Review Article

An Updated Review on Gastroretentive Drug Delivery System: An Approach to Enhance Gastric Retention

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ABSTRACT

In recent years, many attempts have been made to enhance the bioavailability of drugs and therapeutic effectiveness of oral dosage forms. The most convenient and accepted route of drug delivery is the oral route. Gastro retentive drug delivery system is a novel drug delivery system and has gained immense popularity in the field of oral drug delivery. This drug delivery system is employed to retain the dosage form in the stomach for an extended period of time, and thereby increase the gastric residence time of drugs and also release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Apart from *in-vitro* characterization, successful GRDDS demands well designed *in-vivo* study to establish enhanced gastro – retention and prolonged drug release. Recently applied gastrointestinal technologies such as expandable, super porous, hydrogels, bio/mucoadhesive, magnetic low and high-density systems have also examined with their merits and demerits. This review focus on various aspects useful in the development of gastro retentive drug delivery systems, including current trends and their application and factors controlling the gastric residence time of dosage forms.

Keywords: Gastro retentive System, Gastro retention time, Bioavailability, Low-Density Systems, High-Density Systems.

INTRODUCTION

Owing to tremendous benefits of oral drug delivery systems have dominated other drug delivery system due to their various advantages like ease of administration, flexibility, cost-effectiveness, easy storage and transport and high patient compliance. But Oral delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the flora, the gastric retention time of the dosage form, surface area and enzymatic activity. Conventional drug delivery systems fail to retain the drug in the stomach and unpredictable rapid gastric rate may cause partial drug release in the absorption zone of the patient's body, hence hampering the efficiency of the dosage.

However, the recent technological development has resulted in many novel pharmaceutical products mainly the controlled release drug delivery systems to overcome this problem. Gastro retentive drug delivery system is one such example where the attribute like gastric retention time coupled with the drug release for an extended time has significantly improved patient compliance. The solubility of the drugs that are less soluble in an elevated pH environment of the intestine can be improved by prolonging the gastric retention of drugs. In the case of drugs having short half-life, they have the tendency of getting eliminated quickly from the systemic circulation; to attain required therapeutic activity, recurrent dosing is needed. However, an oral sustained controlled release formulations with gastric retention properly can avoid these limitations, by releasing the drug slowly in the stomach [1].

Stomach Physiology [2]

In GRDDS, the stomach has an important role and a good understanding of the anatomy and physiology of the stomach is a prerequisite for successful development of the gastro retentive dosage form. The stomach is divided into two parts; The Proximal Stomach and The Distal Stomach. The mobility pattern in the stomach is said to be myoelectric complex (MMC), and the different phases are given in Table 1. The human anatomy categories stomach in three main parts; Fundus, Body and Pylorus. The gastric emptying rate during the fed state is delayed, causing a slowdown of gastric emptying rate.

Table 1: Phases of MMC

Phase	Description	Duration (Min)
Phase I	Idle state with rare contractions or without any contractions	30 - 60
Phase II	Intermittent Contractions	20 - 40
Phase III	Also termed as housekeeper's wave. This Phase represents long and regular contractions	10 - 20
Phase IV	Transitional Phase occurs between Phase III & Phase I	0 - 5

Gastro retentive Drug Delivery System

Gastro retentive Drug Delivery Systems are oral dosage forms which have the ability to be retained in the GI tract and resist rapid gastric emptying. This system is a promising approach for drugs having a narrow absorption window. The effectiveness of the system depends on

several factors like gastric transit time, food effects and site of absorption of the drug. The efficiency of this system depends on the drug release rate and transmit time along the GI tract. Gastro retentive Drug Delivery System remains I the stomach for several hours thus prolonging the gastric residence time, which might be in favour of improving the bioavailability of NAW drugs. Prolonging the gastric residence time enhances the solubility of the drugs which are more soluble at low pH and might improve the bioavailability.

Factors Controlling the Gastric residence time of dosage forms [3]

Several factors controlling the Gastro retentive Drug Delivery System are shown in Table 2, and some of the factors have given below:

Table 2: Factors Controlling GRDDS

Formulation Factors: Dosage Form Related Factors		Food Intake and Its Nature		Patient Related Factors	
1	Density of Dosage Form	1	Fed or Unfed State	1	Gender
2	Size of Dosage Form	2	Nature of Meal	2	Age
3	Shape of Dosage Form	3	Caloric Content	3	Disease State
4	Viscosity Grade of Polymer	4	Frequency of Food	4	Emotional State of Subject
5	Single or Multiple Unit Formulation			5	Posture - Upright Position/ Supine Position

Density

Dosage forms with a density lower than the density of the gastric fluid can experience a floating behaviour and greater residence time, while high density sinks into the bottom of the stomach. The density required for floating properly is less than 1.0 gm/cm^3.

Size of the Dosage form

As the size of the dosage form increases the gastric residence time because the larger size would not allow the dosage form to pass rapidly through the pyloric sphincter into the small intestine. Size should not be more than 7.5 mm in diameter. While designing gastro retentive delivery systems one fact should be taken into consideration is that this dosage form should dissolve or erode to decrease in size to allow this dosage form to pass through the pyloric sphincter into small intestine after achieving the required therapeutic effect.

The Shape of the dosage form

Round or Spherical shaped dosage form exhibits better property related to other shapes.

Food intake and the nature of food

It was found that the nature of meal pregnancy of feed, nature of the meal, calorie content. The viscosity of the meal has a great effect on GRT. High amount of total meal and other indigestible polymers slow down the gastric relation time due to reaction in gesture motility. A high protein and fat-rich diet increase GRT by 4 to 10 hrs. Gastric relation time is less during fasting condition due to rise in gastric motility.

Effect of gender, posture age and disease state

Males have greater GRT than females. GRT is more in geriatric patients and less in neonatal and children. GRT can vary between supine and upright ambulatory states of the patient. Gastric diseases like diabetes, Chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers fluctuates the GRT.

Simultaneous Administration of Drugs

Combination of some drugs along with gastric motility enhances or depressants affect GRT. Some drugs such as anticholinergic agents, opiates, optokinetic agent decrease the motility of the GIT so it can prolong the gastric residence time.

CURRENT PHARMACEUTICAL TECHNOLOGIES OF GRDDS[4, 5]

The main mechanism of GRDDS devised to improve the period of retainment of the oral dosage form in the stomach includes floating, sinking, swelling, effervescence, mucoadhesion, expanding systems, high-density systems and other delayed gastric emptying devices. Current technologies are given in Figure 1 and are explained in detail below in figure 1.

Low-Density Systems (Floating Systems)

Low density/floating systems are the most practical and extensively studied gastro retentive dosage forms. This system is classified into two types; based on the mechanism of buoyancy, non-effervescent floating and effervescent floating systems (given in Fig 1.). This property allows the system to remain buoyant in the stomach for a prolonged period of time.

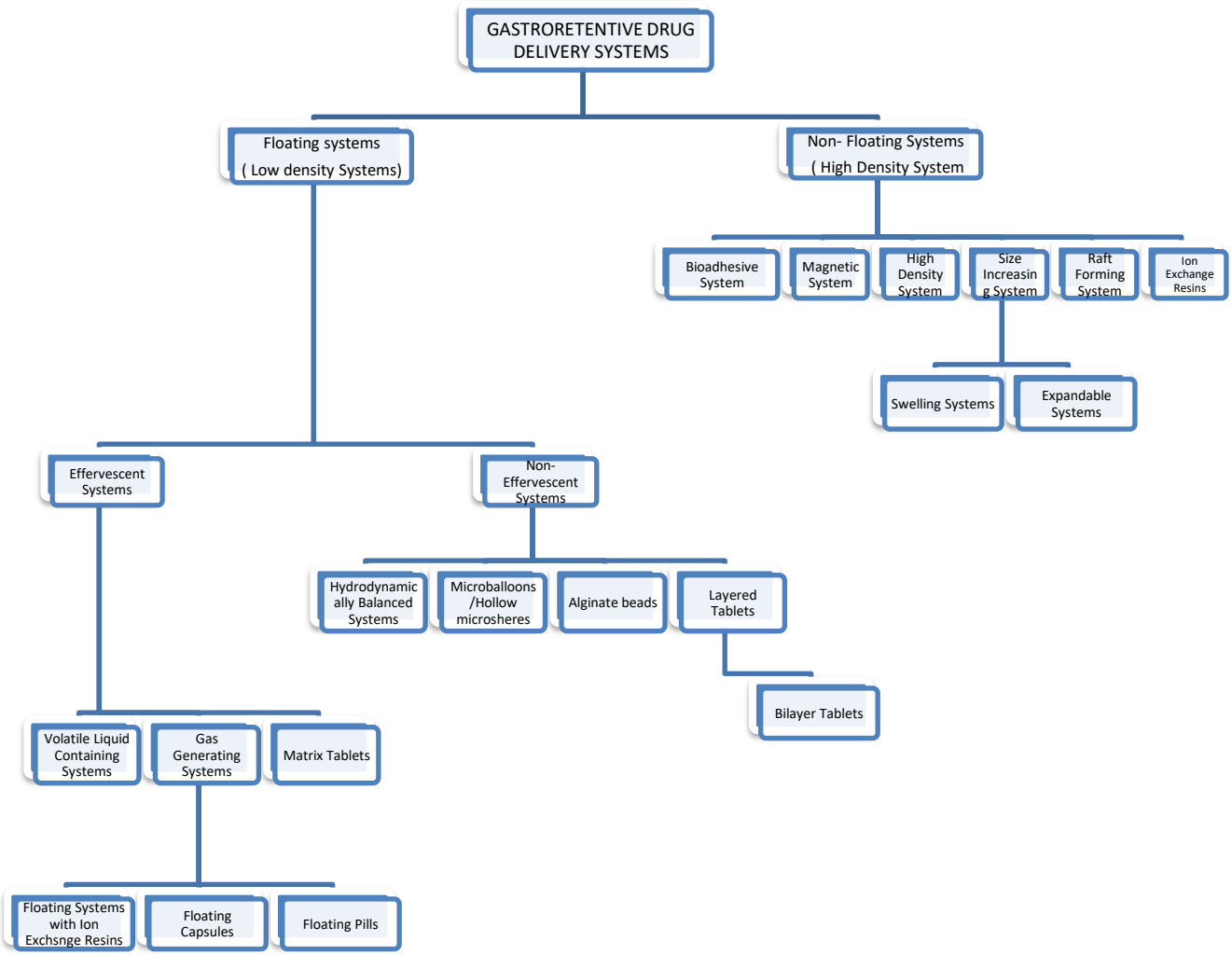

Figure 1: Types of Gastroretentive Drug Delivery Systems

Non-Effervescent Floating Systems [6]

Highly swellable cellulose derivatives or gel-forming polymers are used in non-effervescent systems. The formulation technique involves mixing of drug with a gel-forming polymer. Various non-effervescent systems include hydro dynamically balanced systems, micro balloons/ microspheres, Alginate beads, layered tablets. Various gel-forming hydrophilic polymers such as HPMC, HPC, Sodium CMC, carrageenan, agar, alginic acid etc. are used to design HBS system. In this system, the drug and polymer is mixed and filled in the gelatine capsule. By simple solvent evaporation or solvent diffusion technique, drug-loaded micro balloons/hollow microspheres are formulated. Polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar are polymers commonly used to design micro balloons. In alginate beads approach, a solution of sodium alginate is dropped into an aqueous solution of calcium chloride and caused the precipitation of calcium alginate. These beads can prolong the GRT for more than 5.5hrs.

Effervescent Floating Systems

This system includes a gas generating system and volatile liquids. This can be applied for single and multiple-unit systems. Effervescent agents such as sodium bicarbonate, calcium carbonate, tartaric acid, citric acid are used in combination with hydrophilic polymers are used in the gas generating floating systems. When this system comes in contact with gastric fluid, CO2 is liberated due to the reaction of the effervescent agent with gastric fluid. The liberated CO2 will provide the tablet buoyancy and influence the drug release properties. This type of floating systems can be classified into single and double layer floating tablets or multiple unit effervescent floating system. Low-Density systems are usually associated with problems such as sticking or being obstructed in the GIT, which can cause gastric irritation. Drugs which cause irritation to gastric mucosa are not suitable candidates for low-density systems.

Volatile liquid containing systems consist of dual chambers having an impermeable, pressure responsive movable bladder separation. The floating bases on the incorporation of volatile liquid as Ether or cyclopentane, introduced inflatable chamber which volatilizes at body temperature allowing the system to increase in size and float over the gastric fluids.

Non Floating Systems (High-Density Systems)[7, 8]

Non-floating systems are class of gastro retentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. High-density systems have a density greater than that of gastric fluid. This system is classified into bioadhesive systems, magnetic systems, swelling and expandable systems, raft forming systems and examples of the polymers are given in Table 1.

Bioadhesive / Mucoadhesive Systems

This system was designed to adhere to the gastric mucosa and prolong the GRT of drug compounds. In this system, drugs are incorporated into a mucoadhesive agent, which may be natural or synthetic polymers. These polymers are usually macromolecules, a hydrophilic gelling substance with hydrogen bond-forming groups and anionic. Example for these polymers are sodium carboxymethylcellulose, sodium alginate, chitosan and carrageenan. An ideal mucoadhesive polymer is inert, non-irritating, nontoxic adheres to the mucosal surface and possesses site-specificity and interacts with the mucin through electrostatic disulphide hydrogen and hydrophobic bonding. The mechanism of mucoadhesion is highly complex and is not fully understood different theories postulated are given below.

a. Wettability – Bioadhesive polymers penetrate and develop intimate contact with the mucous layer.

b. Diffusion – Physical entanglement of mucin strands and flexible polymer chains.

c. Adsorption – Bio adhesion is due to primary forces and secondary forces between surfaces.

d. Electronic – Attractive electrostatic forces between the main network and bioadhesive material. Various studies have focused on the combination of floating and mucoadhesive properties in order to improve the GRT of the dosage form by forming a mucoadhesive floating drug delivery system. Therefore a dual working system would overcome the drawbacks associated with bioadhesive and floating systems and would have a significant effect on improving the therapeutic outcomes.

Swelling and expanding Dosage forms.

This type of drug delivery systems is designed to have a longer GRT through an increase in their volume or shape. Swelling should be above the diameter of the sphincter. The diameter of the pyloric sphincter varies among individuals, it is reported 12.8 +/- 7.0 mm, but because the sphincter contains muscles, it has the ability to stretch and allow even large dosage form to pass through the sphincter during the migration myoelectric complex MMC. To avoid this defect the size of the dosage form should be greater than 20 mm. The main mechanism for swelling and drug release from the system is diffusion. In these systems hydrophilic polymers (eg; HPMC, Poly ethylene oxide and corbopol that can absorb water from the gastric fluids are used. It is important to select a suitable polymer with appropriate molecular weight, viscosity grade and swelling properties to maintain a sustained release profile of the dosage forms. Some of the limitations of expandable systems are difficulty in storing easily hydrolysable biodegradable polymers, being difficult to manufacture and may not be cost-effective, difficulty in maintaining the structural integrity and may cause bowel obstruction, intestinal adhesion and gastropathy.

Raft- Forming systems

This type of system formulated with effervescent excipients and get forming polymers in order to achieve sustained drug delivery. This can effectively be used for the management of gastric oesophageal reflux diseases because floating rafts act as blockages between oesophagus and stomach. Systems with a density of 1.3g/ml or higher are expected to be retained in the lower part of the stomach. This system is mainly used for delivering antacid drugs, because the raft can remain intact in the stomach for several hours, promoting the sustained release of the drug. In this system sodium alginate used as get-forming polymer, sodium bicarbonate and acid neutralizer as gas generating agents. This type of polymer forms a viscous and cohesive gel when it swells and entraps CO_2 bubbles produced by the reaction of carbonates and gastric fluid.

Super- Porous Hydrogel System

When compared to normal swelling type systems, this system is highly porous because different category of water-absorbent polymer system is used and this system has a high degree of porosity and high mechanical strength. It has a pore size greater than 100µm and swells rapidly to an equilibrium size due to water uptake through an open porous structure by capillary force. Highly swellable polymers such as croscarmellose sodium and sodium alginate are used in these systems. Super porous hydrogel system swells up to 100 times or more and gains enough mechanical strength to withstand the pressure of gastric contraction and this can be attached by co-formulation of hydrophilic particulate material.

Magnetic Systems

This system consists of an active pharmaceutical ingredient, excipients and also a small amount of internal magnet. Studies have proved that GRT and bioavailability are improved by magnetic tablets. In this system, extracorporeal magnet is placed over the stomach to control the position of the dosage form containing an internal magnet, and plasma concentration can be increased in the presence of an extracorporeal magnet. In this system, main drawback is the specific positioning of the magnet is difficult to achieve and which results in low patient compliance.

Ion Exchange Resin Systems [9]

This ion-exchange resin system consists of cross-linked water-insoluble polymer that can be either cationic or anionic. By designing this system, the drug can be released in a controlled manner. This system is applicable to cationic

drugs and drugs should be released in the stomach and suitable resins should be selected according to drug properties. The release rate of the drug from resins depends on the properties of the resins such as particle size, cross-linking density, type of ionogenic group. This system when combined with another system, for example, floating systems or bioadhesive system, GRT can be prolonged. In this system, a specific amount of resin is poured on a known drug concentration and mixed homogeneously for a certain period. The ions of drugs from the solution get adsorbed on to the resin matrix and displace cations from the resin. Such loaded drug resin complexes are called resonates. This system has some limitations, it is difficult to estimate the amount of bound resin with drug and safety issues concerning its ingestion.

APPLICATIONS AND RATIONALE USE OF GRDDS [10, 11]

The rationale for the use of GRDDS is given in Figure 2.

Figure 2: Rationale for the use of GRDDS

Sustained Drug Delivery

GRDDS float on the gastric contents over a prolonged period of time, as these systems have bulk density <1.

Site-Specific Drug delivery

This delivery system is very useful for drugs that are absorbed from the stomach or the proximal part of the small intestine, especially with respect to their application for the treatment of H. Pylori infections.

The fluctuation of Drug Concentrations can be minimized

This feature is important for drugs with a narrow therapeutic index. Fluctuations in drug effects are minimized and concentration-dependent adverse effects that are associated with peak concentration can be prevented.

Absorption Enhancement

This is important in the case of drugs that are absorbed from the upper part if the GIT and by formulating this type of drugs as GRDDS can improve the poor bioavailability, thereby maximising their absorption.

CONCLUSION

Gastro retentive drug delivery systems are more patient-friendly than conventional immediate release dosage forms. These drug delivery systems emerged as an efficient means of prolonging the drugs retaining ability in the

stomach and thereby improves the bioavailability of drugs. A thorough understanding of the anatomy and physiological state of the stomach and process variables on dosage form quality is a prerequisite for the successful formulation of GRDDS. More focus on a combination approach of GRDDS to achieve better product quality.

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