REVIEW ARTICLE

Recent Approaches of Gastroretentive Drug Delivery System – A Review

Sarovar Reddy Vantimitta, S. Jeganath*

Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India

Abstract

The most effective and approved drug delivery method was the oral route. Due to the enormous therapeutic advantages of orally controlled release dosage forms, enhanced medicinal benefits are favored as the important perspective in the pharmaceutical field. Gastroretentive drug delivery system (GRDDS) is an innovative drug delivery method that has an advantage due to its ability to keep extended stomach retention and thus improve drug stomach residence time and also enhance drug bioavailability. Many technological methods, such as swelling and expansion, mucoadhesive, high density, ion exchange, raft forming, magnetic, and floating drug delivery systems, are used to prolong gastric residence time. The objective of this analysis on GRDDSs was to assemble of different gastroretentive approaches that are previously leading methods in the field orally administered controlled release drug delivery.

Key words: Effervescent system, floating drug delivery system, gastroretentive drug delivery system, high density, non-effervescent system

INTRODUCTION

While different drug delivery systems are used to optimize the therapeutic index and to reduce the adverse effects of drugs, oral route maintains the favored, reliable, and efficient pathway for the administering of therapeutic agents. Even though small therapy costs, ease of administration, adaptability in the methodology, and managing lead to greater patient conformance levels. Approximately 50% of the drug delivery systems on the economy are oral drug delivery systems.[1] Even though considerable progress has been made in the *de novo* design for an oral controlled drug delivery system over the past two decades, it has mixed success in medications with poor uptake across the gastrointestinal tract (GIT) system. This method is bedded with many physiological problems, such as the unwillingness to restrict and locate the controlled drug delivery system within the targeted GIT due to unpredictable gastric refilling and motility. In addition, a comparatively short stomach refilling time in humans that usually extend 2–3 h through the main absorption zone, that is, the abdomen and upper part of the intestine, can occur in inadequate drug release from the drug delivery system resulting in a reduced dose efficacy.[2]

For drugs with minimum gastrointestinal tract absorption, short half-life, poorly soluble at alkaline pH, and local ability to interact in the upper part of the intestinal tract, gastroretentive drug delivery system (GRDDS) is essential to eradicate *Helicobacter pylori*.[3-5] Several action mechanisms have been used to establish common GRDDS controlled release systems, as well as bio/mucoadhesive, superporous hydrogel, raft-forming, magnetic, ion exchange, expandable, and low- and high-density systems.[6-9] In addition, excipient physicochemistry plays a key role in different GRDDS. In effervescent floating systems, for instance, excipient density and effervescent agent structure are important considerations. Throughout the situation of superporous hydrogel processes, the formation of a superporous hydrogel requires high swelling excipients along with crospovidone and sodium carboxymethyl cellulose.[10-16]

Address for correspondence:
Dr. S. Jeganath, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Chennai, Tamil Nadu, India. Mobile: +91-9442302356.
E-mail: jeganaths@gmail.com

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PHYSIOLOGY OF STOMACH

The stomach plays a very important role throughout the GRDDS. The stomach has the main role in distribute the meat progressively, handle, and release it gradually into the ascending colon.[17] The fundus and body serve mainly as containers of undigested food, while the antrum serves as a pump to assist with a pushing action in gastric emptying.[18] The system of stomach adaptability is attributed to as the MMC; Table 1 describes the separate MMC stages. Gastric emptying occurs across both feed and fasting states, but the gastric emptying process may differ greatly between certain two regions. In the fasted state, every 90–120 min, there is an interdigestive series of electrical activities cyclically through both abdomen and small intestine.[5] The size of the superior vena cava rises to about 19 mm during the interdigestive phase.[19] Objects smaller than pyloric sphincter diameter can affectively evacuate either from the pylorus to the duodenum throughout most of the interdigestive system.[20] Nevertheless, in the fed state, following digestion of a feed, physical movement is induced 5–10 min and persists so long as it in the stomach, which may prolong the gastric emptying frequency.

Table 1: Four phases of the migrating myoelectric complex

Phase	Comments	Duration
Phase 1	A remarkably stable duration usually extended	30–60 min
Phase 2	Mechanisms for intermittent activity and expansion which growing slowly in severity and frequency as the process continues	20–40 min
Phase 3	Stressful, large, and multiple short phases of periods. This stage is called the "housekeeper wave" because it allows all indigestible components to be dragged out from the stomach and back in time to the intestine	10–20 min
Phase 4	It takes place in a short but intense transitional phase, respectively, Phase 3 and Phase 1 of two successive cycles	0–5 min

APPROACHES TO GASTRIC RETENTION

A multitude of strategies was used by a wide range of principles to improve the GRT of a medication type in the stomach.[21] These have to do with:

Low-density systems

Most technical and extensively tested gastroretentive dosage aspects are low-density/floating systems.[22,23] Davis adopted the floating system for the 1st time in 1968. A selective gastric retention can be achieved to an optimized stage of drug bioavailability. A unique concept for that same is the floating drug delivery scheme.[24] The drugs with an absorption window in the stomach or small intestines are required. This procedure has no effect on gastric emptying level over a long period of time.

Types of floating drug delivery systems (FDDSs)

Two different processes were used in the implementation of FDDS based on the flotation mechanism:[25]

1. Effervescent system
2. Non-effervescent system.

Effervescent system

Effervescent methods including the use of gas-generating agents, carbonates, as well as other organic acid in the formulation are to produce carbon dioxide (CO_2) gas, thus reducing the density cycle and enable to float the gastric fluid. The alternative is to incorporate a sequence involving part of the fluid that produces gas that evaporates at body temp. These are further categorized into two types.[26]

1. Gas-generating systems
2. Volatile liquid/vacuum containing systems.

Gas-generating systems

Intragastric single-layer floating tablets or hydrodynamically balanced system (HBS)

These are often developed by closely stirring in the matrix tablet the carbon dioxide generating operatives and the drug. They have a bulk density lower even than that for gastric electrolytes and thus continue to remain floating for a longer period of time in the stomach unappealing the rate of gastric emptying. The drug is announced gradually from those in the floating system at the required rate as well as the residual process is ejected from either the stomach after comprehensive discharge. This results in an increase in GRT and enhanced regulation of plasma drug concentration fluctuations.[27]

Intragastric bilayer floating tablets

These are also compressed tablet and containing two layers.

1. Immediate release layer and
2. Sustained release layer
3. Multiple unit type floating pills.

These processes come in the form of pills. Whenever the process is completely absorbed in body temperature dissolution form of media, it sunk one after the other and forms swollen pills such as balloons that float because they have lower density. The lower density is caused by carbon dioxide generation and processing in the process.[28]

Volatile liquid/vacuum containing systems

Intragastric floating gastrointestinal drug delivery system

This process of system is designed to float in the stomach due to a floating compartment which may be vacuumed or packed with air or poisonous gas whereas the drug tank is encapsulated on the inside of a microporous compartment.

Inflatable gastrointestinal delivery systems

In inflatable gastrointestinal delivery systems processes, the compartment containing liquid ether gasifying at body temperature which causes the compartment to inflate in the stomach. By packing the inflatable compartment with such a drug storage tank that can be a medication and implanted polymer matrix, such mechanisms are manufactured and instead encapsulated in a gelatin capsule.[8]

Intragastric osmotically controlled drug delivery system

This consisting of a concentration gradient-regulated drug delivery system and an inflatable floating device in an environmentally friendly capsule. The capsule rapidly breaks down into the stomach to start releasing the drug delivery appliance that is osmotically controlled by intragastric. The front inflatable help shapes a spherical hollow polymer bag containing a fluid which gasses at body temperature to inflate the bag. Drug delivery devices regulated by concentration gradient take the form of two elements; drug reservoir and osmotically active container.

NON-EFFERVESCENT SYSTEMS[11]

Non-effervescent systems incorporate a high degree of several gel-forming, expanding, cellulosic hydrocolloids and sodium carboxymethyl cellulose, polysaccharides, or matrix-formed polymers through tablets or capsules. When these gel formers, polysaccharides, and polymers came into contact with gastric fluid, they moisturize as well as construct a colloidal gel obstacle which regulates the stimulation level of fluid into the appliance and discharge of drugs subsequently. As the outer surface disintegrates by both dose forms, the hydration of the adjacent hydrocolloid coating keeps the gel layer.[17] The air collected by the enlarged polymer reduces the volume and gives the shape of dose elasticity. The preceding methods have been used in the development of floating intragastric systems.

HBSS OR COLLOIDAL GEL BARRIER SYSTEM

These are single-unit dosage forms that involve one or even more hydrophilic polymers, hydroxypropyl methylcellulose has been the most frequently used excipient, even though HEC, HPC, NaCMC, agar, and alginic acid are also used. The polymer is blended with both the drugs and is generally given in a capsule of gelatin. These capsules disappear quickly in the gastric fluid and a floating mass is formed by hydration and swell of the ground polymer. The secretion of drugs is regulated by the development of the surface hydrated boundary.[10]

MICROPOROUS COMPARTMENT SYSTEM

This design is focused on encapsulation within a microporous chamber of a drug storage tank with pores through its upper and lower walls. To avoid any personal contact of the gastrointestinal surface with both the undissolved medication, the peripheral walls of the substance reservoir chamber are properly closed. In the belly, there is compressed air in the flotation compartment allowing the distribution network to flow over most of the gastric material. Gastric fluid reaches the aperture and disintegrates the drug and brings the dissolved drug to absorb it continuously through the intestine.[12]

ALGINATE BEADS

Freezing dried calcium alginate has produced floating dose types of multiple units. Curved beads with such an expected diameter of 2.5 mm can be ready by falling into aqueous calcium chloride solution with sodium alginate, causing calcium alginate to precipitate. Then Remove the beads, snap frozen in liquid nitrogen, and freezed for 1 day (24 h) at −40°C, resulting in the creation of a porous structure that can sustain a floating force for more than 12 h. Such floating beads provided more than 5.5 h of prolonged residence.[22]

MICROBALLOONS OR HOLLOW MICROSPHERES

Using simple solvent evaporation or solvent diffusion process, microballoons/hollow microspheres filled with drugs in their other polymer shelf are prepared to prolong the dosage type GRT. Polymers extensively used throughout the construction of such structures. Elasticity and the discharge of drugs from the dose form change based on the volume of polymers, the polymer-plasticizer ratio, and the formulation solvent used. Such microballoons constantly floated over most of the ground of a surfactant-containing acid dissolution media for >12 h. Hollow microspheres are generally deemed some of the most successful buoyant processes since they incorporate the benefits of multiunit system with strong floating.

EXPANDABLE SYSTEMS

Expandable drug delivery products are built to improve their density or size by having a better GRT. They have been originally used only for animal health purposes and immediately broadened to humans in their applications.[18] For the normal functioning of the process, three particular

installations should be viewed: Smaller size for quick oral intake, improved stomach shape to avoid passage through the pyloric sphincter, and system reduced size since comprehensive launch of the drug to allow rescue operations. This process is also called a "plug-type system" as it is capable of blocking the pyloric sphincter. Process expansion happens by two strategies, swelling and taking shape, in both allowing adjustment of volume and shape.[12] Diffusion is the primary method for swelling and release of drugs from the process.

BIOADHESIVE/MUCOADHESIVE SYSTEMS

Park and Robinson first launched the mucoadhesive/bioadhesive process in 1984. It was programmed to adhere to the ground of the gastric epithelial cell and extend the drug compound GRT. Drugs are implemented in this attitude into a mucoadhesive agent that can be whether natural or synthetic polymers. The bioadhesive polymers are used which are adhere to the GIT epithelial surface. Polymer binding to the epithelial surface is broken into three distinct categories: Bonding-mediated adhesion hydration-mediated adhesion, bonding-mediated adhesion, and receptor-mediated adhesion. Both forms of systems bind to the stomach's biological membrane (mucosa) and establish long-term close contact with the membrane, while maintaining their sustained release in the stomach.[12,14]

RAFT-FORMING SYSTEMS

Raft-forming processes are also another type of GRDDS and built with effervescent excipients and polymer-forming gel for both the brief term supply of drugs. Raft system integrates alginate gels which have a carbonate element and create bubbles in the gel when reacted with gastric acid, allowing floating. Rafting formation mechanisms have received considerable publicity for the delivery of drugs for GI illnesses and diseases. The process involves the vicious cohesive gel formation in interaction with fluids of gastric and each part of the fluid swells makes up a constant layer termed a raft.[5]

SWELLING SYSTEMS

Such drug types swell after being consumed to a scale that prohibits them from going through the pylorus. As a consequence, for a long time, the medication type is stored in the stomach. Often these devices are called plug-type systems because they usually remain stuck at the pyloric sphincter. For the past few hours, sometimes in the feeding state, these polymeric matrices continue to operate in the gastric cavity. Continuous and governed release of drugs can be accomplished by choosing a polymer with the right molecular weight and swelling characteristics. The polymer soaks water and swells when it comes into contact with fluid of gastric. The inflammation of such polymers results from the existence of physical-chemical crosslinks in the hydrophilic polymer system. This link prevents the polymer from dissolving and thus preserves the bodily integrity of the dosage form. The amount of cross-linking between both the polymer chains provides a balance between certain magnitude and length of the swelling.[17,18] A high degree of cross-linking delays the scheme's swollen capacity and maintains its bodily integrity for an extended period of time.

HIGH-DENSITY SYSTEMS

High-density structures surpass gastric fluid density. Barium sulfate, zinc oxide, iron powder, and titanium dioxide are widely used excipients of these systems.[17] In 1930, Hoelzel first described many animal groups' effects of dosage type size on both the GRTs. The densities of the dosage forms examined varied between 0.9 and 10.5 g/cm^3. The creator stated that materials of high density had slower GRTs than materials of light density. The influence of dosage type density on GRT was examined subsequently. It stated that, due to their persistence in the antrum rugae or folds, small high-density pellets were able to withstand gastric peristaltic motions, raising the GIT time from 5.8 to 25 h. In addition, just a few clinical studies have been recorded in the literary works on high-density pellet formulations; as a consequence, the predictive validity of these structures remains questionable. Moreover, to assess the scientific validity of such dosage types, the future approaches must be based on animal experiments.

CONCLUSION

GRDDS has evolved as an effective means of extended stomach retention capacity, thus increasing the gastric residence time of drugs and also enhancing drug bioavailability. Despite numerous challenges in achieving prolonged stomach retention, a large number of companies are focused on marketing this technique. Today, multiple strategies are used to enhance gastric retention. FDDS is even more critical since it provides numerous benefits over the traditional dosage type. FDDSs success is a testimony to its utility. The FDDS shows more hope for a promising future day after day.

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