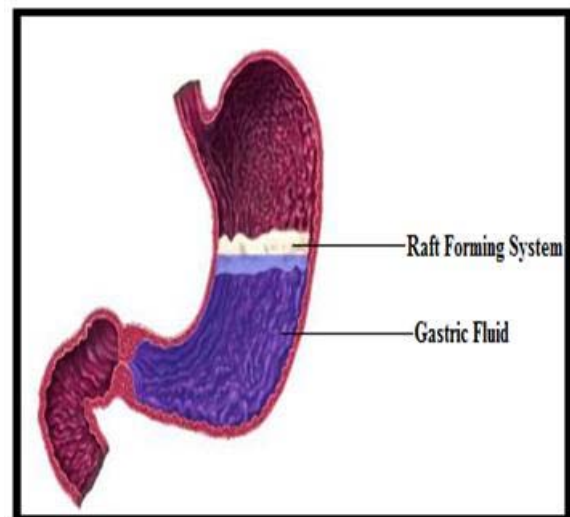


Figure 5: Raft Forming System

Effect of Sodium bicarbonate on the drug release from raft forming system

Sodium bicarbonate is used as a gas generating agent. Gas generating agent sodium bicarbonate interacts with the gastric acid and generates carbon dioxide which gets entrapped within the swellable matrix. Carbonate or bicarbonate may be present in the amount ranges from 5% to 50% and preferably from about 10% to 30% by weight of composition. Increasing the concentration of bicarbonate decreases the floating lag time because of faster and higher carbon dioxide generation. At higher concentration of effervescent agent, coating of the tablet becomes less stable. This is because of increase in the internal pressure and there by rupturing the polymer coating which ultimately results in sudden increase in drug release.

Advantages of Raft Forming System

- It is used for the treatment of heartburn and oesophagitis. It is also useful to treat laryngo pharyngeal reflux (LPR) and gastro esophageal reflux disease.
- It does not interfere with activity of anti secretory agent e.g. cimetidine.
- Rapid and long duration of action can be achieved. It shows its action within seconds.
- It may not interfere with the function of pyloric sphincter.
- Improved patient compliance.

Expandable System¹

- This system may be of two types: 1) unfoldable system and 2) swellable polymer.
- Unfoldable systems uses biodegradable polymer. This concept uses carrier such as capsule in which compressed system is incorporated which extends in the stomach.
- Swellable systems are retained due to their mechanical property. The swelling is resulted from absorption of water.
- The resultant bulk enables gastric retention and maintains the stomach in the fed condition.
- The whole expandable system is coated with the polymeric membrane. This outer coat is permeable to both, drug and body fluid. This outer coat also controls the drug release.
- This system is gradually reduced in the size and rigidity. This results in reduction of drug and expanding system. This results in elimination of system.

Superporous Hydrogel^{1,6,7}

- Conventional hydrogel have pore size ranging from 10 nm to 10 μ m. This hydrogel possess 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 >100 μ m. 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^{6,7}

This approach of increased gastric retention time is base 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.

Figure 7 represents general situation for working of magnetic system.

Disadvantages of this system are as follows:

- External magnet needs to be positioned with the degree of precision.
- Patient non compliance

Due to these disadvantages this system is not commonly used.

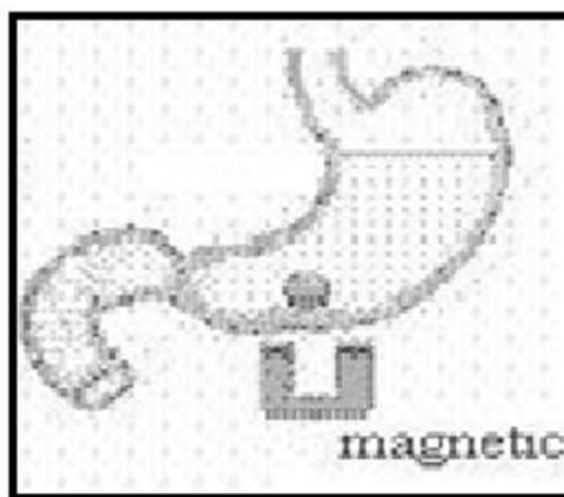


Figure 6: Magnetic System

High Density System^{1,6,7}

- 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 8 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.

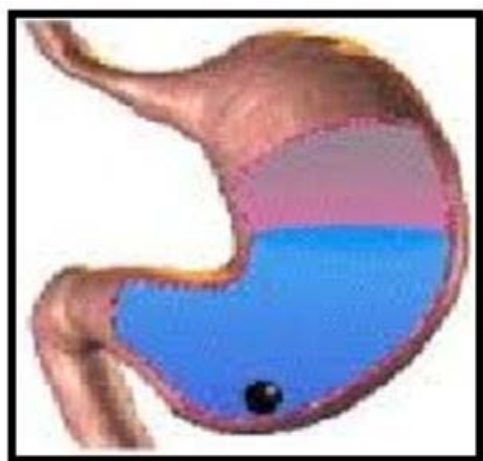


Figure 7: High Density System

Advantages of GRDDS^{1,2,3,6,7}

Floating dosage form remains in the stomach for longer period of time.

- Floating dosage form is advantageous for producing local action in the stomach.
- Controlled delivery of the drug is possible.
- Reduction in the mucosal irritation is possible by releasing drug slowly.
- Ease of administration
- Improved patient compliance can be achieved.
- Site specific drug delivery is possible.
- GRDDS is advantageous for the drug absorbed through the stomach.
- Bioavailability of therapeutic agents is significantly enhanced.
- For the drug with short half life, sustain release can be achieved and also reduce the frequency of the dosing.
- Gastro-retentive dosage form minimizes fluctuation of the drug concentration.
- GRDDS minimize counter activity of the body and ultimately increase the drug efficacy.

Disadvantages of GRDDS^{1,3,7,8}

- Bioadhesion in the acidic environment high mucus turn over may arise the question about the effectiveness of the system
- Not suitable for the drug which may produce gastric irritation.
- Mucus on the stomach wall is in continuous renewal state so unpredictable adherence may result.
- Retention time in the stomach is depends on the digestive state. So floating system should be administered after meal.

- Ability to float is depends upon the hydration state of the dosage form.
- This system is unsuitable for the drugs which have limited acid solubility.
- This system is also unsuitable for the drugs which are selectively absorbed from the stomach.
- Floating system is unsuitable for the drug which have stability problem in the stomach.

Applications of GRDDS^{2,8}

Sustained drug delivery

Floating system remains in the stomach for longer period and release the drug over a prolong period of time. This system has bulk density less than 1 so it may float on the gastric content.

Site specific drug delivery

This system is particularly advantageous for the drugs which are absorbed from the stomach or proximal part of the small intestine.

Absorption enhancement

Drugs having a poor bioavailability are potential candidate for formulating as a floating system to enhance its absorption.

Maintenance of constant blood flow

This system provides an easy way for maintaining constant blood flow with relatively ease of administration.

Comparison of GRDDS with the Conventional Dosage Form¹

Table 1 represents comparison of GRDDS and conventional dosage form

Table 1: Comparison of GRDDS with conventional dosage form

Conventional Drug Delivery System	Gastroretentive Drug Delivery System
High risk of toxicity	Very low risk of toxicity
Less patient compliance	Improves patient compliance
Not suitable for delivery of drugs with narrow absorption window in small intestine region	Suitable for delivery of drugs with narrow absorption window in small intestine region
Not much advantageous for -Drugs having rapid absorption through GIT -Drugs which degrade in the colon -Drugs acting locally in the stomach	Very much advantageous for -Drugs acting locally in the stomach -Drugs which degrade in the colon -Drugs having rapid absorption through GIT

Potential Drug Candidates for GRDDS^{1,6,7}

- Drugs which are acting locally in the stomach. e.g. antacids.
- Drugs which are primarily absorbed in the stomach e.g. amoxicilline.

- Drugs which are poorly soluble at alkaline pH. e.g. furosemide.
- Drugs having narrow absorption window. e.g. levodopa.
- Drugs that are absorbed rapidly from the stomach. e.g. tetracycline.
- Drug which are degrade in the stomach. e.g. ranitidine.

Drugs those are unsuitable for GRDDS⁶

- Drugs which have very low acid solubility. e.g. phenytoin.
- Drugs which are unstable at lower pH. e.g. erythromycin.
- Drugs which are intended to be release in the colon. e.g. corticosteroids.

Factors Affecting Efficacy of GRDDS^{3,6,7,8}

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.

CONCLUSION

GRDDS proves advantageous for the drugs having poor bioavailability. This system also provides an advantage for the drugs that are primarily absorb in upper GIT. Different approaches of GRDDS have their own advantages and disadvantages.

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