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Advancements in Gastro Retentive Drug Delivery Systems: Optimizing Drug Efficacy and Prolonging Gastric Retention– A Review

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ABSTRACT:
Gastro Retentive Drug Delivery Systems (GRDDS) is a very unique and developed method of the drug-delivering system that is designed to keep drugs in the stomach for a longer time, increasing drug absorption and effectiveness. These systems are particularly useful for drugs that have optimal absorption in the stomach or broken down in the intestines. Gastro Retentive Drug Delivery Systems use methods such as Floating, Swelling, Mucoadhesive, High-Density, Magnetic and Raft-Forming methods for optimizing effectiveness, targeted and controlled drug release that increases the gastric retention time of the drugs. Although Gastro Retentive Drug Delivery Systems have many benefits, such as better drug absorption, localised treatment, and reduced dosing frequency, they also have limitations, such as gastric emptying, pH changes, enzymatic degradation, and patient variability that affect the therapeutic of the drug. Recent advances in 3D printing technology and AI-driven drug manufacturing are increasing the efficiency and customization of Gastro Retentive Drug Delivery Systems.

KEYWORDS: GRDDS, Residence Time, FDDS, Polymeric Expansion Systems, mucoadhesive systems,
High-Density Systems, Magnetic Drug Delivery Systems, Raft-Forming Systems.

I. INTRODUCTION

Gastro Retentive Drug Delivery Systems (GRDDS) are one of the specialised drug delivery mechanisms designed to retain drugs in the stomach for a greater period, therefore enabling better bioavailability and improved therapeutic effects of the drugs[1]. These delivery systems are very useful for drugs when there is a narrow absorption window in the upper gastrointestinal (GI) tract, when a drug is unstable within the intestinal environment, or when drugs get absorbed mainly in the stomach.

GRDDS overcome several barriers including increased gastric emptying and pH variations, hence ensuring that drugs remain in the stomach long enough for appropriate absorption to be occurring. Floating, swelling, bio-adhesive, and high-density systems are some of the other techniques primarily used for providing increased gastric residence time to the drug. GRDDS thus improves the gastric retention and absorption of drugs, minimizes dosing frequencies, improves patient compliance, and results in a better outcome of therapy for those drugs having very low bioavailability in the intestines[2].

Overview of Gastro retentive Drug Delivery Systems (GRDDS):

GRDDS focuses primarily on the prolongation of the residence time of a pharmaceutical agent within the stomach and the upper GI tract. This prolonged gastric residence time is essential for drugs whose optimal absorption usually takes place in the upper GI tract, or whose agent requires a longer contact time with the gastric mucosa. GRDDS can very highly enhance drug efficacy, by keeping the dosage form within the stomach for longer times[3].

Challenges in Gastro retentive Drug Delivery Systems:

In contrast, Gastro retentive drug delivery systems suffer many barriers that affect the release of drugs. Another potential challenge to the GI tract is pH variation. The stomach is more acidic than the intestines, while the intestines are more alkaline. Such fluctuations might cause the degradation of medicines, especially for drugs that are sensitive to pH changes. This means that there would be

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instances when the effectiveness of the medications is lost even before the desired site for absorption is achieved[4].

A further challenge arises as regards the gastric emptying time, which varies extensively and is dependent on several factors such as the intake of food, age, and health condition. Rapid gastric emptying would lead to early loss of the drug from the stomach, lowering the absorption period and limiting its effectiveness[5].One major problem regarding enzymatic degradation exists in pharmacology. There are digestive enzymes in the stomach such as the active medicine, which are mostly proteins and peptides. This would lead to the lowering of the drug's bioavailability and hence its efficacy as a result of biochemical degradation[6].

Additionally, the mucosal barrier – a thick layer of mucus that covers the stomach and intestines – may block drug absorption. This barrier eliminates the effective diffusion of large or hydrophilic molecules, thus restricting the complicating administration of some drugs. Some of the additional constraints of GRDDS systems include the capacity for limited drug loading, especially in floating or bioadhesive systems. The available space in these systems to load drugs is minimal and may require multiple doses, thereby making them complicated or necessarily large systems. Apart from all this, variability among patients such as age, gastric motility, and health conditions can affect the performance of GRDDS. These individual variations suggest the system might vary greatly in potency from patient to patient, complicating uses in drug delivery with unreliable results[7].

Advantages of Gastro retentive Drug Delivery Systems (GRDDS):

This system has several advantages such as[8][9] :

1. Enhanced Bioavailability:

- **Increased Absorption:** The GRDDS expands the gastric or upper GI residence time which allows for better absorption of poorly soluble or unstable drugs in the intestinal environment and may achieve higher concentration levels of drugs in systemic circulation.
- **Reduced Drug Degradation:** GRDDS can significantly reduce chemical degradation which is caused by the enzymes or pH changes, thereby well maintaining the drug's efficacy.

2. Improved Absorption:

- **Controlled Delivery:** GRDDS can be designed to deliver the drug in a controlled manner to specific sites in the GI tract, anddrugs that act locally or are absorbed in such specific sites can be targeted that improve the absorption.
- **Consistent Drug Levels:** Long gastric retention provides stabilization of plasma drug levels that can improve therapeutic outcomes and reduce the frequency of dosing of drugs.

3. Targeted Drug Release:

- **Localized Treatment:** For drugs designed to be locally acting in the stomach or upper GI tract- for example, in the treatment of gastric ulcers- GRDDS will ensure that delivery of the drug actually will reach the target site of activity.
- **Site-Specific Release:** Advanced GRDDS technologies could be used for targeted site-specific drug delivery.

II. DIFFERENT TYPES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS:

Many types of systems are used in GRDDS such as:

1.Floating Drug Delivery Systems (FDDS):

A floating Drug Delivery System (FDDS) is an appropriately designed drug delivery system that floats within the stomach and thus elongates its stay within the gastric environment. This method has a high prominent for drugs that have good absorption in the upper gastrointestinal tract or drugs that are targeted for localized therapeutic applications in the stomach. There are merely two types of Floating Drug Delivery Systems: effervescent and non-effervescent[10].

- **Effervescent Systems:**

The objective of the Effervescent Floating Drug Delivery Systems (FDDS) is to produce gas through a chemical reaction when it comes in contact with gastric fluids which causes the drug to float in the stomach's gastric juices. By increasing the drug's half-life in the stomach, this floating mechanism increases the drug's better drug absorption and therapeutic efficacy[11].Two effervescent materials that are mainly used in the effervescent systemto keep it working are sodium bicarbonate and citric acid. When these effervescent materials come in contact with stomach fluids, they produce carbon dioxide gas. these produced gases get trapped in the matrix system of the drug polymer, and the gas forms structures like foam, which gives the drug its buoyancy. This floating movement of the drug helps to keep the drug in the upper part of the stomach, which increases the drug

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retention time. Additionally, the gases that are captured by the matrix system, maintain the system's buoyancy and provide rigidity to the drug[12].

- **Non-Effervescent Systems:**

The non-effervescent Floating Drug Delivery Systems (FDDS) expand or inflate the drug physically which causes the drug buoyancy without creating any gas. when non-effervescent Floating systems have come in contact with the gastric fluids they absorb gastric fluids, causing them to expand. As a result, the density of the drug will decrease, allowing it to float on top of the stomach fluids.Different Superabsorbent polymers are used in this system because of their ability to keep their buoyancy when the drug swells. cellulose derivatives are very commonly used polymers in non-effervescent systems because of their ability to absorb water and expand. These polymers ensure that the drug systems will remain in the upper portion of the stomach[13].

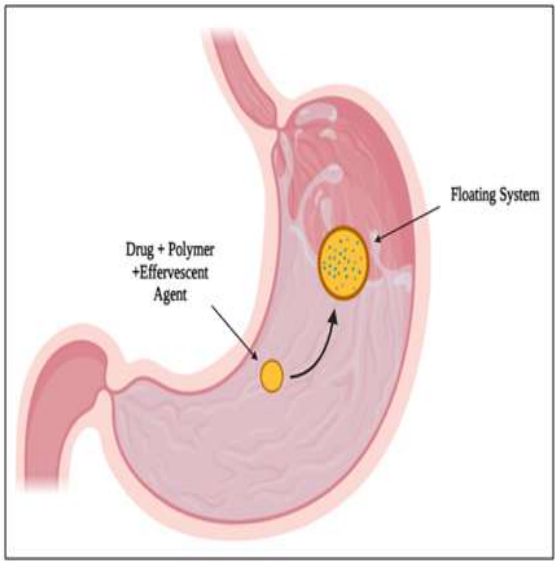

FIG1: FLOATING DRUG DELIVERY SYSTEM

2. Swelling and Expanding Systems:

Swelling and expanding systems are used in GRDDS to prolong the gastric residence time of the drug by swelling the dosage form after contact with the stomach fluids. These swelling and Expanding Systems are very useful in controlled-release preparations and pharmacological agents that need longer exposure to the stomach[14].

- **Hydrogel-Based Systems:**

One of the popular ways of the swelling system established to enhance the drug buoyancy and retention time in the stomach is hydrogel-based systems. These systems absorb fluids when exposed to gastric juices of the stomach, increasing their retention time and effectiveness for sustained-release drug administration. Swelling causes the increase in size of the drug that prevents it from passing the drug through the pyloric sphincter[6]. Hydrogel systems use hydrophilic types of polymer and have the purpose of absorbing the fluids of the stomach environment. As the fluid gets absorbed by the polymer, the hydrogel expands significantly.This absorption causes the drug's density to decrease, which allows it to float on top of the stomach. Alongside synthetic polymers like polyvinyl alcohol (PVA) and polyacrylamide, natural polysaccharides like chitosan and alginate, which are valued for their high water absorption ability and biocompatibility, these polymers are also used to develop hydrogel-based systems[15].

The hydrogel-based systems control drug release profiles, this feature is very important in the case of controlled-release formulations due to its swelling behaviour and improved structural stability. Thus, extending the contact time of the drug with the mucosa of the gastric region provides an improvement in the therapeutic effects of the drug. The choice of the polymer, matrix formulation and pH of the stomach greatly influence swelling and effectiveness of the drug[16].

- **Polymeric Expansion Systems:**

GRDDS systems like polymeric expansion use polymers that increase the volume upon contact with gastric fluids. That polymeric expansion of the system causes absorption of the stomach fluids and can increase the retention time of the drug by preventing the drug from passing through the pyloric sphincter[14].These systems use hydrophilic polymers, such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), Carbopol, and Poloxamers, which are cellulose derivatives that are known for expanding and absorbing the fluids. A naturally occurring polysaccharide like pectin is also used for its capacity to form a gel. This feature is very helpful for this type of drug delivery system because it maintains the drug in the gel matrix for a longer time and provides rigidity to the system, causing increases in retention time[17].

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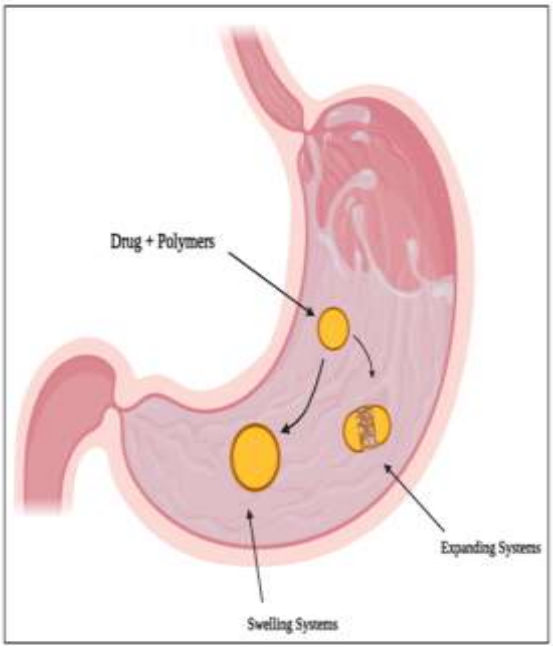

FIG2:SWELLING AND EXPANDING SYSTEM

3. Bioadhesive or Mucoadhesive Systems:

Bioadhesive and mucoadhesive are the types of drug delivery systems that are designed to stick to the stomach's mucosal surfaces. The drug's time of residence at the site of action is extended by this adhesion method, which improves drug absorption and therapeutic efficacy[18].

- **Polymeric Mucoadhesive:**

The process of polymeric mucoadhesion plays an important role in prolonging the half-life of the drug in the upper gastrointestinal (GI) tract. This method uses bioadhesive polymers to improve the therapeutic efficacy of the drug through targeted or sustained release.The process of polymeric mucoadhesion plays an important role in prolonging the half-life of the drug in the upper gastrointestinal (GI) tract. This method uses bioadhesive polymers to improve the therapeutic efficacy of the drug through targeted or sustained release. The mechanism starts when the mucosal surface comes into contact with the bioadhesive polymer, and stomach fluids improve the polymer's interaction with the mucosa[19].

After getting into contact with mucosa, the chains of polymers entangle each other by entering through the mucin glycoproteins that are in the mucus layer. This polymeric interaction is dependent on various factors such as several factors, such as the molecular weight, concentration, and swelling capacity of the polymer.Stronger adhesive bonds are formed between the polymer and mucosa layer during the consolidation process. These reactions make sure the drug form stays at the application site for longer periods of time.Bioadhesive polymers can be made from natural or synthetic materials. While natural biomaterials like xanthan gum, chitosan, and alginate are used as bioadhesive polymers, synthetic biomaterials like polycarbophil and polyvinyl alcohol (PVA) have been chosen for their long-lasting adhesive properties for these systems. This technology is very useful for targeted and sustained-release drug delivery systems[20].

- **Mucoadhesive Microparticles:**

Mucoadhesive microparticles are advanced and specially designed particles that provide targeted as well as controlled drug delivery by adhering to the mucosal surfaces of the stomach. This system allows localised treatment that increases the therapeutic efficacy of drugs.

In the case of polymeric mucoadhesion, the mucoadhesive polymers are used that adhere to the mucosal layer of the stomach. Mucoadhesive microparticles, on the other hand, consist of tiny drug-loaded particles that have been coated with a mucoadhesive polymer. these microparticles adhere to the mucosa individually, giving a more distributed surface area that increases drug distribution and specific delivery. This enables greater efficiency and drug absorption[21].

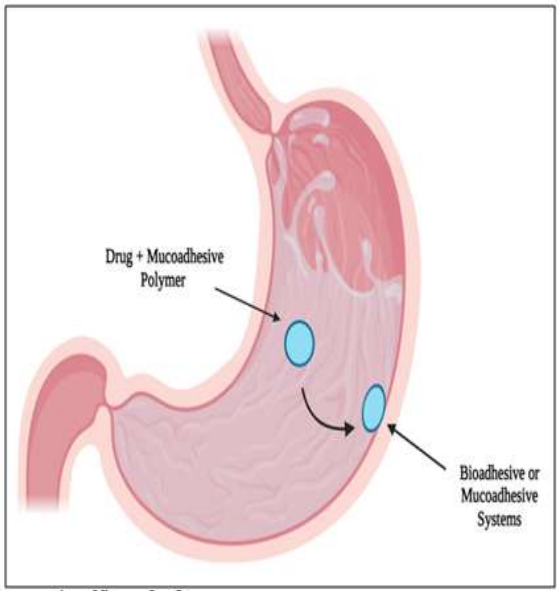

FIG3: MUCOADHESIVE SYSTEM

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4. High-Density Systems:

High-density systems are one of the prominent gastro-retentive drug delivery systems that are designed to extend the time that dose forms remain in the stomach. By using materials that are high in density, which allow the dose form to remain in the stomach for extended periods, this technique bypasses the effects of gastric motility and prevents early emptying of the drugs[22].

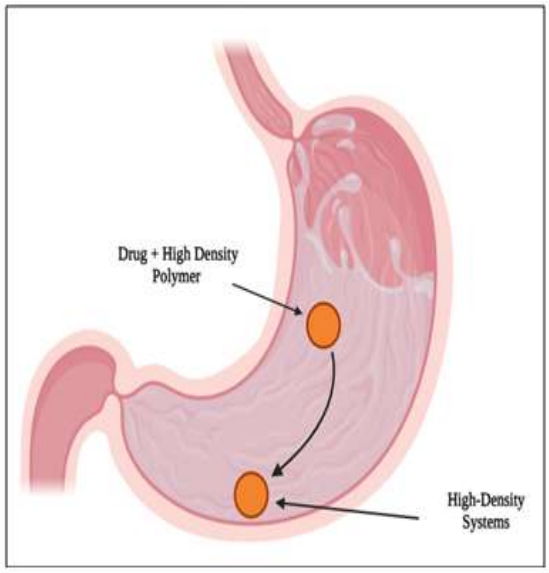

FIG 4: HIGH-DENSITY SYSTEM

The method uses materials that have a density greater than that of gastric fluids present in the stomach (around 1.004 g/cm³) to ensure that the drug will fall and stay at the bottom of the stomach. The greater density of this type of formulation helps in its resistance to stomach motions. Materials that are often used in high-density systems include barium sulphate, and calcium carbonate, which are heavy, non-toxic, biocompatible materials[23]. These compounds have been chosen according to their ability to increase density without interacting with the release, absorption or therapeutic effects of drugs.High-density systems are useful for drugs that require a longer stomach residence time to increase bioavailability or therapeutic effectiveness. for controlled-release formulations which provide a constant, prolonged release of the drugs, they are particularly helpful for this type of system.

5. Magnetic Systems:

Magnetic systems are a very innovative and advanced approach to GRDDS, which employs magnetic fields or magnets to improve drug positioning and retention time in the GI tract. This system improves the therapeutic effects and drug bioavailability of the drug by maintaining the drug in a particular area of the stomach[11].To enhance drug retention in a specific region of the stomach or intestine, external magnetic fields are applied to position within the gastrointestinal tract. This technique is known as a magnetic system for gastrointestinal drug delivery[24].

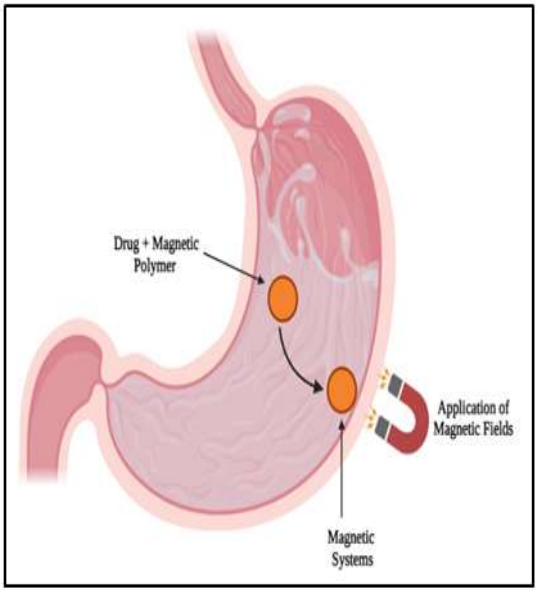

FIG 5: MAGNETIC SYSTEM

Superparamagnetic iron oxide nanoparticles (SPIONs) are used as coating of the drug form and are derived from magnetic materials. An extracorporeal magnet is set over the stomach to bring the internal drug into contact with an external magnetic field. This extends the dose form's retention time and prevents early emptying from the stomach by enabling precise control over the location it is placed inside the stomach or GI tract. This increases the drug's bioavailability by improving its plasma drug concentration in the blood.Therefore, magnetic systems provide an effective way of enhancing the GRDDS. They offer an innovative approach to the field of gastroretentive drug delivery technologies that significantly increase the therapeutic efficacy of many drugs[1].

6.Raft-Forming Systems:

The raft-forming system is a very unique cutting-edge GRDDS technique. Its purpose is to create a gel-like structure to produce a covering or raft that causes the drug to float on top of stomach

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contents. This floating gel is especially useful for conditions affecting the gastrointestinal mucosa because it creates a larger surface area for the drug release, enabling more targeted therapy and extended drug release[25].

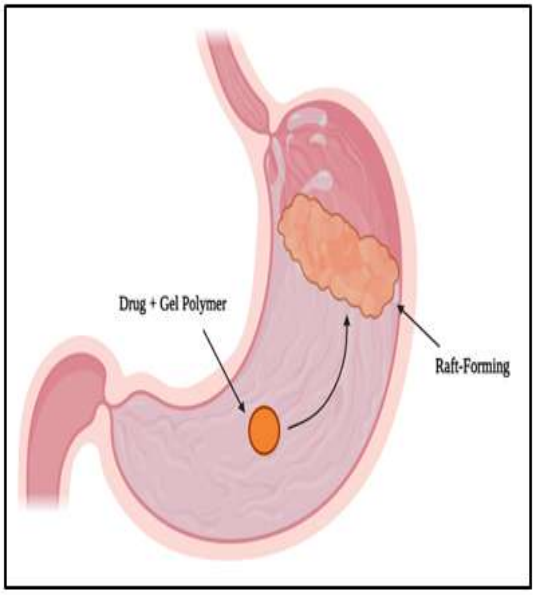

FIG 6: RAFT-FORMING SYSTEM

Alginates and bicarbonate-based polymeric formulations are used in raft-forming systems. Alginates are naturally occurring polysaccharides that are derived from seaweed that get in contact with gastric acid to form a gel that floats on top of the stomach fluids[6]. these systems also produce carbon dioxide when bicarbonate salts, such as sodium or potassium bicarbonate react with stomach acids that provide stability and grate buoyancy. Ingredients used in these formulations, like alginates and bicarbonate salts, give the drug a stable release while increasing the duration of the drug in the stomach. these floating barriers are also useful in treating conditions like gastro-oesophageal reflux disease because can help in reducing acid reflux[26].

III. EMERGING TRENDS IN GRDDS:

Different Emerging Future Trends Gastro Retentive Drug Delivery Systems (GRDDS) are changing the industry by using cutting-edge technologies and materials[27].

- **Personalized Medicine and 3D Printing**:

Personalized Medicine and 3D Printing technology can help in personalised GRDDS with precise control over drug loading and drug release profiles can be utilised.

For example, Eli Lilly's 3D-printed oral dosage forms can used as customized and precise doses for individual patients[28].In the same way, specially designed 3D printed tablets can used for the patients with cancer, which enable precise dose administration for chemotherapy components to specific regions of the GI tract, improving the effectiveness of the drug while reducing the adverse effects and cost[29].

- **Artificial Intelligence and Machine Learning in Formulation Design:**

Various methods such as Machine learning methods can help in identifying the optimal formulation for sustained-release insulin delivery devices, while DeepMind's AI can mimic the normal stomach and pancreatic function to improve glycaemic management to keep blood sugar levels within the normal range[30]. Furthermore, IBM Watson analyses the data from earlier GRDDS experiments from their database to optimise drug release and formulation of the drug, which can speed up the development of future GRDDS[31].

- **Biodegradable and Stimuli-Responsive Polymers:**

Biodegradable floating tablets are made of polymer-like poly(lactic-co-glycolic acid) (PLGA), which easily breaks down within the system while releasing drug components to cure stomach ulcers. Stimuli-respond hydrogels use polymers like carbopol or chitosan, which can expand or contract depending on the changes in the stomach's pH. This makes it possible to control the drug release that is dependent on particular pH values[32].These developments in GRDDS show how customised and sustained drug release may contribute to better patient compliance, increased therapeutic efficacy, and better drug delivery.

IV. CONCLUSION:

Gastro Retentive Drug Delivery Systems provide a bright spot for improved bioavailability and efficacy of drug molecules especially for drugs that require prolonged gastric residence. The various methods, such as floating, swelling, bioadhesive, high-density, magnetic, and raft-forming systems, each offer unique benefits for overcoming challenges such as gastric emptying, pH variability, and enzymatic degradation etc. Technologies such as 3D printing and AI-guided formulation

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approaches are enhancing the GRDDS, to offer precise and controlled drug release kinetics. However, outbound technologies like 3D printing, AI-driven formulation design, and the use of biodegradable and stimuli-responsive polymers are poised to optimize GRDDS, paving the way for more personalized, efficient, and controlled drug delivery solutions in the future.

List of abbreviations:

Table 1: Abbreviations

Sl.no	Abbreviation	Full Form
1	GRDDS	Gastro Retentive Drug Delivery Systems
2	FDDS	Floating Drug Delivery Systems
3	GI	Gastrointestinal
4	PVA	Polyvinyl Alcohol
5	AI	Artificial Intelligence
6	HPMC	Hydroxypropyl Methylcellulose
7	MC	Methylcellulose
8	SPIONs	Superparamagnetic Iron Oxide Nanoparticles
9	PLGA	Poly(Lactic-Co-Glycolic Acid)

Author contributions:

Ayan Chandra has carried out extensive research on the Gastro Retentive Drug Delivery Systems, and other related topics to gather relevant information. The abstract, title and all information were collaboratively written by Sumit Prasad Bhakat and Ayan Chandra. All authors contribute to different sections and ensure coherence and clarity throughout the document. All authors participated in reviewing and refining the abstract, incorporating feedback, and ensuring the accuracy of information.Final approval for the submission was given by all authors.

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