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INNOVATIVE APPROCHES USED INGASTRORETENTIVE DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Pharmaceutical research has recently placed significant emphasis on the development of gastroretentive oral drug delivery systems (GRDDS) to improve drug bioavailability and efficacy. Gastric retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration is ideal to achieve known pharmacokinetic and pharmacodynamic advantages of various categories of drugs. These systems have been designed to address the challenges associated with drugs that are unstable in alkaline pH, soluble in acidic pH, have a limited absorption window, and target specific sites within the stomach. Consequently, a diverse range of dosage forms has emerged, catering to these requirements. Various innovative approaches have been employed in the development of GRDDS, which are discussed in this review. These approaches include the use of novel polymers, such as hydrogels and nanoparticles, as well as the incorporation of stimuli-responsive components, such as pH-sensitive and temperature-sensitive materials. Additionally, the utilization of advanced manufacturing techniques, such as 3D printing, has enabled the creation of complex and personalized drug delivery devices. Furthermore, it explores the various applications of these systems in the field of pharmacy and includes a comparative diagrammatic representation to highlight their key features.

KEYWORDS: Gastroretention, GRDDS, Bioavailability, gastric emptying, 3D printing, controlled release.

INTRODUCTION

Oral ingestion is the primary and preferred route for drug delivery due to its convenience and wide acceptance. The effectiveness of oral drug delivery relies on various factors such as the process of gastric emptying, the transit time of the dosage form through the gastrointestinal tract (GIT), drug release from the dosage form, and the site of drug absorption.[1,2] Time-controlled oral drug delivery systems offer numerous advantages compared to immediate-release forms. They help minimize fluctuations in drug concentrations in both the plasma and the target site over extended periods, leading to optimized therapeutic levels and reduced side effects. Additionally, these systems allow for a lower total dose of the drug while maintaining similar therapeutic effects, as well as a reduced frequency of administration, thereby improving patient compliance. These considerations have led to the development of Gastroretentive drug delivery systems (GRDDS), a unique oral controlled release dosage form with gastro retentive properties.[3-4]

Gastroretentive drug delivery systems (GRDDS) offer significant advantages for drugs with specific characteristics such as low absorption in the lower gastrointestinal tract (GIT), instability and poor solubility at alkaline pH or colonic environment, short half-life, and targeted local activity in the upper part of the intestine to eradicate Helicobacter pylori.[5,6] Various formulation strategies have been employed to develop effective controlled-release GRDDS, including super porous hydrogels, bio/mucoadhesive, raft-forming substances, magnetic substances, ion-exchange, expandable, and low and high density systems.

ANATOMY AND PHYSIOLOGY OF STOMACH[7,8]

A thorough comprehension of the anatomy and physiology of the various regions of the stomach, which includes the proximal stomach comprising the fundus and body, and the distal stomach consisting of the antrum and pylorus, is indispensable for the development of GRDDS. It is essential to possess a profound knowledge of these specific stomach regions to ensure the successful design and formulation of medications that can be retained in the stomach for a desired duration, thus enhancing drug absorption and therapeutic outcomes. The stomach is a vital organ that plays a critical role in the digestion and breakdown of food. It is divided into distinct regions, as depicted in Fig. 1, each with its own unique anatomical and physiological characteristics. A comprehensive understanding of these

different regions is necessary for understanding the functions and processes that occur within the stomach.

1. Proximal Stomach (Fundus and Body): The fundus is the uppermost part of the stomach, located above the cardiac notch, while the body occupies the central portion extending towards the pyloric region. The fundus and body primarily serve as reservoirs for ingested food. They store and mix the food with gastric secretions, promoting the initial stages of digestion. The fundus also plays a role in accommodating gas during gastric distention.

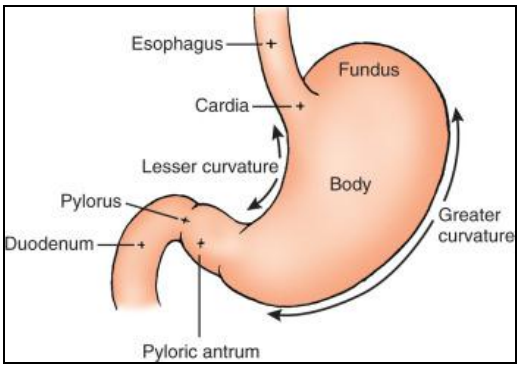

Fig. 1: Physiology of different regions of the stomach.

2. Distal Stomach (Antrum and Pylorus): The antrum is the lower portion of the stomach, situated between the body and the pylorus. The pylorus is the narrow, muscular region connecting the stomach to the small intestine. The antrum is responsible for the grinding and mixing of food, breaking it down into smaller particles. It contracts vigorously to propel the partially digested food (chyme) towards the pylorus. The pylorus acts as a gatekeeper, regulating the passage of chyme into the small intestine.

3. Gastric Secretions: Throughout the stomach, specialized cells produce various substances that aid in digestion. For example, chief cells secrete pepsinogen, which is converted to pepsin, an enzyme responsible for protein digestion. Parietal cells, on the other hand, secrete hydrochloric acid, creating an acidic environment necessary for proper digestion and the activation of enzymes. Gastric secretions also facilitate the breakdown of food and the destruction of potentially harmful microorganisms. The acidic environment in the stomach helps denature proteins, allowing enzymes to work efficiently. The secretions are regulated by hormonal and neural signals to maintain the balance of stomach acid. Understanding the anatomy and physiology of different regions of the stomach is crucial for developing targeted treatments and gastro retentive dosage forms. This knowledge enables researchers to optimize drug delivery, enhance absorption, and improve therapeutic outcomes. By considering the unique characteristics of each region, advancements in medical interventions and treatments can be made to better address various gastric conditions and promote overall digestive health.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)[9,10]: These are the class of oral drug delivery systems designed to prolong the residence time of drugs within the stomach or upper GI tract, allowing for absorption in these regions. Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs allowing for controlled and sustained release of the drug. This improves the drug absorption and bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. These systems are particularly useful for drugs that have specific absorption sites in the stomach or unstable in the alkaline environment of the intestine. It is also suitable for local drug delivery to the stomach and proximal small intestines.

CLASSIFICATION OF GRDDS[11-13]: GRDDS can be classified into several types based on their mechanisms of retention in the stomach:

Swelling and Floating Systems: These systems are designed to float on the gastric contents due to their low density. They contain buoyant materials or gas-generating agents that create a floating effect, keeping the dosage form in the stomach for an extended period. Also, hydrocolloids and polymers that can swell or generate gas upon contact with gastric fluids have been used to develop floating dosage forms. These systems can remain buoyant in the stomach for an extended period, enhancing drug absorption. Materials like hydroxypropyl methylcellulose (HPMC) and low-density polymers are commonly employed in these formulations.

Mucoadhesive Systems: Mucoadhesive dosage forms adhere to the gastric mucosa, prolonging their residence time. They utilize bioadhesive polymers or polymers with mucoadhesive properties have been extensively studied for gastroretentive drug delivery systems. These polymers can adhere to the mucosal lining of the gastrointestinal tract, prolonging the residence time of the dosage form. Examples include chitosan, alginate, and carbomer derivatives.

Expandable Systems: These systems expand or swell upon contact with gastric fluid, which helps in their retention within the stomach. They can be formulated using superdisintegrants, swellable polymers, or osmotically active agents.

Superporous Hydrogel Systems: These systems have three-dimensional networks that can absorb large amounts of water, leading to rapid swelling. These materials have shown promise in gastroretentive systems due to their ability to swell quickly and maintain their structural integrity. Superporous hydrogels based on polymers like poly(acrylic acid) and poly(vinyl alcohol) have been investigated for this purpose.

High-Density Systems: High-density drug delivery systems are designed to sink in the gastric contents,

thereby preventing their passage into the intestine. They are formulated using heavy materials or dense polymers to increase their density.

Magnetic Systems: Magnetic drug delivery systems utilize magnetic materials to enhance gastric retention. External magnets or magnetic fields are applied to keep the dosage form in the desired position within the stomach. Magnetic materials such as superparamagnetic iron oxide nanoparticles have been explored for use in gastroretentive systems. By incorporating these materials into dosage forms, researchers aim to control the retention and localization of the drug in the stomach using external magnetic fields.

3D PRINTING TECHNOLOGY[14-17]: 3D printing has emerged as a promising tool for fabricating personalized GRDDS with complex geometries. Researchers have utilized various polymers compatible with 3D printing techniques to create customized drug delivery systems for improved gastric retention. Following are the recent studies and advancements in 3D printing for drug delivery in the field of pharmaceuticals, offering personalized drug delivery solutions and novel dosage forms.

Personalized Dosage Forms: 3D printing enables the customization of drug doses according to individual patient needs. This personalization can be based on factors such as age, weight, and specific medical conditions, leading to improved treatment outcomes and patient compliance.

Complex Geometries: Researchers have explored the use of 3D printing to fabricate drug delivery systems with intricate geometries that are challenging to achieve with traditional manufacturing methods. These complex structures can provide controlled drug release profiles and enhance drug efficacy.

Multi-Drug Delivery Systems: 3D printing technology allows for the incorporation of multiple drugs within a single dosage form, enabling the development of combination therapies tailored to individual patient requirements. This approach can simplify dosing regimens and improve treatment outcomes.

Controlled Drug Release: By utilizing different printing techniques and materials, researchers have been able to design drug delivery systems with precise control over drug release kinetics. This control can be achieved through modifications in the design of the dosage form, such as porous structures or multilayered constructs.

Printable Pharmaceuticals: The development of printable pharmaceutical formulations, including drug-loaded filaments and inks compatible with 3D printing, has facilitated the fabrication of patient-specific dosage forms. These formulations can be tailored to meet the unique therapeutic needs of individual patients.

Biodegradable and Biocompatible Materials: The use of biodegradable polymers and other biocompatible materials in 3D printing has enabled the production of drug delivery systems that are safe, effective, and well-tolerated by the body. These materials offer the potential for sustained drug release and reduced toxicity.

3D PRINTED DRUG DELIVERY SYSTEMS[18-20]: Researchers have utilized various polymers compatible with 3D printing techniques to create customized drug delivery systems for improved gastric retention. Many researchers and scientist developed specific 3D printed drug delivery systems that highlight the diverse applications of 3D printed drug delivery systems, ranging from orally disintegrating tablets to implantable devices which are given below.

Spritam (Levetiracetam):Spritam is an orally disintegrating tablet containing the antiepileptic drug levetiracetam. It was the first 3D printed drug to receive FDA approval. This tablet was designed to disintegrate rapidly in the mouth, making it easier for patients who have difficulty swallowing conventional tablets.

ZipDose Technology: Aprecia Pharmaceuticals developed ZipDose technology, a 3D printing platform used to create rapidly disintegrating oral dosage forms. This technology allows for the production of high-dose medications even at high dose loads of up to 1,000 mg in a porous, water-soluble matrix, facilitating rapid drug dissolution and absorption.

PolyPill: Researchers have explored the concept of the "Polypill," a single dosage form containing multiple medications for the simultaneous treatment or prevention of multiple conditions. 3D printing technology could be used to customize the composition of the Polypill based on individual patient needs.

Gastroretentive Systems: 3D printing has been utilized to create gastroretentive drug delivery systems that can remain in the stomach for an extended period, improving drug absorption and bioavailability. These systems can be tailored to release drugs at controlled rates based on patient-specific requirements.

Implantable Devices: Researchers have investigated the use of 3D printing to fabricate implantable drug delivery devices that can be placed directly at the site of action. These devices can provide sustained release of medications, reducing the need for frequent dosing and improving patient compliance.

Personalized Dosage Forms:3D printing technology allows for the creation of personalized dosage forms tailored to individual patient needs. By adjusting parameters such as drug concentration, release profile, and geometry, healthcare providers can optimize treatment outcomes for each patient.

Table 1: Marketed Productsof GRDDS.[21-29]

Sl. No	Active ingredient	Brand Name	Dosage Form/ Technology	Company, Country
1	Aluminium hydroxide, Magnesium carbonate	Liquid gavison®	Effervescent floating liquid alginate preparation	Glaxosmithkline, India
2	Aluminium-magnesium antacid	Almagate float coat	Floating dosage form	Pierre fabre drug, France
3	Aluminum–magnesium (antacids)	Topalkan®	Raft-forming system	Pierre Fabre Medicament, Paris, France
4	Baclofen	Baclofen GRS	Floating capsule	Sun pharma, India
5	Carvedilol	Coreg CR®	Floating capsule –osmotic system	Glaxosmithkline, Philadelphia, PA, USA
6	Cefaclor LP	Cefaclor LP	Minextab Floating®: floating and swelling systems	Galanix, Pessac, France
7	Ciprofloxacin	Cifran OD®	Effervescent floating system (film-coated tablet)	Ranbaxy, Mumbai, India
8	Ciprofloxacin HCl	Cipro XR®	Erodible matrix-based system	Bayer, Whippany, NJ, USA
9	Ciprofloxacin	proQuin XR®	Polymer-based swelling system: Acuform™	Depomed, Newark, CA, USA
10	Carbidopa/ levodopa	Accodrion Pill®	Expandable system (unfolding)	Intec Pharma, Tel-Aviv, Israel
11	Diazepam	Valrelease®	HBS floating capsule	Roche, Hertfordshire, UK
12	Ferrous sulfate	Conviron®	Colloidal gel-forming floating system	Ranbaxy, Mumbai, India
13	Gabapentin	Gabapentin GR®	Floating tablet	Depomed, USA
14	Levodopa benserzide	Madopar HBS ®	HBS Floating capsule	Roche, Hertfordshire, UK
15	Levodopa and benserazide HCl	Prolopa HBS®	HBS floating capsule	Roche, Hertfordshire, UK
16	Misoprostal	Cytotec ®	Bilayer floating capsule	Pfizer, Sandwich, UK
17	Metformin HCl	Metformin HCl	Minextab Floating®: floating and swelling systems	Galanix, Pessac, France
18	Metformin HCl	Riomet OD®	Effervescent floating system (film-coated tablet)	Ranbaxy, Mumbai, India
19	Metformin HCl	Glumetza®	Polymer-based swelling system: Acuform™	Depomed, Newark, CA, USA
20	Metformin HCl	Metformin GR™®	Polymer-based swelling system: Acuform™	Depomed, Newark, CA, USA
21	Nisoldipine	Sular®	Geomatrix™	Skyepharma, Shionogi Pharma Inc., London, UK
22	Ofloxacin	Oflin OD®	Gas generating floating tablet	Ranbaxy, India
23	Ofloxacin	Zanocid OD®	Effervescent floating system (film-coated tablet)	Ranbaxy, Mumbai, India
24	Prazosin HCl	Prazopress XL ®	Effervescent and swelling based floating system	Sun Pharma, Gujarat, India
25	Simethicone and aluminum–magnesium salts	Inon Ace Tablets®	Floating and swelling systems	Sato Pharma, Akasaka, Japan
26	Tramadol LP	Tramadol LP	Minextab Floating®: floating and swelling systems	Galanix, Pessac, France
27	Verapamil HCl	Covera HS®	OROS	DURECT Corporation, Cupertino, CA, USA

APPLICATIONS OF GRDDS[30-32]**:** Following are the categories of drugs that can benefited from GRDDS.

1. Proton Pump Inhibitors (PPIs): Drugs like omeprazole and pantoprazole, which are used for the treatment of gastroesophageal reflux disease (GERD) and peptic ulcers, can benefit from gastroretentive systems. By prolonging their gastric residence time, these systems can enhance drug release and improve their efficacy in reducing gastric acid secretion.

2. Antiviral Agents: Certain antiviral drugs, such as acyclovir and oseltamivir, are known to have low oral bioavailability due to their poor solubility and limited absorption in the small intestine. Gastroretentive systems can enhance their solubility and prolong their exposure in the stomach or upper GI tract, thereby improving their bioavailability.

3. Antidiabetic Drugs: Drugs like metformin, which is commonly used for the treatment of type 2 diabetes, often exhibit limited absorption in the small intestine. Gastroretentive systems can improve drug solubility and prolong drug release, leading to enhanced absorption and better glycemic control.

4. Antiemetics: Drugs used to manage nausea and vomiting, such as ondansetron and granisetron, can benefit from gastroretentive delivery systems. These systems can provide sustained drug release, ensuring prolonged antiemetic action and reducing the frequency of dosing.

5. Antibiotics: Certain antibiotics, including clarithromycin and amoxicillin, can be formulated as gastroretentive systems. These systems can improve drug solubility, enhance gastric residence time, and target drug delivery to the upper GI tract, optimizing their absorption and efficacy against gastrointestinal infections.

6. Analgesics: Drugs like tramadol, which is used for the management of moderate to severe pain, can benefit from gastroretentive systems. By prolonging drug release and exposure in the stomach, these systems can provide sustained pain relief and reduce the frequency of dosing.

FORMULATION CONSIDERATIONS[33]: There are various factors to be consideredduring the formulation of GRDDS. These includes the choice of suitable polymers, drug release mechanisms, dosage form design, and compatibility with the physiological environment of the stomach, density and size of the dosage form, gastric motility, food intake, and patient-specific factors. Apart from these, GRDDS must be effective retention in the stomach to suit for the clinical demand, must have sufficient drug loading capacity. It should control the drug release profile and must have full degradation and evacuation of the system once the drug release is over. Simultaneously, it should not have any effect on gastric motility including emptying pattern and other local adverse effects.

CHALLENGES ASSOCIATED WITH THE FORMULATION OF GRDDS[34,35]

Formulation Complexity: Designing GRDDS requires intricate formulation techniques to ensure sustained drug release while maintaining gastro-retention properties.

Gastrointestinal Variability: The variability in gastrointestinal conditions among individuals can affect the performance and consistency of GRDDS formulations.

Gastric Emptying: Achieving prolonged gastric retention without compromising on the timing of drug release can be challenging due to factors influencing gastric emptying rates.

Safety Concerns: Ensuring the safety of GRDDS formulations, such as preventing dose dumping or adverse effects due to prolonged drug release, is crucial.

Biocompatibility: Materials used in GRDDS must be biocompatible and safe for long-term gastrointestinal use to avoid irritation or other adverse reactions.

Drug Compatibility: Certain drugs may not be suitable for GRDDS formulation due to their chemical properties or interactions with the delivery system. Regulatory Approval: Meeting regulatory requirements for GRDDS formulations, including demonstrating efficacy, safety, and consistency, can be a lengthy and challenging process.

Manufacturability: Ensuring scalability and reproducibility of GRDDS production processes while maintaining the desired drug release profiles can be technically demanding.

Cost: Developing GRDDS formulations may involve higher research and development costs due to the complexity of formulation and testing requirements.

Market Acceptance: Convincing healthcare providers and patients of the benefits and advantages of GRDDS formulations over conventional dosage forms may present a challenge in terms of market acceptance and adoption.

ADVANTAGES OF GRDDS[36,37]: GRDDS formulations offer several advantages in terms of enhanced bioavailability, improved patient compliance, reduced side effects, and targeted therapy as summarized as follows;

Enhanced Bioavailability: GRDDS enhances the bioavailability of drugs compared to non-GRDDS by optimizing drug absorption in the gastrointestinal tract.

Enhanced First-Pass Biotransformation: It sustains drug metabolism, particularly by enzymes like cytochrome P450, leading to increased efficacy and reduced side effects.

Sustained Drug Delivery: GRDDS provides sustained drug release, reducing dosing frequency and improving patient compliance.

Targeted Therapy: It enables targeted therapy for ailments in the upper gastrointestinal tract, maintaining local therapeutic levels while minimizing systemic exposure.

Reduced Fluctuations: These formulations minimizes fluctuations in drug concentration, reducing side effects and ensuring more consistent drug effects.

Improved Selectivity: By controlling drug concentration fluctuations, GRDDS can enhance selectivity in pharmacological effects.

Reduced Counter-Activity: Slow drug input minimizes counter-activity of the body, improving drug efficiency.

Extended Critical Concentration Time: For drugs with non-concentration dependent effects, these formulations extends the time over critical therapeutic concentrations, enhancing pharmacological effects.

Minimized Colon Activity: Retaining drugs in the stomach with GRDF can prevent unwanted drug activities in the colon, reducing side effects and potential resistance development.

Site-Specific Delivery: These formulations are beneficial for drugs with limited absorption sites in the upper small intestine, providing local therapeutic levels, limiting systemic exposure, and reducing dosing frequency.

However, these systems also have limitations, including inter- and intra-patient variability, potential food-drug interactions, and the risk of gastric retention-related adverse effects.

CONCLUSION

Gastroretentive drug delivery systems (GRDDS) have emerged as crucial innovations in the past thirty years, offering distinct advantages such as targeted, gradual, and regulated drug release from diverse gastroretentive dosage forms. These systems enhance patient adherence and diminish side effects by reducing dosing frequency. Overall, GRDDS provide a promising approach to optimize oral drug delivery and improve the therapeutic outcomes of medications. Consequently, it is anticipated that numerous pharmaceutical firms will increasingly adopt gastroretentive drug delivery technologies in the future to gain significant advantages, extend patent lifecycles, and enhance the efficacy of their existing formulations on the market.

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