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Nanomaterials: An Improvised Drug Delivery System through the Gastroretentive Drug Delivery System †

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Abstract: Oral drug administration is among the most popular options in terms of patient compliance. The absorption window's influence enables the majority of commercially available modified-release dosage forms to have the desired physiological impact. In order to achieve the desired activity against the body's challenges, the formulator must keep the dosage form in the stomach, which is the aim of gastroretentive drug delivery (GRDD). In this process of maintaining the gastrointestinal (GI) tract, influenced by the nature of excipients and driven by the type of formulation to achieve therapeutic goals, a GRDD system is comparable to an improvised CDDS (control drug delivery system) before it reaches the absorption site. The most prevalent kind of preferred modified release system in use is solid oral dosage forms. To achieve the desired release profile, fewer doses are required when using these forms. Each drug candidate has a unique GIT absorption window, so there are many challenges. Solvability characteristics, pH-dependent variables, stability, physiological region, etc. Due to the barriers that have been added to this system, many products have been created. This review article contains nanomaterials used in GRDDS as novel drug delivery, factors affecting, and challenges to formulate nanomaterials, evaluation and advance technology used for application of nanomaterials.

Keywords: nanomaterials; GRDDS; control drug delivery; GI tract; advance technology

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1. Introduction

Drug delivery via the oral route is one of the most preferred routes in terms of patient compliance compared to other routes. The absorption window is the influential parameter due to which most commercially available modified-release dosage forms act in this physiological region for their desired effect [1]. The body's gastrointestinal (GI) tract is where most drugs are administered. Simple medication administration for compliance therapy, a broad surface area for systemic absorption, and the adaptability of the GI tract to handle various food types are all advantages. The benefits of the GI tract in medicine distribution include a variety of formulations [2]. This route suffers from a number of physiological issues, including erratic gastric emptying, a short GI transit time (80–12 h), and a drug absorption window in the upper small intestine. Efforts are being made to address these issues, and a novel drug delivery mechanism is required [3].

The gastroretentive drug delivery system (GRDDS) aims to hold the dosage form in the stomach to attain the desired activity by the formulator against the challenges involved with the body [4]. As an improvised CDDS (control drug delivery system), before reaching its site of absorption as compared to conventional drug delivery, the GRDDS comparably prevails in this process of sustaining in the GI tract, influenced by the nature of excipients and driven by the type of formulation to attain therapeutic goals. Solid oral dosage forms

are the leading class of preferred modified release system in action, which minimizes the frequency of dosing on an account to minimize multiple dosing to attain this desired release profile [4,5].

This review article describes the physiology, anatomy, and mechanism of absorption through the GI tract, physiological problems, how to overcome problems, novel gastroretentive drug delivery systems, preparation techniques, and their advantages over conventional drug delivery systems.

2. Physiology of the Stomach

The anatomy, physiology, and mechanism of digestion are briefly described below.

2.1. Anatomy

The stomach has four main parts: the heart, the fundus, the body, and the pyloric. The heart is in the upper part of the stomach, near the opening. The upper curve that continues downwards to the left of the cardia is called the fundus, and just below the fundus is the body, or store of undigested matter. Figure 1 illustrates the physiology and anatomy of the stomach. The pyloric antrum, the pyloric canal, and the pylorus, which connects to the duodenum, make up the pyloric region, an essential area for mixing food in the stomach. The pyloric sphincter is what allows the pylorus and small intestine to communicate. Lesser curvature refers to the concave area, while greater curvature refers to the convex area [6,7].

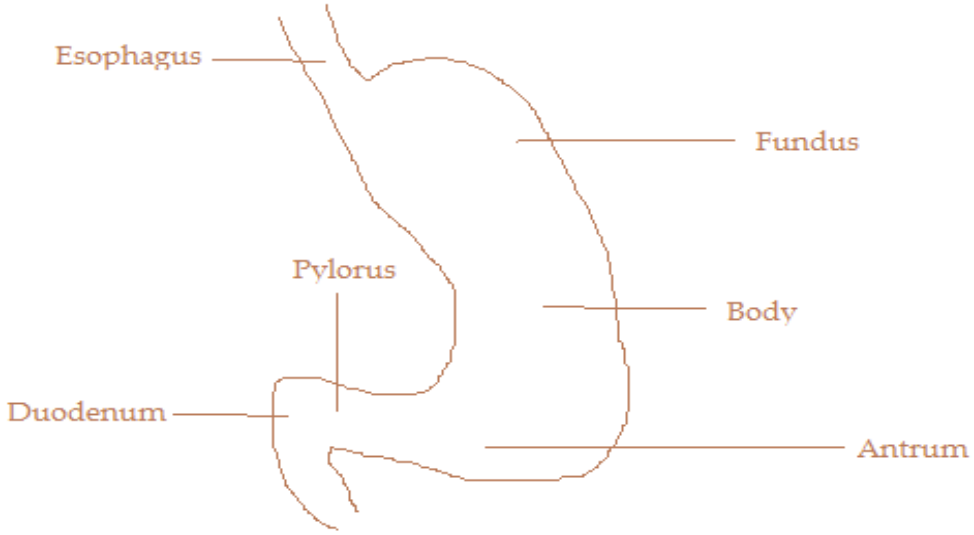

Figure 1. Physiology of the stomach.

2.2. Histology

The mucosa, submucosa, muscular, and serosa are the four fundamental layers of the stomach. Lamina propria, or surface mucosa cells, are found in the mucosa layer. Epithelial cells distend through the lamina propria and muscularis mucosae, which prompts the development of gastric organs, and when these organs are organized in a certain way where pits are created, they are called gastric pits. There are three types of exocrine gland cells in the stomach: chief cells, parietal cells, and mucus neck cells. The submucosa of the stomach is a thick layer of loose connective tissue that surrounds the mucosa. These cells contribute to the section of gastric fluid that accounts for 2 to 3 L. Nerves, lymphatic vessels, and blood vessels are also found in this layer. Organs might be implanted in this layer [6,7].

2.3. Mechanisms of Digestion

Every 15 to 25 s, mixing waves pass over the stomach. As soon as food reaches the pyrolus, each mixing wave periodically forces 3 mL of chyme into the duodenum, a

phenomenon known as gastric emptying. These waves are responsible for the maceration of food known as chyme. This chyme then reaches the pylorus [6,7].

2.4. Migrating Myoelectric Cycle

A series of electrical events occur during this whole process in this fasting state between the stomach and intestine every 2 to 3 h, governed by the enteric nervous system called the migrating myoelectric cycle (MMC), which has four phases [8] as shown in Table 1.

Table 1. Four phases of the migrating myoelectric cycle (MMC).

Sr. No.	Phases	Name	Functioning
1	I	Basal	40 to 60 min with rare contractions
2	II	Pre-burst phase	40 to 60 min of irregular contractions linearly increase in contractions with progression in phase.
3	III	Burst phase	Intense contraction lasting 4 to 6 min.
4	IV	-	Lasts for 0 to 5 min and occurs between phases III and I of two consecutive cycles.

3. Ideal Drug Candidates for GRDDSs

Ideal drugs for GRDDSs have properties such as locally acting drugs in the stomach, drugs having a narrow absorption window in the GI tract, drugs having a narrow absorption window in intestinal or colonic conditions, and drugs having a low solubility in the GI [9].

Advantages of GRDDSs [9,10]:

- ➢ Improvement in the bioavailability aspects of the therapeutic agents;
- ➢ Drugs having a short half-life and sustained release action may result in flip-flop pharmacokinetics, which reduce the frequency of dosing;
- ➢ Local therapy in the GI and intestines with sustained action;
- ➢ Minimize the fluctuation of drug concentration-related effects, which is advantageous for drugs with a narrow therapeutic index.

Disadvantages of GRDDSs [9,10]:

- ➢ Drugs that are degraded by an acidic pH are challenging;
- ➢ Absorption-dependent drugs are challenging to formulate;
- ➢ Dose dumping is a variable concern in this system;
- ➢ Poor In-Vivo/In-Vitro Correlation;
- ➢ The scalability of GRDD formulations is challenging.

4. Strategies for GRDDs

4.1. Pharmacological Approach

Co-administration of drugs with GI-altering agents, such as anti-muscarinic agents, e.g., atropine and benztropine, which delay gastric emptying.

4.2. Physiological Approach

The use of fat derivatives, e.g., triethanolamine myristrate, which stimulate duodenal or jejunal receptors, which slow gastric emptying.

4.3. Pharmaceutical Approach

The pharmaceutical approach is one of the most relevant approaches used to attain gastric retention, as the first two approaches pose alterations to the physiology of the body and may lead to undesired consequences for the circadian rhythm of the body [11,12].

4.4. High-Density System

This approach involves the use of heavy materials with a formulation strategy of coating it with heavy materials or mixing it with iron powder, zinc oxide, or barium sulfate, which allows the formulation to settle in the stomach and retard action due to the high density of the formulation. The formulation of this system is challenging, and no such marketed formulation exists [13].

4.5. Floating System

The floating system is also known as the low-density system. It is also considered one of the most developed formulations as it does not change the motility activity of the GI tract. Many commercial formulations are available worldwide with this approach.

There are two types of floating systems: effervescent and non-effervescent. Effervescent systems have different techniques, such as gas-generating systems, single-layer floating tablets, bilayer floating tablets, multiple-unit floating pills, ion exchange resins, intragastric floating gastrointestinal delivery systems, inflatable gastrointestinal delivery systems, and volatile liquid-containing systems. Non-effervescent systems have a number of different techniques, such as single-layer floating tablets, bilayer floating tablets, alginate beads, and hollow microspheres [14,15].

4.6. Super Porous Hydrogels

These dosage forms have a polymer pore size less than 100 µm, which rapidly causes swelling of the polymer, which is one of the primary properties of this formulation, as delayed swelling may lead to premature evacuation of the dosage form [16,17].

4.7. Mucoadhesive System

This system retains the dosage form by adhering to the gastric region. Different natural, synthetic, and semi-synthetic polymers are used for the development of a muco-adhesive system. This adhesion leads to retention in the GRDDS with the desired release profile with appropriate tailoring of the formulation [17,18].

4.8. Magnetic System

This system simply implies the placement of a magnetic system inside the formulation variable and another magnetic system that will be placed above the abdomen to retain the formulation in the gastric region to achieve gastric residence time [19].

4.9. Raft Forming System

Raft-forming systems are preventive formulations gaining hold over gastro-esophageal reflux that irritates the esophageal region. These formulations form a thick, viscous layer above the gastric contents, restricting the gastric contents from reaching the lower esophageal sphincter, which provides a preventive action for gastric esophageal reflux disease patients. This formulation actually floats on water that is either thick or thin, with a density lower than the gastric contents. Such a type of system is termed as the RAFT system [20,21].

4.10. Nanoparticles

Nanoparticles are materials with overall dimensions below 100 nm. In recent years, these materials have become significant components of modern medicine. Contrast agents in medical imaging and carriers for introducing genes into individual cells are two examples of their applications. Nanoparticles are distinguished from bulk materials simply by virtue of their size, and some of these characteristics include chemical reactivity, energy absorption, and biological mobility [22,23]. Nanoparticles are beneficial to modern medicine in a number of ways. In fact, there are various circumstances in which the utilization of nanoparticles makes it possible to carry out procedures and analyses that would be impractical without them. However, nanoparticles also present their own particular challenges,

especially in terms of toxicity, to society and the environment. The major contributions that nanoparticles have made to modern medicine and the environmental and societal aspects of their application are the focus of this review [24,25].

5. Nano-formulations Targeting Gastroretentive System

5.1. Zero-Valent Iron Nanoparticle

According to Sharma and colleagues, zero-valent iron nanoparticle (ZVINP) gastroretentive high-density pellets were made and characterized. The high-density component was made of barium sulfate, and the release retarding agent was Carbopol ®. The optimized pellets immediately sank in the sinking time test, but the inclusion of Carbopol ® enabled them to delay iron release for 19 h in vitro. The plasma iron concentration remained high for 24 h with few fluctuations, indicating that the pellets released iron in a controlled manner, according to an in vivo study on male Wistar rats that found that the pellets remained in the stomach for 10 h [26].

5.2. Gliadin Nanoparticle

Amoxicillin-containing mucoadhesive gliadin nanoparticles (GNP) and their efficacy in eliminating *Helicobacter Pylori* were demonstrated by Umaheshwari et al. [27], whereby the desolvation method was used to make GNP-bearing amoxicillin (AGNP). Particle size, shape, gliadin concentration, initial drug loading, entrapment efficiency, in vitro release profile, and GNP's mucoadhesive property were all evaluated in relation to process variables. The in vivo gastric mucoadhesive capacity of rhodamine isothiocyanate-entrapped GNP formulations was tested on albino rats. The mucoadhesive property of GNP increased as the concentration of gliadin increased. Typically, the maximum amount of nanoparticles that were still present was 82.4 percent, indicating that GNP had a stronger mucoadhesive propensity and was more specific for the stomach. Growth inhibition experiments on an isolated H. pylori strain were used to measure AGNP's in vitro antimicrobial activity. Due to the controlled drug delivery of amoxicillin from AGNP, the amount of time required to eradicate the infection completely was longer with AGNP than with amoxicillin. Following oral administration of AGNP to infected Mongolian gerbils, the in vivo clearance of H. pylori was investigated. In this experimental model of infection, both amoxicillin and AGNP had an effect on H. pylori, but AGNP required a lower dose to completely eradicate the bacteria than did amoxicillin. The prolonged gastrointestinal residence time attributed to mucoadhesion made AGNP more effective than amoxicillin in eliminating H. pylori from the digestive tract. In order to completely eradicate H. pylori, a dosage form containing antibiotic-bearing mucoadhesive nanoparticles [13,27].

5.3. Floating Nanospheres

The creation of amphiphilic materials based on (meth)acrylate and (meth)acrylamide derivatives that are capable of self-assembling in core–shell structures could be of great interest, given that poly (meth)acrylates are biocompatible materials that are widely used in humans [14,28]. Atom transfer radical polymerizations (ATRP), oxyanionic polymerizations, and reversible addition–fragmentation chain transfer polymerizations (RAFT)—all of which have undergone extensive testing—have already been utilized in order to accomplish this. Amphiphilic block-copolymer preparation has been demonstrated to be quite simple using these tools. The polymerization process will also make use of macromonomers based on polyethylene glycol (PEG), poly monoglycerol methacrylate (PGMA), poly(oligo(ethylene glycol) methyl ether methacrylate polymer (POEGMA), poly (p-phenylene oxide) (PPO), and Polydimethylsiloxane (PDMS). The final assembled particles will benefit from their flexibility and low density/floating properties [15,29].

5.4. Dendrimer Nanocarriers

Dendrimers are one-of-a-kind polymers whose size and structure are clearly defined. One of the most common structures found in all biological systems is dendritic architecture. The following are some examples of dendritic-structured nanometric molecules: glycogen, amylopectin, and proteoglycans. In contrast to linear polymers, the following elements can be distinguished in the structure of dendrimers: a center, dendrons, and surface dynamic gatherings. Dendrons are attached to a single atom or molecule at the core (only if it has at least two functional groups that are identical). The monomer molecules known as dendrons, or dendrimer arms, are linked to the core, resulting in the formation of layers and successive generations (their growth is constrained by space). Surface functional groups determine dendrimers biocompatibility and physicochemical properties [30].

6. Discussion

Recently, many medications have been developed as floating drug delivery systems with the goal of ensuring prolonged release and restricting drug release to the stomach. The concept of buoyant preparation provides a simple and effective method for prolonging the dosage form's stomach residence duration and ensuring sustained medication release. The polymer-mediated non-effervescent and effervescent FDDS that is currently available seem to be a very successful approach for managing controlled oral medication administration based on delayed stomach emptying and buoyancy principles. The most important criteria for the creation of a floating medicine delivery system are that the density of the dosage form be less than that of gastric fluid. GRDDSs have the potential to significantly increase the therapeutic efficacy of medications with a limited window of absorption, high solubility at acidic pH, and instability at alkaline pH. The successful design of a GRDDS requires a detailed understanding of the anatomy and physiological state of the stomach, as well as research into the effects of formulation and process variables on dosage form quality. Even though different GRDDS, including bio/mucoadhesive, magnetic, and low- and high-density systems, have been described in the literature, their clinical importance must be investigated. This leads to the conclusion that these dose types are the most successful for attaining nanomaterial-based drug delivery.

7. Conclusions

Over the years, a number of mechanisms, including magnetic, effervescence, swelling, floating, and sinking, have been proposed. Only a few of the proposed systems have demonstrated efficacy in vivo, despite the majority displaying promising dissolution profiles and in vitro retention. The most common marketed forms at this time are polymeric swelling monolithic systems.

Nanoparticles are very effective for targeted drug delivery in the stomach, including dendrimers, iron oxide nanomaterials, and antibiotics such as amoxicillin to treat esophageal reflex. Novel drug delivery systems, such as nanoparticulate-based drug delivery systems, colloidal carriers, and miscellaneous delivery systems, are introduced to overcome some limitations of large dosages. These systems mainly help in reducing the toxicity and increasing the efficacy of drugs, thus increasing the therapeutic effect of treatment at the site of action.

Future nanomaterial-based GRDDS initiatives may need to concentrate on a combination strategy in order to improve product quality, considering the pharmaceutical industry. In addition, a quality by design (QbD) strategy can be utilized to better comprehend how formulation and process variables affect the performance of the final product.

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