Review on Gastroretentive Drug Delivery Systems with Emphasis on Film Type

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Abstract:

Gastroretentive drug delivery systems (GRDDSs) are highly promising methods for the enhancement of the bioavailability and therapeutic effectiveness of some orally administered medications. The present review focused on gastroretentive film drug delivery methods, specifically developed to extend the duration of medication presence in the stomach which is most likely to enhance their absorption and efficacy. The review examines different types of gastroretentive films, such as floating, mucoadhesive, and expandable films, emphasizing their respective modes of action, benefits, and drawbacks. Furthermore, the review includes an evaluation of gastroretentive films, which include *in vitro* buoyancy, swelling index, tensile strength, and drug release kinetics. The prospective clinical uses of these systems in the management of gastrointestinal problems and other medical conditions are also investigated. Lastly, the paper examines the difficulties and potential opportunities for the advancement and commercialization of gastro-retentive film drug delivery systems.

Keywords: Expandable, film, gastroretentive, mucoadhesive.

مراجعة لأنظمة توصيل الأدوية المُحتجَزة في المعدة مع التركيز على نوع الاشرطة

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الخلاصة:
إن أنظمة توصيل الأدوية المُحتجَزة في المعدة هي طرق واعدة للغاية لتحسين التوافر الحيوي للأدوية التي يتم تناولها عن طريق الفم. ركزت المراجعة الحالية على طرق توصيل الأدوية من خلال الاشرطة المُحتجَزة في المعدة، والتي تم تطويرها خصيصًا لتمديد مدة وجود الأدوية في المعدة، وتعزيز امتصاصها وفعاليتها. تدرس المراجعة أنواعًا مختلفة من الاشرطة المُحتجَزة في المعدة، مثل الاشرطة العائمة، والاشرطة اللاصقة المخاطية، والاشرطة القابلة للتمدد، مع التركيز على طرق عملها وفوائدها وعيوبها. علاوة على ذلك، تتضمن المراجعة تقييمًا للأشرطة المُحتجَزة في المعدة، والتي تشمل الطفو داخل المختبر، ومؤشر الانتفاخ، وقوة الشد، وتحرر الدواء. اضافة الى الاستخدامات السريرية المستقبلية لهذه الأنظمة في إدارة مشاكل الجهاز الهضمي وغيرها من الحالات الطبية. أخيرًا، يدرس المقال الصعوبات والفرص المحتملة لتطوير وتسويق أنظمة توصيل الأدوية المُحتجَزة في المعدة.

الكلمات المفتاحية: قابلة للتمدد، أغشية، المُحتجَزة في المعدة، لاصق مخاطي.

Introduction

The dominance of oral drug delivery systems over other drug delivery methods for human administration can be attributed to their several advantages, including convenient administration, formulation flexibility (immediate, delayed, and sustained drug release formulations), cost-effectiveness, convenient storage and transportation, and optimal patient compliance. However, some factors may affect the bioavailability of some drugs taken orally such as the variety of the gastrointestinal system, pH of the gut flora, gastric retention time of the dosage form, enzymatic activity, surface area, narrow absorption widow, short half-life, degradation in alkaline pH, physicochemical properties of the drug, disease states, drug interaction and genetic factor. These factors may also have a negative effect on the development of sustained-release oral formulations. Scintigraphy studies assessing gastric emptying rates have shown that orally delivered controlled-release dosage forms typically have two main problems, an unpredictable rate of gastric emptying and short gastric residence time (SGRT) [1]. The effect of short gastric transient time is particularly evident in the bioavailability of drugs with narrow absorption window [2–4].

An innovative strategy in this field is gastroretentive drug delivery systems (GRDDSs) which are dosage forms that can be retained in the stomach for a prolonged period. The primary benefits of their prolonged retention are the ability to improve bioavailability, provide targeted drug delivery for the treatment of GI disorders, and the need for repeated dosing is reduced, leading to a reduction in GI disorders [5]. However, a drawback of GRDDSs is their incompatibility with compounds that irritate the stomach mucosa, as compared to conventional dosage forms [6].

Physiology of Stomach

Understanding the anatomical and physiological structure and function of the stomach is crucial for effectively developing gastroretentive pharmaceutical formulations. The stomach is anatomically divided into three regions as seen in Figure 1: the fundus is the proximal portion towards the esophagus, the body which serves as a reservoir for undigested substances, and the antrum. The antrum is the final part that links the body to the small intestine and also is the main part of mixing motions. It acts as a pump for gastric emptying by propelling action. Gastric emptying occurs in both states, such as fasting and fed state [6].

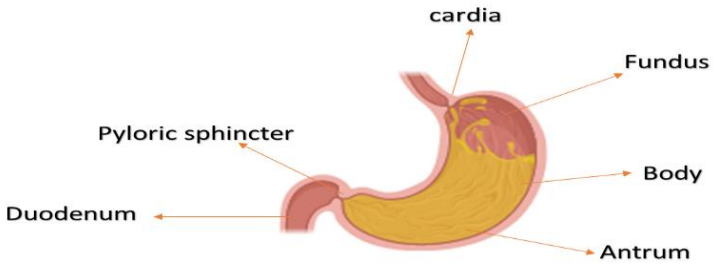

Figure (1): Anatomy of the stomach [7]**. Created with biorender**

The migrating myoelectric cycle (MMC) refers to a series of contractions that take place cyclically in the stomach and intestine every 120-180 minutes during the fasting condition. In the fed state after a meal, the gastrointestinal motility pattern remains for 4–6 hours, or longer for high-fat or large meals, before transitioning back to the fasting state and the MMC [8]. MMC is further subdivided into four distinct stages. Digestive motility pattern refers to the alterations in contraction patterns during a fed condition. This pattern consists of four phases: Phase 1, Basal phase; Phase 2, Pre burst phase; Phase 3, Burst phase; and Phase 4 as seen in Figure 2 [9]:

1- **Phase I (Basal phase)**: This phase shows rare contraction that lasts from 40-60 min.

2- Phase II (Pre-burst phase): This phase shows contraction and intermittent potential lasts 40-60 min.

3- Phase III (Burst phase): This phase shows regular and intense contraction that lasts from 4-6 min for a short period. This is due to the undigested materials being swept out of the stomach and into the intestine, and this is also known as housekeeper waves [10].

4- Phase IV: This phase occurs between phase III and phase I of two consecutive cycles. Commonly referred to as the digestive motility pattern, this involves ongoing contractions similar to those seen in phase II of a fasting condition. These contractions decrease the size of food particles to less than 1mm, which are then driven into the pylorus in a suspended state. In the fed condition, the initiation of MMC is postponed, leading to a decrease in the stomach emptying rate [11].

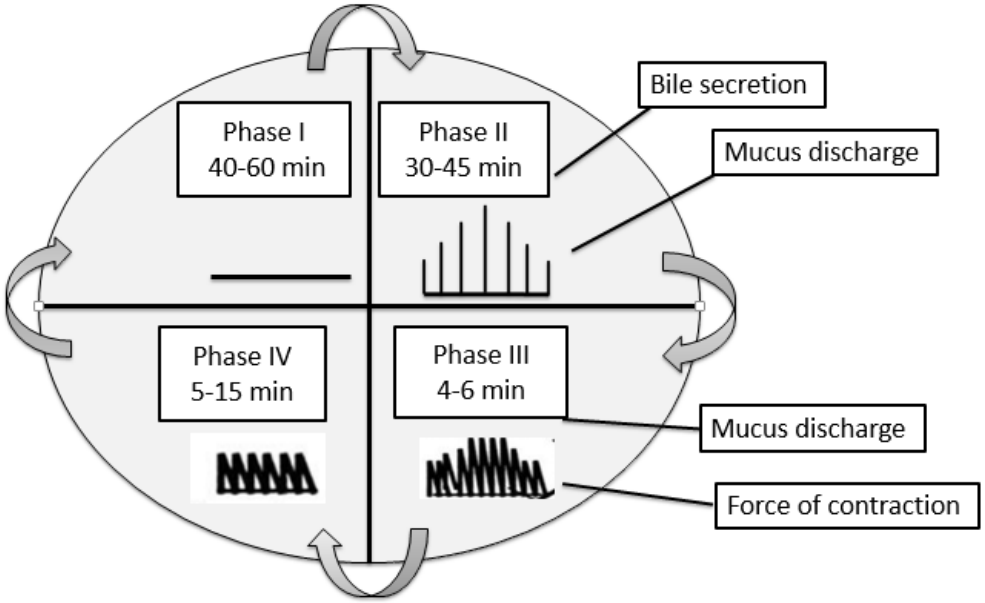

Figure 2: The migrating myoelectric cycle MMC phases [12].

Factors Affecting Gastric Retention Time

1- **Meal intake**: The gastric emptying rate can be significantly reduced by various factors, including meal composition, frequency of food consumption, and caloric content. Fat, particularly fatty acids, suppresses gastric secretions, while proteins and starch influence stomach emptying to a lesser extent. Increased viscosity of stomach fluid also contributes to this reduction. Consecutive meals can increase gastric residency time by over 6 hours due to low motile motility contractions. Also, meals with high proteins and fats can increase gastric residence time by 4-10 hours [13].

2- Gastrointestinal pH: Gastric emptying is delayed at low stomach pH and accelerated at higher or alkaline pH. Chemicals causing changes in gastrointestinal pH modify gastric emptying [14]. As the molecular weight of acids increases, their inhibiting effect on stomach emptying diminishes in the following order: hydrochloric>acetic>lactic>tartaric>citric. Additionally, a low base concentration (1% $NaHCO_3$) in alkaline solutions enhances the stomach emptying rate more significantly than a greater concentration (5%) [15].

3- Effect of Drugs: Drugs that decrease gastric emptying include narcotic analgesics, (morphine, codeine), antacids (aluminum hydroxide), tricyclic antidepressants (imipramine, amitriptyline), anticholinergic (atropine, propantheline, hyosine), domperidone, metoclopramide, ondansetron and calcium channel blocker (verapamil, diltiazem). While cholinergic drugs such as domperidone and antiemetic drugs such as metoclopramide stimulate gastric emptying [16].

4- Disease states: Pyloric stenosis, gastric ulcer, gastroenteritis, hypothyroidism, diabetes retard gastric emptying. Hyperthyroidism and duodenal ulcers increase gastric emptying rate [17].

5- Exercise: Intensive physical activity retards gastric emptying [18].

6- Density of Dosage Form: Dosage forms should be lower than the gastric fluid density of 1.004 g/mL to achieve buoyancy ensuring prolonged stomach retention [19].
7- Body Position: Gastric emptying is preferred when standing and resting on the right side.
8- Sex: Females have a slower rate of gastric emptying (4.6 ± 1.2 hours) compared to males(3.4 ± 0.6 hours), regardless of their weight, height, and body surface area [20].
9- Size of Dosage Form: The stomach often retains indigestible materials larger than 1-2mm throughout the postprandial period, which are then expelled by cyclical recurrent bursts of interdigestive gastric contractions[21].
10- Emotional State: The impact of emotional variables on stomach motility depends on whether the emotional state is characterized by aggressiveness or depression[22].

Advantages and Disadvantages of Gastroretentive Drug Delivery Systems:

GRDDSs offer significant advantages in improving the therapeutic effectiveness of medications such as enhanced bioavailability, and the possibility of achieving sustained release of medications which reduces dose frequency and minimizes the fluctuation in plasma drug levels. Figure 3 summarizes the advantages of GRDDSs [23].

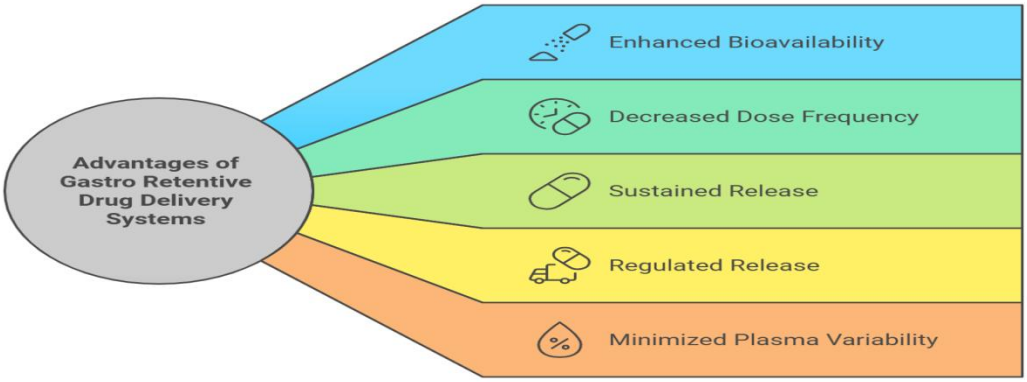

Figure (3): Advantages of gastroretentive drug delivery systems [24].

However, some disadvantages regarding GRDDSs can affect their effectiveness and applicability. These challenges arise from physiological factors, formulation constraints, and the unique characteristics of the gastrointestinal environment. Figure 4 highlights the main factors that may limit the use of GRDDSs and reduce their effectiveness [25].

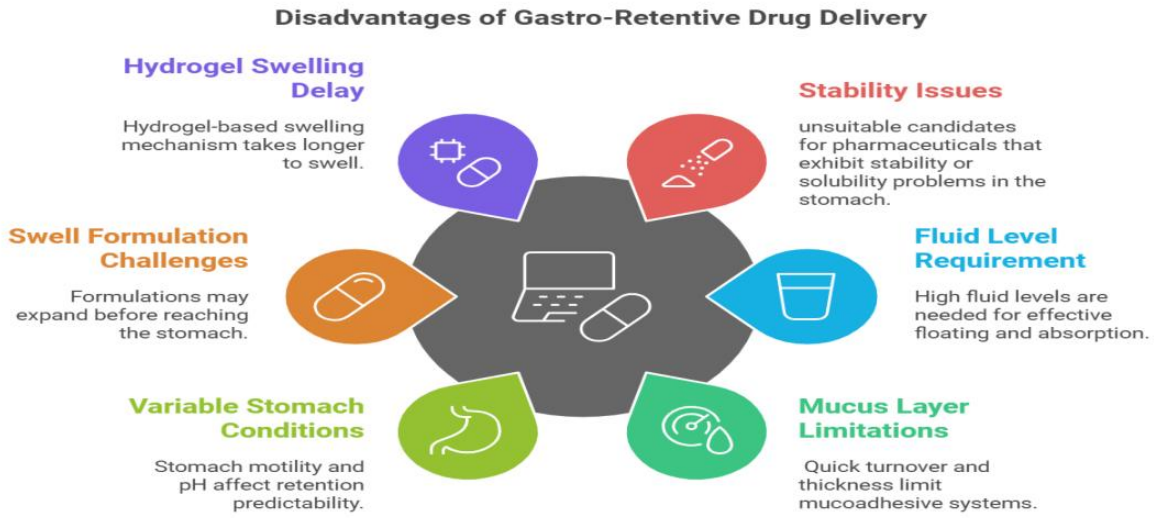

Figure (4): Disadvantages of gastroretentive drug delivery systems[26]**.**

Drugs Candidates for Gastrortentive Drug Delivery System.

1- Drugs with local effects in the stomach, such as antacids and misoprostol [27].
2- Antibiotics that are potentially effective against the bacterium Helicobacter Pylori [28].
3- Drugs unstable in the colon and small intestine environment like captopril and metronidazole [29].
4- Drugs with a limited window of absorption in the stomach and upper parts of the small intestine like baclofen and furosemide [16].
5- Drugs with limited solubility in areas with high pH like diazepam [30].

Approaches of Gastroretentive Drug Delivery System

GRDDSs utilize various approaches to enhance gastric retention and improve drug bioavailability. These approaches are designed to address physiological challenges and ensure prolonged residence time in the stomach, thereby optimizing drug delivery to the upper gastrointestinal tract. In general, the gastric retention strategies are divided into two main types which are floating and non-floating drug delivery systems and each type has its classification as seen in Figure 5. [31]. In the next paragraphs details on each type will be demonstrated.

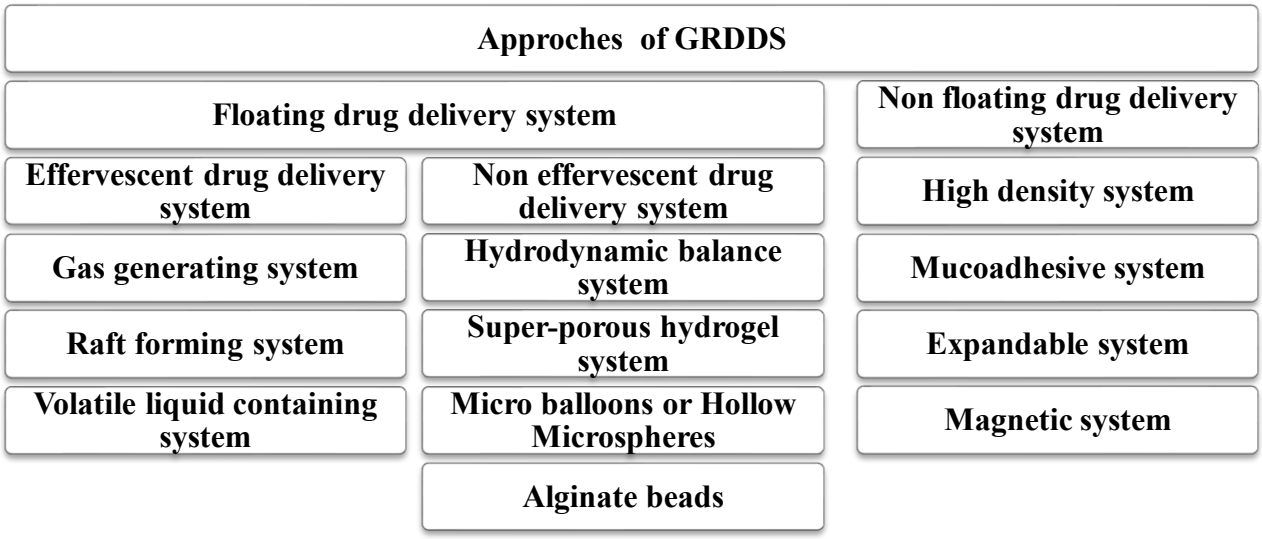

Figure (5): Approaches of GRDDS [31].

1- Floating drug delivery system

Floating drug delivery systems (FDDSs) are low-density systems that exhibit enough buoyancy to float over the gastric contents and maintain buoyancy in the stomach for an extended duration without influencing the rate at which the stomach empties. Typically, this is accomplished by gas-generating reactions or by using low-density material [32]. During the period when the system floats on the gastric contents, the medication is slowly released. Following drug release, the remaining system is evacuated from the stomach. Consequently, this leads to an elevated GRT and improved regulation of the variations in plasma drug concentration, so increasing its absorption and enhancing its bioavailability [33]. This system includes **effervescent and non-effervescent drug delivery systems.**

A. **Effervescent drug delivery system**

I. Gas generating system

The present approach depends on a chemical reaction to produce gas, therefore facilitating the buoyancy and prolonged GRT of medication in the stomach. Typically, the process requires a chemical interaction between salts of carbonate or bicarbonate and an acid, such as citric or tartaric acid, to generate gaseous carbon dioxide (CO_2). Upon generation, the CO_2 gas becomes entrapped within a hydrocolloid layer, therefore reducing the density of the system and causing it to float above the gastric content[34]. Floating of the drug delivery system prolongs its presence in the stomach, therefore enabling a more regulated and prolonged release of the drugs as seen in previous research done by Morya N *et al*. which formulated an anti-diabetic drug (metformin hydrochloride) by gas generating system. The system showed *in vitro* drug release of 95.95±1.89% within 24 hours [35].

II. Raft forming system

A raft-forming system is GRDDS specifically developed to extend the residence time of the drug in the stomach. Typically, these systems are accomplished by employing polymers like alginate, which reacts with gastric acid to produce a viscous gel like layer over the gastric content called raft as seen in Figure 6-A. The raft remains floating and gradually releases the drug [36]. This technique is especially beneficial for

managing gastrointestinal disorders, such as gastroesophageal reflux disease and infections, by prolonging the solubility of the medication in the stomach [37], as seen in research done by Shah S *et al*. for the formulation of rabeprazole as raft forming system. Rabeprazole enteric-coated formulations have shown a wide fluctuation in the plasma profile. To control the fluctuation of the plasma profile, a raft-forming formulation for prompt delivery of rabeprazole was developed. The study also aimed to maintain the stomach pH above 3.5 for an appropriate period and improve the bioavailability of rabeprazole because rabeprazole degradation in the stomach is high at pH below 2.5. The result shows a release of 99.93 % rabeprazole at 20 min [38].

III. Volatile liquid-containing system

In general, the system includes two compartments: one that holds the medication and the other that holds an osmotically active chemical in conjunction with a volatile liquid. Upon exposure to the gastrointestinal liquid, the volatile liquid undergoes evaporation, resulting in the formation of gas. By increasing the pressure within the system, this gas effectively regulates the drug release through a delivery orifice. Furthermore, the gas produced also facilitates the buoyancy of the system, therefore extending its duration in the stomach and enabling a more regulated and continuous release of the medication [39]. Dangre *P et al*. designed a floating osmotic drug delivery system of pioglitazone hydrochloride for gastroretention by incorporation of a gas-generating agent together with HPMC-K4M. The optimized formula (OF-O) showed a floating lag time of 35.55 ± 2.5 Sec and *in vitro* drug release of 93.27 ± 2.2 % and showed prolonged release of PGH over 8 hours in 0.1 N HCl (pH 1.2). Also, the in *vivo* estimation of buoyancy in human showed that the tablets stayed buoyant in gastric fluid for 8 hours [40].

B. Non effervescent drug delivery system

I. Hydrodynamic balance system (HBS)

Hydrodynamically balanced systems (HBS) are single-unit pharmaceutical formulations consisting of one or more hydrophilic polymers that form a gel layer to provide optimal floating and drug release. This formulation involves combining the drug with a hydrophilic gel-forming polymer that undergoes hydration and swelling when exposed to gastric fluid, forming a colloidal gel layer. This mechanism forms a system with a density lower than that of the stomach fluid which is 1g /cm^3 [41]. Kim S *et al*. studied the preparation of non-effervescent gastroretentive tablets containing pregabalin for once-daily administration using HPMC. The study developed gastroretentive tablets with floating and swelling properties, resulting in buoyancy for over 24 hours and an increase in GRT [42].

II. **Super-porous hydrogel system**

Super-porous hydrogels (SPHs) are three-dimensional structures composed of hydrophilic polymers. Their porous structure allows them to sequester water up to several hundred times their own weight. An essential characteristic of SPHs is their capacity to undergo rapid swelling when exposed to fluid as seen in Figure 6-B. The rapid swelling results from the open porous structure, allowing rapid water absorption [43]. The main application of SPHs is in drug delivery systems. They can retain medications in the gastrointestinal by rapidly expanding and maintaining their structural integrity in harsh stomach conditions. The fast swelling enables the gel to remain in the stomach for a longer duration, therefore facilitating regulated and sustained release of the medication [44]. In a research done by Safa M. *et al.,* trifluoperazine HCl was used as a model drug to study the effect of using high

molecular weight cross-linkers on the physical properties of SPHs and drug release behavior. Around 80% of the drug was released over 12 hours and drug release kinetics was zero order [45].

III. **Microballoons system**

Microballoons, also known as hollow microspheres, are spherical hollow particles free of a central core. This system is classified as a multiple buoyant unit dosage form because of its excellent floating characteristics resulting from the hollow core within the microsphere [46]. Their mechanism of floating is derived from their low density which allows them to float over the gastric fluid and slowly release the drug for a prolonged period. Several procedures, such as evaporation, diffusion, polymerization, and spray drying, have been employed to fabricate microballoons [47]. *Ponnaganti H et al.* developed gastroretentive floating microspheres of rilpivirine hydrochloride. The optimized formulation has shown good percentage yield, and encapsulation efficiency and the drug release was 98.25% at the end of 12 hours. As a result, it was concluded that floating microspheres of rilpivirine HCl could be an effective tool in improving the bioavailability of the drug [48].

IV. Alginate beads system

Alginate beads are typically manufactured using sodium alginate, a naturally occurring polymer obtained from brown seaweed. Calcium alginate beads are formed when sodium alginate is dropped into a calcium chloride solution, a phenomenon known as ionotropic gelation. These beads can be engineered to float on gastric content, therefore facilitating their prolonged retention in the stomach. Their buoyancy is attributed to their low density and the creation of a gel-like matrix. The therapeutic substances can be encapsulated within the alginate beads and gradually released. This regulated release guarantees a consistent provision of the drugs, enhancing their efficacy and decreasing the frequency of administration [49]. Bangun H *et al.* reported a study that aimed to determine the anti-ulcer effect of the GRDDSs of alginate beads containing turmeric extract solid dispersion compared to alginate beads containing turmeric extract (without solid dispersion) and negative control. Alginate beads containing turmeric extract solid dispersion were effective in the treatment of gastric ulcer in rats [50].

Non-floating drug delivery system

I. High-density system

The formulation of these systems includes substances with a density greater than the density of gastric fluids, resulting in their sequestration and retention within the stomach instead of rapid passage into the intestines as presented in Figure 6-C. In this type, the drug can be coated or mixed with heavy, nontoxic materials such as barium sulfate, zinc oxide, iron powder, and titanium dioxide. Retention of these systems in the stomach for an extended period can offer an extended release of the medication, enhancing its bioavailability and overall therapeutic effectiveness [51]. Sharma A *et al.* developed gastroretentive high-density pellets lodged with zero-valent iron nanoparticles ZVINPs by simple extrusion and spheronization process using barium sulfate as high-density material, carbopol as sustain release polymer, and DCP and MCC as diluents. *In vivo*, results revealed more than 2-fold increases in the oral bioavailability of iron by pellets compared to plane ferrous sulfate. Toxicological studies indicated no evidence of liver damage in acute treatment; however, few complications were observed in chronic treatment groups. These results indicated that ZVINP pellets successfully improved oral iron

bioavailability [52].

II. Mucoadhesive system

Mucoadhesion is the process by which the dosage form adheres to the mucosal surface which lines various parts of the body, such as the gastrointestinal tract, respiratory tract, urogenital tract, eyes, and oral cavity. This adhesion enhances the bioavailability of drugs by maintaining them in contact with the absorption surface for a longer period. The present technique integrates the concepts of mucoadhesion and gastroretention to improve the efficacy of drugs that are predominantly absorbed within the gastric or upper-intestinal regions. This system uses mucoadhesive polymers to attach to the mucus layer of the stomach lining, therefore assuring prolonged retention of the medication within the stomach as demonstrated in Figure 6-D [53]. Farhadnejad H *et al* fabricated famotidine as mucoadhesive gastroretentive bio-nanocomposite hydrogel utilizing montmorillonite and chitosan. The optimum hydrogel showed a controlled and sustained release of famotidine for up to 12 hours. [54].

III. Expandable system

The expandable gastroretentive drug delivery system is a novel drug delivery technology specifically developed to extend the duration of drug retention within the stomach. Usually, these systems are folded or compressed into a small size and enclosed within a hard gelatin capsule that can be readily ingested. Upon contact with stomach fluids, they undergo expansion to a size that is larger than the pyloric sphincter, therefore preventing their passage into the small intestine as seen in Figure 6-E. The expansion of these systems enables them to withstand the normal process of gastric emptying, therefore facilitating extended retention of the drug within the stomach[55]. A previous study by Jadhav RP *et al.* reported the preparation of expandable gastroretentive tablets of diltiazem hydrochloride. The swelling index % of the optimum formulation was 188.73% which allowed the tablet to be retained in the stomach. The enhancement in retention time resulted in 99.31 ± 0.01% of the drug being released within 12 hours [56].

IV. Magnetic system

This technique utilizes magnetic ingredients in the pharmaceutical formulation and an external magnetic field to maintain the drug localization in the stomach for a prolonged duration. The pharmaceutical formulation includes magnetic particles that exhibit a response to an external magnetic field. To attract and keep the magnetic drug formulation in position, an external magnetic field is applied to the stomach region as seen in Figure 6-F. Magnetic forces can prolong the retention of the medicine in the stomach, therefore improving its absorption and efficacy [57]. Ito R *et al* studied magnetic granules for specific drug delivery to esophageal mucosa. The purpose of the study was to deliver local chemotherapy for esophageal cancer and other diseases of the alimentary canal. Brilliant blue (B.B) ferrite particles in the granules were attracted by the stronger magnetic field during the application of the circuit so the release of B.B. from the granules was accelerated. This tendency should be utilized for the control of drug release from the magnetic granules that adhere [58].

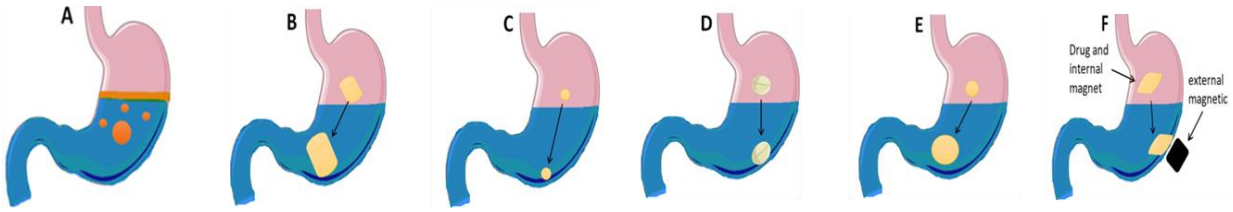

Figure (6): A- Raft forming system, B- Super-porous hydrogel system, C- High-density system, D- Mucoadhesive system, E- Expandable system, F- Magnetic system [59]**. created with biorender**

Type of Gastroretentive Films

GRDDSs are formulated in several dosage forms, such as tablets, capsule beads, granules, and film. Films as GRDDSs are divided into three types which are floating film, expandable film, and mucoadhesive film, and may combine floating and expandable types.

1. Floating Film

These films remain buoyant on the gastrointestinal juices, facilitating a gradual and controlled release of the medication. This property is especially advantageous for drugs mostly absorbed in the stomach or the upper section of the small intestine or for drugs that exhibit reduced solubility at elevated pH levels present in the intestines [60]. A typical composition of these films is a combination of polymers, active medicinal components, film-forming agents, and plasticizers. Floating is due to using low-density polymers or using gas-generating agents, that maintain buoyancy in the stomach for a prolonged duration [61]. The retention of the film in the stomach will allow the drug to be slowly released for an extended period which will reduce dosing frequency, minimize fluctuation in plasma drug level, and enhance drug absorption. Film retention will also enhance the effectiveness of drugs acting locally in the stomach because the drug will remain at the site of action for an extended period. [28]. The limitation of these systems is the efficacy of the floating films, which can be affected by the existence of consumed food and the pH level of the stomach environment. Maintaining consistent buoyancy in such a system is challenging. If the system loses its buoyancy and sinks, the drug may be released too quickly, which could reduce its effectiveness [62]. Mehta MHR *et al.* developed gastroretentive floating films of lafutidine by using different film forming polymers like HPMC and Ethylcellulose. PEG 400 was used as a plasticizer, and the optimum formulation T5 exhibited a good appearance and better mechanical strength with acceptable flexibility. Also, T5 deminsrated more than 90 % drug release after 12 hours and 97.56 % drug content. The films floating lag time was 1 min and floating period was up to 12 hours [63].

2. Mucoadhesive Film

The film is specifically designed to adhere to the gastric mucosa, thereby prolonging its duration of action within the stomach. This characteristic is particularly advantageous for drugs that exhibit enhanced absorption in the stomach or have a short half-life. A mucoadhesive film is defined by its ability to adhere to the mucosal lining of the gastrointestinal tract, typically achieved through the incorporation of polymers with a strong affinity for mucus. This enables the film to remain attached to the stomach mucosa, gradually releasing the active pharmaceutical ingredient [64]. However, a key limitation of this system is its persistent adhesion to the stomach mucosa, which may

occasionally cause irritation or discomfort. Also, the strength of adhesion is influenced by the condition of the stomach mucosa, and the presence of mucus. Detachment from the gastric mucosal surface may compromise the effectiveness of these systems [65]. Safaa Hamdi D*, et al.* formulated metoclopramide HCl gastroretentive film and the result exhibited that the mucoadhesive strength for two optimized formulas was 57 g and 49.5 g respectively with drug release for 24 hours [66].

3. Expandable Film

A gastroretentive expandable film is a small compact film when ingested but upon reaching the stomach, the film undergoes expansion. This expansion is frequently initiated by exposure to stomach secretions [67]. The film may undergo swell or unfolding due to the inclusion of hydrophilic substances or polymers that can absorb water and expand in size, increase the film's size, and alter its structure, preventing it from passing through the pyloric sphincter [68]. However, excessive expansion or inadequate shape memory may lead to gastric obstruction or premature passage through the pyloric sphincter [69]. Porwal *et al.* reported the preparation of gastroretentive bilayer film for sustained release of atorvastatin calcium and immediate release of amlodipine. The film demonstrated a sustained release of atorvastatin for 8 hours (96.76% ± 0.71) and an immediate release of amlodipine within 25 min (98.07% ± 0.62) [70].

Methods Used for Film Preparation

Multiple methods have been developed to fabricate films depending on the desired application and a brief description of each method can be seen in Figure 7. The methods include solvent casting, electrospinning, hot-melt extrusion, and printing technologies. However, the method that is extensively used in film preparation is solvent casting. This method allows the formation of films with smooth surfaces and uniform thickness. Also, multilayered film can be prepared using solvent casting. The limitation of solvent casting is the long drying times required for solvent evaporation [71,72]. Conversely, hot-melt extrusion eliminates the use of solvents, making it suitable for heat-stable materials [73,74]. The active pharmaceutical ingredients and polymers needed for film formation are heated, melted, and mixed through the extruder. A continuous film is formed by pressurizing the molten liquid via a die. Followed by cooling and solidification of the extruded film [75].

Electrospinning is favored for producing nanofibrous films due to its ability to control fiber morphology. The procedure generally involves preparing a polymer solution by dissolving the polymer and medicament in an appropriate solvent. The process of fiber formation involves the application of a high voltage to generate an electric field, which causes the polymer solution to be stretched into thin fibers. These fibers are then deposited onto a collector to produce a non-woven mat or film [76].

The printing method for film formation includes inkjet and 3D printing. Inkjet printing is especially suitable for thin films and controlled drug release [77], while 3D printing enables the fabrication of complex, multilayered structures, offering customization and scalability[78].

Each of these methods provides unique advantages and is selected based on the material properties, desired film characteristics, and specific application requirements[79].

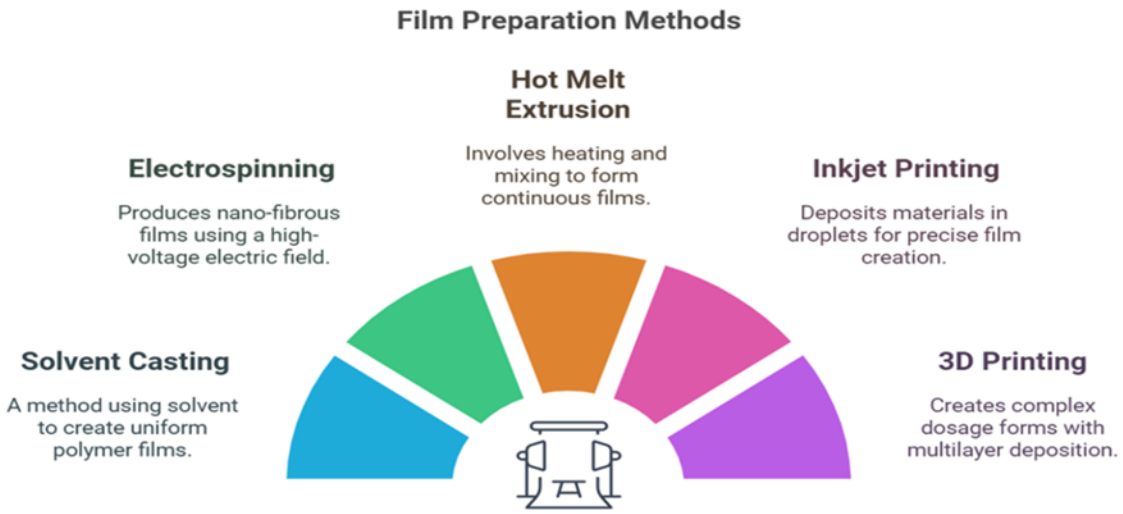

Figure (7): Methods Used for Film Preparation [80]**.**

Evaluation of Gastroretentive Film Dosage Form

1) Weight Uniformity

Weight uniformity ensures consistency across film batches. Randomly selected films (mainly 3) are weighed individually, and the mean weight and standard deviation are calculated to verify uniform manufacturing[81].

2) Thickness

The uniformity of the film thickness is measured using a micrometer screw gauge. Multiple measurements at different points are averaged to ensure consistency, which is essential for controlled drug release[82].

3) Folding Endurance

Folding endurance evaluates the mechanical strength and flexibility of films. It is determined by repeatedly folding the film at the same point until it breaks. Higher folding endurance indicates better mechanical durability[83].

4) Drug Content Uniformity

Drug content uniformity is assessed by dissolving a specified film area in a suitable medium. The drug concentration is analyzed using a UV spectrophotometer, ensuring even drug distribution throughout the film[84].

5) Swelling Index

After being in contact with swellable dosage form into media, the dosage form is taken out at regular time intervals and changes in dimensions are measured in terms of increase in film thickness/dimensions with proportion to time. [85].

$$swelling\ index\ (\%) = \frac{W2 - W1}{W1} \times 100 \ldots\ldots\ldots \text{Eq1}$$

Where; **W2**=Weight of wet film

W1= Weight of dry film

6) Mechanical Properties

Tensile Strength measures the maximum stress the film can withstand before breaking. It is calculated using the force applied and the film's cross-sectional area.

% Elongation at Break indicates the film's flexibility by measuring the percentage increase in length before rupture[86].

$$Tensile\ strength = \frac{force\ at\ break}{\text{cross-sectional area of the sample}} \quad \text{…….. Eq2}$$

$$\%\ Elongation\ at\ break = \frac{\text{increase in length}}{\text{original length}} \times 100 \quad \text{……. Eq3}$$

7) *In Vitro* Drug Release

Drug release studies are conducted using a dissolution apparatus. The cumulative drug release over time is analyzed to evaluate the film's controlled-release properties [87].

8) Surface Morphology (SEM)

Scanning electron microscopy (SEM) is used to examine the surface structure and uniformity of the film. This provides insights into the porosity, roughness, and distribution of drug particles within the film[88].

Mucoadhesion Strength for mucoadhesive film

For mucoadhesive films, the adhesion strength is assessed by measuring the force required to detach the film from a mucosal surface, ensuring effective retention in the gastrointestinal tract[89].

***In vitro* buoyancy (floating lag time and floating duration) for floating film**

The floating lag time refers to the time it takes for the film to rise to the surface of the media, whereas the floating duration specifies the length during which the film remains consistently floating on the surface of the media [90].

Unfolding behavior for expandable film

The film dimensions were measured after 480 minutes to calculate the percentage of film growth based on area [91].

Literature review on films as gastroretentive drug delivery system

Table 1 provides a literature review on various types of films as GRDDS. The table highlights different types of films and the type of retention mechanism whether floating, expansion, mucoadhesion, or a combination of more than one mechanism. The table also highlights the advantages achieved due to film formation. The goal is to offer a comprehensive overview of recent advancements in the development of GRDDSs for controlled and sustained drug release.

Table (1): Literature review on films as a gastroretentive drug delivery system.

Drug	Type of retention Mechanism	Polymers used	Problem and aim of study	Advantage achieved	R.no
Furosemide	Floating and expanding	Gelatin, sodium carboxymethyl cellulose, sodium alginate, and sodium hydroxide	Furosemide solubility is pH dependent and is poorly soluble in gastric pH with high permeability. The study aims to increase the drug solubility and gastric retention to enhance its bioavailability.	Films floating up to a maximum period of 18.58 ± 2 hours and 86.78±0.86 % drug release up to 12 hours.	[92]
Itopride Hydrochloride	Expanding by unfolding	Eudragit L100, poloxamer P407 sodium bicarbonate	Itopride has a narrow absorption window and a short half-life of 5–6 hours with the upper GIT as a primary site of absorption. The study aims to prolong the release of the drug for up to 12 hours thus improving bioavailability.	Prolong the release of IH for a minimum of 12 hours.	[93]
Losartan Potassium	Expanding by unfolding	Ethyl Cellulose Hydroxypropyl methylcellulose K4M	Losartan potassium has a short half-life (2 hours). The study aims to prolong retention in the upper gastrointestinal tract to increase its absorption and exposure to CYP450 enzyme subfamilies that convert the drug to the more potent active metabolite.	Provided sustained drug release throughout 12 hours.	[94]
atorvastatin calcium and amlodipine	Expanding by unfolding	Hydroxypropyl methylcellulose K3, Eudragit RSPO, and Carbopol 934P	Due to the poor solubility of atorvastatin at pH 4 and below, most of the drug passes through the upper GI tract without absorption. This research aimed to formulate a novel bilayer expandable unfolding film and one layer contains atorvastatin as a sustained release layer.	Sustained release of atorvastatin for 8 hours (96.76% ± 0.71) and immediate release of amlodipine within 25 min (98.07% ± 0.62).	[70]
metoclopramide HCl	Mucoadhesive	Hydroxypropyl methylcellulose K4M and E5 and Carbopol 934	Metoclopramide has a narrow absorption window. The study aims to formulate a mucoadhesive film for the sustained release of the drug.	Their mucoadhesive strength was 57 g and 49.5 g with extended-release for 12 hours.	[66]

Luteolin	Expanding by unfolding	polylactic acid, polyethylene glycol 400 and Hydroxypropyl methylcellulose	luteolin has poor aqueous solubility. The research aims to enhance the drug's oral bioavailability and sustain its release.	Prolonged gastric retention time of approximately 8 hours. Furthermore, the pharmacokinetic studies indicated a 354 % increase in the oral bioavailability.	[95]
5-fluorouracil	Floating	Eudragit S-100 and methylcellulose	5-fluorouracil has a narrow absorption window and multiple dosing is needed. The study aimed to formulate a film for controlled and localized delivery of the drug for the treatment of gastric cancer.	Released 90% of encapsulated therapeutic after 12 hours.	[96]
Hydralazine HCl	Mucoadhesive	Hydroxypropyl methylcellulose K4M, sodium alginate, and carbopol 940	Hydralazine HCl has short half life. The study aimed to decrease dose frequency and control drug release.	Provide controlled release of drugs with a release drug profile of up to 24 hours.	[97]
prazosin hydrochloride	Mucoadhesive and unfolding mechanism	Hydroxypropyl methyl cellulose K4M, Carbopol 971P NF and polyethylene glycol 400	The study aimed to improve the bioavailability of prazosin because it is absorbed only in the initial part of the gastrointestinal tract (GIT).	99.02 % drug release at the end of 12 hours.	[98]
Ritonavir	Mucoadhesive	Hydroxypropyl methylcellulose K15M, Polyvinyl alcohol, and polyethylene glycol 400	Ritonavir has low bioavailability. The research aims to sustain the drug release to enhance bioavailability.	99.08% drug release at 12 hours.	[99]
Dipyridamole	Floating	Hydroxypropyl methylcellulose K4M and Hydroxyethyl cellulose	Dipyridamole bioavailability decreases with increasing gastric pH. The research aims to control the drug release and enhance bioavailability.	Its percent drug release was found 85.78% in the 9th hour and floating time for 9 hours.	[100]

Marketed Product for Gastroretentive Drug Delivery Systems

The marketed product of GRDDSs is summarized in Table 2 below some utilizing various gastroretentive delivery systems and highlighting their unique mechanisms[101].

Table (2): Marketed Product for Gastroretentive Drug Delivery Systems.

Brand Name	Active Ingredient	Gastroretentive Type	Manufacturer
Cifran OD®	Ciprofloxacin	Gas- generating floating system	Ranbaxy, India
Madopar ®HBS	Levodopa and Benserazide	Floating capsule	Roche
Glumetza®	Metformin	Floating extended-release tablet	Bausch Health
Valrelease®	Diazepam	Floating capsule	Hoffmann-La Roche
Conviron®	Ferrous sulfate	Colloidal gel forming FDDS	Ranbaxy, India
Liquid Gaviscon®	sodium alginate, sodium bicarbonate, and calcium carbonate	Raft forming system	Reckitt Benckiser
Oxybutynin ®XR	Oxybutynin	Floating system	Watson Pharmaceuticals
Cytotec ®	Misoprostol	Bilayer floating capsule	Pharmacia, India

Conclusion

In the field of controlled drug delivery, gastroretentive film drug delivery systems are a notable development that can improve the bioavailability and therapeutic effectiveness of orally delivered medications. By employing processes such as floating, mucoadhesion, and expansion, these systems can extend the duration of medication presence in the stomach, therefore enhancing therapeutic absorption in the upper gastrointestinal tract. This review focuses on the many formulation methodologies and evaluation criteria that are crucial for the advancement of efficient gastroretentive films. Despite the encouraging benefits, it is necessary to focus on issues such as the variability in stomach retention time and patient-specific variables. Future investigations should prioritize the optimization of these systems for clinical use, the examination of technologies, and the execution of comprehensive in vivo investigations to verify their effectiveness and safety. Also scale up for large-scale production is problematic in film dosage form. Process-related challenges in film formulation and manufacturing are critical considerations that impact product quality and performance. One major challenge is achieving uniform film thickness during the casting process, as variations can influence drug release profiles and mechanical properties. Additionally, optimizing the drying process is essential, as insufficient drying may result in residual solvent retention, while excessive drying can lead to brittleness, compromising film integrity. Mechanical properties, particularly strength and flexibility, must also be carefully balanced to ensure that films remain robust enough for handling while maintaining sufficient flexibility for effective adhesion to the gastric mucosa. Furthermore, precision in

cutting and handling is crucial, as producing uniform strips without tearing or fraying becomes increasingly difficult at higher production speeds. Lastly, scaling up from laboratory-scale to industrial manufacturing presents significant hurdles, as techniques such as solvent casting, hot-melt extrusion, and electrospinning often require substantial modifications to accommodate large-scale production demands. Addressing these challenges is essential for ensuring the consistency, efficacy, and manufacturability of pharmaceutical films. In general, gastroretentive film drug delivery systems show significant potential for enhancing patient outcomes and broadening the therapeutic efficacy of oral drugs.

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