International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

Gastro-retentive Drug Delivery Systems with Special Emphasis on its Components, Evaluation Methods and Recent Advancements

Farhat Jahan*, HimanshiRathaur, Amit Semwal
College of Pharmacy, Shivalik Campus, Dehradun, Uttarakhand (248001)

Submitted: 10-06-2023 Accepted: 21-06-2023

ABSTRACT
This review article explores the potential benefits and challenges of gastroretentive drug delivery systems, which are designed to optimise drug absorption and enhance bioavailability, particularly for drugs that are best absorbed in the upper gastrointestinal tract (GIT). Although these systems present an exciting advancement in pharmaceutical technology, their development requires careful consideration of complex pharmacokinetic and pharmacodynamic parameters, and individual physiological variations. The design must ensure that the dosage form remains in the stomach for a sufficient duration, a challenge given the stomach's natural progression mechanism. Different forms of gastroretentive systems, including high density, floating, expandable, unfoldable, swelling, superporous, bioadhesive, and magnetic systems, each with their own unique advantages and limitations, are discussed. The article highlights ongoing efforts to create an array of these delivery systems for various drugs and anticipates their growing significance in future pharmacotherapies. The successful development and application of gastroretentive drug delivery systems could mark a revolutionary shift in pharmaceutical science, improving both drug delivery efficiency and patient outcomes.

Keywords: Gastroretentive Drug Delivery Systems, Bioavailability, Pharmacokinetic and Pharmacodynamic Parameters, Dosage Form Design, Individual Physiological Variations

I. INTRODUCTION

Within the diverse palette of dosage forms developed for human use, oral formulations have carved out an important niche. In many scenarios, these traditional oral delivery systems have presented bioavailability challenges due to reasons like quick gastric-emptying time, among others. Yet, the landscape of pharmaceutical innovation, fueled by recent technological strides, has given rise to novel products, predominantly controlled-release drug delivery systems designed to tackle this issue.(Tripathi et al. 2019)

The Gastro-retentive drug delivery system (GRDDS) stands as a noteworthy instance of this innovation, with its key features like prolonged gastric retention time and extended drug release playing a significant role in improving patient adherence to medication. This novel delivery system has been the focus of interest due to certain intrinsic limitations of traditional oral drug delivery systems. Rapid gastric emptying, a typical attribute of conventional oral medications, poses a challenge to the bioavailability of many drugs, including pranlukast hydrate, metformin HCl, and baclofen, whose principal absorption sites are the stomach or the proximal part of the small intestine, or those which encounter absorption problems in the distal portion of the intestine.(Kumar, Singh, and Mishra 2008)

Drugs less soluble in the high pH environment of the intestine can see an enhancement in solubility by lengthening their gastric retention. There are multiple drugs (such as captopril, metronidazole, ranitidine HCl, etc.) susceptible to degradation in the colonic region. For drugs with shorter half-lives, repeated dosing becomes necessary to achieve the therapeutic effect, given their rapid systemic circulation elimination. However, an oral sustained-controlled release formulation featuring additional gastric retention capability can mitigate these issues, slowly releasing the drug in the stomach and upholding an effective drug concentration in systemic circulation over an extended timeframe.(Emara et al. 2013)

Aside from systemic action, GRDDS has demonstrated local effectiveness in treating gastric and duodenal ulcers, including esophagitis, by eradicating Helicobacter pylori that lies deep within the stomach's submucosal tissue. The development

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

of GRDDS formulations traces back almost three decades, and the fundamental fabrication techniques, inclusive of their in vitro characterizations, have been firmly established.(Verma et al. 2016)

Although recent years have seen several reviews on GRDDS, their focus largely lies on formulation aspects or in vitro characterization studies conducted by various researchers, or an overarching view of GRDDS. The industrial considerations of GRDDS encompassing physicochemical, biopharmaceutical, and regulatory aspects have been evaluated. However, the quantity of marketed gastro-retentive formulations is still minimal.

Given this context, it is critical to delve into the in vivo studies conducted with GRDDS to understand the pharmacokinetic performances of the systems developed and their pivotal roles in successful dosage form commercialization. To our knowledge, no review to date has emphasized the in vivo performances of GRDDS, particularly recent developments. Therefore, the objective of this review is to consolidate the in vivo studies on GRDDS, focusing on pharmacokinetic parameters, gastric retention times, and the inherent challenges or limitations for in vivo evaluations noted by various researchers.(Mandal, Chatterjee, and Senjoti 2016)

Anatomy and physiology of stomach:

Anatomically, the stomach can be segmented into three areas: the fundus, the body, and the antrum (also known as the pylorus). (C. Cheng, Sun, and Zhang 2019)

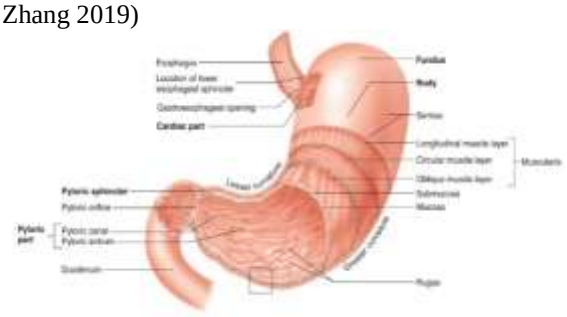

Figure 01: Anatomy of stomach

The fundus and the body, which make up the proximal part, serve as a reservoir for undigested material. Conversely, the antrum primarily handles mixing movements and functions as a pump for gastric emptying via propulsive actions. Gastric emptying is a process that takes place in both fasting and fed states. However, the motility pattern significantly differs between these two states.(Wickham et al. 2012)

In the fasting state, an interdigestive sequence of electrical activities, known as the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), takes place cyclically in the stomach and intestine every 2 to 3 hours. As per Wilson and Washington's classification, this MMC can be divided into four distinct phases (Braeckmans et al. 2020):

1. **Phase I** (also referred to as the basal phase) lasts for 45 to 60 minutes, characterized by few contractions.
2. **Phase II** (known as the pre-burst phase) also persists for 30 to 45 minutes, featuring sporadic action potentials and contractions that gradually increase in intensity and frequency as the phase progresses.

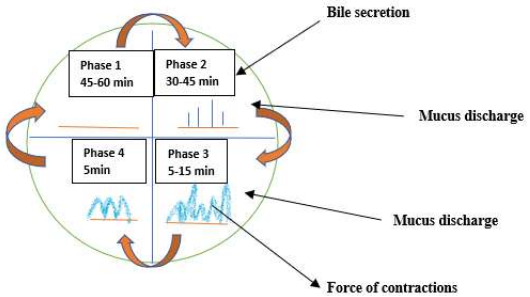

Figure 02: Wilson and Washington's classification of MMC

3. **Phase III** (termed the burst phase) is much shorter, spanning only 5 to 15 minutes. This phase is marked by strong, regular contractions over a brief period. It is this wave that effectively clears all undigested material from the stomach and propels it into the small intestine. This wave is also commonly referred to as the housekeeper wave.
4. **Phase IV**, lasting for 0 to 5 minutes, is an interim period that occurs between phases III and I of two successive cycles.

Upon the consumption of a mixed meal, the contraction pattern transitions from that of the fasted state to the fed state. This change in motility pattern, also known as the digestive motility pattern, encompasses continuous contractions analogous to phase II in the fasting state. These contractions facilitate the reduction of food particles (to less than 1mm in size), which are subsequently propelled

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

towards the pylorus in a suspended form.(Heissam et al. 2020)

During the fed state, the onset of MMC is delayed, leading to a deceleration in the gastric emptying rate. Scintigraphic investigations designed to determine gastric emptying rates have unveiled that orally administered controlled-release dosage forms are typically subjected to two primary complications: a brief gastric residence time and an unpredictable gastric emptying rate.(Vrbanac et al. 2020)

II. FACTORS AFFECTING GASTRIC RETENTION

1. Risk Factors Associated with Gastroparesis
2. Role of System Size in Gastric Retention
3. The Influence of Meal-Related Factors on Gastric Emptying
4. The Effect of Dietary Conditions on Gastric Retention Time
5. The Role of Regional Gastric Emptying Measurements in Gastric Retention
6. Health Conditions Increasing the Risk of GERD and their Impact on Gastric Retention
7. Gastritis Risk Factors: Bacterial Infections and Their Influence on Gastric Retention
8. Physicochemical Factors Influencing Gastric Retention Time

1. **Risk Factors Associated with Gastroparesis:** Gastroparesis, commonly referred to as "stomach paralysis", is a condition characterized by delayed gastric emptying in the absence of mechanical obstruction. Factors that can increase one's risk for developing gastroparesis include diabetes, abdominal or esophageal surgery, certain infections, particularly viral, specific medications that slow the rate of stomach emptying such as narcotic pain medications, and certain connective tissue diseases such as scleroderma. Diseases affecting the nervous system, such as Parkinson's disease, also pose a risk.(Schol et al. 2021)

2. **Role of System Size in Gastric Retention:** The concept of "system size" here may refer to the volume or capacity of the stomach, which can influence the rate and extent of gastric emptying and hence retention. However, none of the provided sources directly address this point, and additional research would be necessary for a complete answer.(Wu et al. 2020)

3. **The Influence of Meal-Related Factors on Gastric Emptying:** Meal-related factors can have a significant impact on gastric emptying. The composition of the meal, including its nutritional components (carbohydrates, proteins, fats), its texture, and its temperature, can influence the rate at which the stomach empties its contents into the small intestine. For instance, high-fat or high-fiber meals can slow down the process, leading to increased gastric retention.(Hens et al. 2020)

4. **The Effect of Dietary Conditions on Gastric Retention Time:** The term "dietary conditions" could encompass factors such as meal frequency, size, and composition, which can significantly influence gastric retention time. Eating large meals or consuming foods high in fat or fiber can slow gastric emptying, thereby prolonging retention time. Likewise, eating smaller, more frequent meals, or consuming more liquids can accelerate gastric emptying and reduce retention time. (Charoenying et al. 2020)

5. **The Role of Regional Gastric Emptying Measurements in Gastric Retention:** Measuring regional gastric emptying can be valuable in assessing gastric retention and managing conditions like gastroparesis. For example, ultrasound can be used to measure the emptying of a liquid meal by serially evaluating cross-sectional changes in the volume of the stomach. This information can aid in diagnosing conditions like gastroparesis and formulating appropriate treatment plans.(Uemura et al. 2020)

6. **Health Conditions Increasing the Risk of GERD and their Impact on Gastric Retention:** GERD, or gastroesophageal reflux disease, is a condition characterized by chronic acid reflux. Various health conditions can increase the risk of developing GERD, including obesity, hiatal hernia, pregnancy, and certain lifestyle habits (like smoking, alcohol consumption). If severe and chronic, GERD can potentially affect gastric retention by damaging the esophageal sphincter and thereby disrupting the normal process of gastric emptying.(Stillhart et al. 2020)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

7. **Gastritis Risk Factors:** Bacterial Infections and Their Influence on Gastric Retention: Certain bacterial infections, such as Helicobacter pylori, are known to cause gastritis, an inflammation of the stomach lining. The inflammation can disrupt normal gastric function, potentially leading to delayed gastric emptying and increased gastric retention.(Birajdar, Deshmukh, and Shete 2021)

8. **Physicochemical Factors Influencing Gastric Retention Time:** Physicochemical factors refer to the physical and chemical properties of the food and liquids we consume, which can affect how quickly they're processed by the digestive system. For instance, high-fiber or high-fat foods, which are more complex and require more digestion, may have longer gastric retention times. Liquids, particularly those high in sugar or alcohol, can also affect gastric emptying rates. However, the specific impact of these factors on gastric retention time can vary greatly depending on individual differences in metabolism, health status, and other factors.(L. Cheng and Wong 2020)

Ideal properties of potential drug candidates for gastroretentive drug delivery systems

Gastroretentive drug delivery systems (GRDDS) are specialized systems that improve the bioavailability and effectiveness of drugs in the body. They are particularly advantageous for certain types of drugs that have specific absorption or solubility characteristics. (Lopes et al. 2016)

Ideal properties of potential drug candidates for gastroretentive drug delivery systems include:

1. **Narrow Absorption Window:** Drugs that have a narrow absorption window, especially in the upper gastrointestinal tract, benefit significantly from GRDDS. This is because these systems can help maintain the drug in its absorption zone for a prolonged period, thus improving the drug's bioavailability. (Tripathi et al. 2019b)
2. **Solubility in Acidic Conditions:** Drugs that are soluble in acidic conditions are ideal for GRDDS because the stomach, where these systems primarily operate, is highly acidic. (Tripathi et al. 2019b)
3. **Instability at Alkaline pH:** Drugs that are unstable at alkaline pH also stand to gain from GRDDS. As the stomach environment is acidic, these drugs can retain their stability and efficacy in the presence of these systems.(Tripathi et al. 2019b)
4. **Local Activity in the Stomach:** Drugs that are intended to have a local effect in the stomach or duodenum are good candidates for GRDDS as these systems allow for the drug to be retained in the stomach for an extended period. (Lopes et al. 2016)

Specific Drug Examples: Certain drugs are specifically mentioned as being suitable for GRDDS, such as albuterol (which is absorbed from the stomach), ranitidine and metformin (which are labile at alkaline pH), and furosemide and diazepam (which are poorly soluble at alkaline pH). (VINCHURKAR et al. 2022)

Gastroretentive drug delivery systems (GRDDS) are designed to enhance the bioavailability and effectiveness of certain drugs by retaining them in the stomach or upper gastrointestinal tract for prolonged periods. However, not all drugs are suitable for these systems. certain drugs may not benefit from GRDDS due to their chemical properties or targeted site of action.(Iglesias et al. 2020)

The properties of drugs that are unsuitable for gastroretentive drug delivery systems include:

1. **Limited Acid Solubility:** Drugs that have very limited solubility in acid, such as phenytoin, are not ideal for GRDDS. These drugs may not be able to effectively dissolve in the acidic environment of the stomach, which is where GRDDS primarily operate. (Salehi et al. 2021)

2. **Instability in the Gastric Environment:** Drugs that are unstable in the gastric environment, like erythromycin, are also unsuitable for GRDDS. If a drug cannot maintain its stability in the stomach's acidic conditions, its efficacy may be compromised.(Porat et al. 2021)

3. **Intended for Selective Release in the Colon:** Certain drugs, such as 5-amino salicylic acid and corticosteroids, are intended for selective release in the colon. These drugs would not benefit from a delivery system designed to retain drugs in the stomach or upper gastrointestinal tract, as this could potentially delay their release and reduce their

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

effectiveness at the intended site of action.(Han et al. 2020)

III. STRATEGIES TO ENHANCE GASTRIC RETENTION OF ORAL DOSAGE FORMS

Several strategies have been developed and employed to enhance the retention time of orally administered dosage forms within the stomach. These techniques aim to optimize drug delivery and maximize therapeutic efficacy by ensuring an extended interaction between the drug and its absorption site. These approaches can be broadly categorized into two domains: the Bioadhesive Approach and the Density Modification Approach. (Niharika, Krishnamoorthy, and Akkala 2018)

Bioadhesive Approach to Gastric Retention

The bioadhesive approach leverages the adhesive properties of certain polymers to secure the dosage form to the epithelial surface of the stomach. Here, the drug delivery system is formulated with bioadhesive polymers which have a propensity to interact with glycoproteins present on the stomach's epithelial surface. This close application fosters a strong adhesive bond, enhancing the retention of the dosage form in the stomach and potentially promoting local drug delivery. Furthermore, this method may also improve bioavailability, particularly for drugs that act locally in the stomach or upper parts of the gastrointestinal tract. (Cvijic et al. 2018)

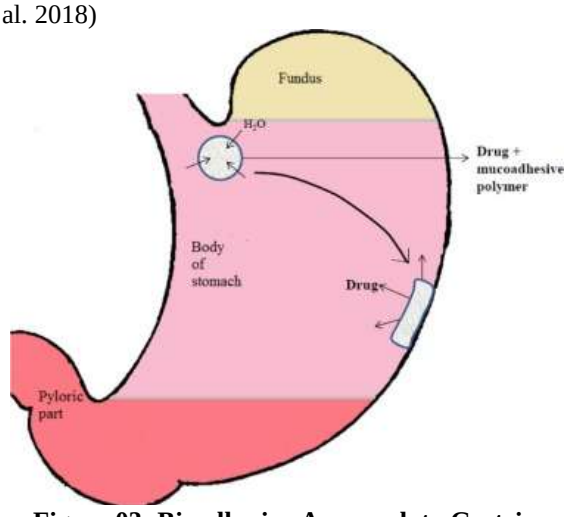

Figure 03: Bioadhesive Approach to Gastric Retention

Density Modification Approach to Gastric Retention

The Density Modification Approach encompasses techniques that adjust the density of the dosage form to either above or below the density of gastric fluids, thus exploiting the principles of sedimentation and buoyancy, respectively. These can be divided into two categories: High-Density and Low-Density Approaches.

High-Density Approach: The High-Density Approach involves formulation strategies that increase the density of the dosage form, often in the form of pellets, to exceed the density of gastric fluids, typically aiming for at least 1.50 g/ml. This is achieved by incorporating the drug into heavy, non-toxic substances, such as barium sulfate or titanium dioxide, either by coating the drug or by mixing it with these materials. The resulting high-density dosage form sinks in the gastric fluid and remains there for an extended duration due to resistance against natural peristaltic movements, thus prolonging the gastric retention time.(More et al. 2018)

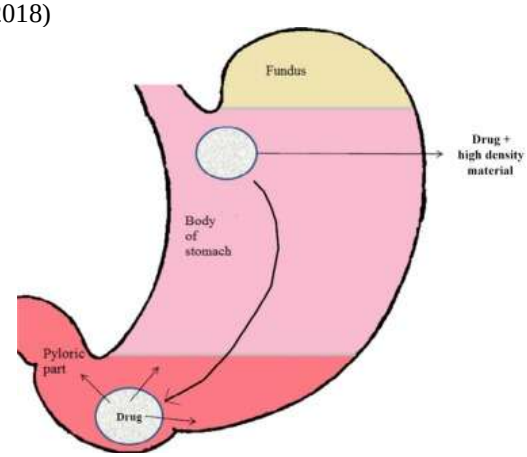

Figure 04:High-Density Approach

Low-Density Approach: Conversely, the Low-Density Approach, also known as Hydrodynamically Balanced Systems (HBS), involves creating dosage forms with a density lower than 1 g/ml. This lower density allows the dosage form to float on the surface of the gastric fluid. This floating behavior extends the gastric retention time as the dosage form remains buoyant in the stomach, providing a sustained release of the drug over a more extended period. This strategy can be particularly beneficial for drugs with a narrow absorption window in the upper gastrointestinal tract.

Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) are a subclass of oral drug delivery systems that employ a unique mechanism to extend the residence time of drugs within the stomach. Due to their lower bulk

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

density compared to gastric fluids, these systems remain buoyant in the stomach without significantly affecting the gastric emptying rate. This extended residence time allows for the sustained and controlled release of the drug from the system.(Bhosale, Shinde, and Chavan 2020)

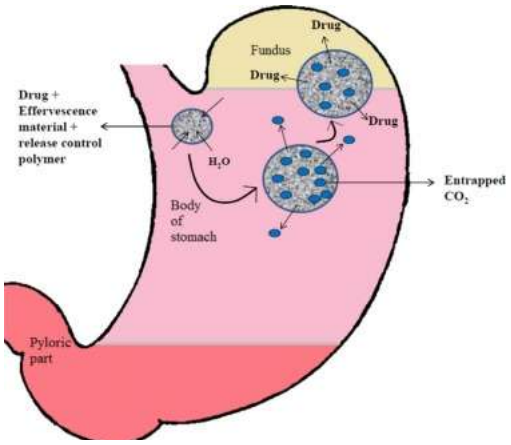

Figure 05: Floating Drug Delivery Systems

Prerequisites for FDDS: Achieving optimal performance with FDDS necessitates certain prerequisites. Firstly, the system should have a minimal gastric content to facilitate buoyancy. Secondly, a minimal level of floating force (F) is necessary to maintain the dosage form reliably afloat on the surface of the gastric content.

The floating force is defined as the force that is required to keep the drug delivery system submerged. The stronger the floating force the better the object will float. (Chauhan, Kataria, and Dashora 2018)
The floating force (F) can be calculated using the formula:

F = F_buoyancy – F_gravity = (D_f – D_s) g v
Where:
F = Total vertical force, D_f = Fluid density (Density of gastric fluids)
D_s = Object density (Density of the dosage form), g = Acceleration due to gravity
v = Volume of the dosage form

Evaluating the Floating Force Kinetics: To monitor the floating force kinetics, a novel apparatus has been reported that continuously measures the force equivalent to F as a function of time. This innovative tool plays a crucial role in optimizing the FDDS in terms of the stability and durability of the floating forces produced. By doing so, it aids in circumventing the drawbacks associated with unpredictability in the intragastric buoyancy capabilities.

Classification of Floating Drug Delivery Systems
1. Single Unit Floating Dosage Systems
a) Effervescent Systems
b) Non-effervescent Systems
2. Multiple Unit Floating Dosage Systems
a) Effervescent Systems
b) Non-effervescent Systems
c) Hollow Microspheres
3. Raft Forming Systems

1. Single Unit Floating Dosage Systems

a) Effervescent Systems: Effervescent floating drug delivery systems operate by producing carbon dioxide gas, which decreases the system's density. As a result, these systems can remain buoyant within the stomach for extended periods, allowing for a controlled, gradual release of the drug at the intended rate. These systems typically comprise of swellable polymers like chitosan and methyl cellulose, and effervescent compounds such as sodium bicarbonate, citric acid, and tartaric acid. These ingredients collectively contribute to the system's buoyancy and drug release properties.

Penners and colleagues developed an innovative expandable tablet consisting of a mixture of polyvinyl lactams and polyacrylates. This formulation quickly swells in an aqueous environment, enabling it to remain in the stomach for an extended period. They further incorporated gas-forming agents, which, upon generating gas, reduced the system's density and facilitated its floating in the gastric environment.

Further advancements in effervescent floating drug delivery systems are exemplified by a study that formulated an effervescent floating tablet of famotidine. The researchers observed that the integration of a gel-forming polymer, Methocel (specifically grades K100 and K15M), and a gas-generating agent such as sodium bicarbonate in conjunction with citric acid was crucial for achieving in vitro buoyancy. Moreover, they found that the drug release from these tablets was satisfactorily sustained, with non-Fickian transport of the drug. (Chauhan, Kataria, and Dashora 2018)

b) Non-effervescent Systems: Non-effervescent systems frequently utilize gel-forming or highly

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

swellable hydrocolloids of the cellulose type, polysaccharides, and matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation methodology involves a straightforward process of extensively blending the drug with the gel-forming hydrocolloid. Upon oral administration, the dosage form comes in contact with gastric fluids, causing it to swell and reach a bulk density of less than 1 g/ml. The entrapped air within the swollen matrix imparts the dosage form with buoyancy.

Iannuccelli and colleagues developed an air compartment multiple unit system aimed at extended gastric retention. These units featured a calcium alginate core, separated from a calcium alginate membrane by an air compartment. Polyvinyl alcohol (PVA) was used as a water-soluble additive in the coating composition, and the subsequent leaching process resulted in a porous structure that increased the membrane's permeability and prevented shrinkage of the air compartment. It was observed that as the molecular weight of PVA increased, so too did the floatation capacity of the units.

Furthermore, Wu et al formulated floating sustained release tablets of nimodipine using hydroxypropyl methylcellulose (HPMC) and polyethylene glycol 6000 (PEG 6000). The process involved incorporating nimodipine into a solid dispersion of poloxamer-188 before compressing it directly into floating tablets. They found that by increasing the HPMC content and reducing the PEG 6000 content, the in vitro release of nimodipine decreased.

However, single unit formulations are not without their challenges, such as the potential for the units to stick together or become obstructed in the gastrointestinal tract, potentially causing irritation. A significant disadvantage of this system is the "all or none" phenomenon, wherein there is a risk of the dosage form moving into the intestinal part during housekeeper waves. To circumvent this issue, multiple unit dosage forms have been designed. (Teaima et al. 2020)

2. Multiple Unit Floating Dosage Systems

Multiple unit dosage forms present an appealing alternative, as they have demonstrated a reduction in inter and intra-subject variabilities related to drug absorption, while simultaneously minimizing the risk of dose dumping. A range of multiple unit floating systems has been devised, taking on various forms and operating based on principles such as the air compartment multiple unit system, hollow microspheres crafted using the emulsion solvent diffusion method, and beads fabricated via the emulsion gelation process. The employment of effervescent and swellable polymers represents an additional strategy in the development of multiple unit floating drug delivery systems (FDDS).

The air compartment multiple unit system, for instance, maintains a state of buoyancy in the gastric environment through the use of entrapped air within each unit. This concept is realized through a core and a surrounding membrane made of substances like calcium alginate, which possess the capability to swell in the presence of gastric fluids.

On the other hand, hollow microspheres utilize the emulsion solvent diffusion technique to create a unique structure. This method involves the dissolution of the polymer and the drug in a solvent, which is then emulsified into an aqueous phase containing a stabilizer. The solvent subsequently diffuses into the aqueous phase, forming a rigid microsphere shell.

The emulsion gelation method, utilized for the preparation of bead-based FDDS, involves the gelation of a polymer within the droplets of an oil-in-water emulsion. This results in a system of gel beads that can remain buoyant in the stomach and gradually release the drug over an extended period.

Lastly, effervescent and swellable polymers can be exploited in the design of multiple unit FDDS. The former generates gas upon contact with gastric fluids, reducing the system's density and facilitating its buoyancy. The latter, on the other hand, swells upon interaction with gastric fluids, entrapping air and providing the dosage form with the necessary buoyancy. (Maraie, Salman, and Yousif 2018)

a) Effervescent Systems: Ichikawa et al. devised an innovative multiple-type floating dosage system, composed of effervescent layers and swellable membrane layers coated on sustained-release tablets. The effervescent layer, embedded with sodium bicarbonate and tartaric acid, was bifurcated into two sublayers to prevent direct interaction between the two agents. This layer was ensheathed by a swellable polymer membrane comprising polyvinyl acetate and purified shellac. Upon immersion in a 37ºC buffer solution, the system sank, allowing the solution to permeate the effervescent layer via the external swellable

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

membrane. The neutralization reaction between the effervescent agents generated CO2, leading to the expansion of the tablets, analogous to inflating balloons, achieving a density less than 1.0 g/ml.

Thanoo et al. fabricated polycarbonate microspheres utilizing the solvent evaporation technique. Polycarbonate dissolved in dichloromethane yielded hollow microspheres that floated on water and biomimetic fluids, as confirmed by scanning electron microscopy (SEM). The method attained high drug loading, and the drug-loaded microspheres were capable of floating on gastric and intestinal fluids. It was found that augmenting the drug to polymer ratio resulted in an increase in both the mean particle size and the drug release rate.

c) Hollow Microspheres: Both natural and synthetic polymers have been exploited in the development of floating microspheres. In one such study, Joseph et al. created a floating drug delivery system for piroxicam, employing hollow polycarbonate microspheres. These microspheres were fabricated using the solvent evaporation method. The process achieved an encapsulation efficiency of approximately 95%.
In vivo studies were conducted using healthy male albino rabbits. Pharmacokinetic assessment was conducted by plotting plasma concentration against time. The results indicated that the bioavailability of piroxicam from the microspheres was 1.4 times greater than that of the free drug. Moreover, it was 4.8 times greater than that of a dosage form comprising microspheres plus the loading dose. This system exhibited the capability for sustained drug delivery over an extended period. (Auriemma et al. 2018)

3) Raft-forming systems

Raft-forming systems have garnered considerable interest for their application in treating gastrointestinal infections and disorders. The underlying mechanism of raft formation involves the creation of a viscous, cohesive gel upon contact with gastric fluids. Each part of the liquid swells, leading to the formation of a continuous layer known as a 'raft'. Due to the reduced bulk density resulting from the formation of CO_2, this raft achieves buoyancy on the gastric fluids.

Typically, the system consists of a gel-forming agent and alkaline bicarbonates or carbonates. These compounds are responsible for CO_2 generation, which in turn makes the system less dense, enabling it to float on the gastric fluids. Jorgen et al. detailed a raft-forming floating system functioning as an antacid. This system incorporates a gel-forming agent, such as sodium alginate, along with sodium bicarbonate and an acid neutralizer. Upon interaction with gastric fluids, this composition forms a sodium alginate gel (raft) that floats.

This floating raft aids in preventing the reflux of gastric contents, including gastric acid, into the esophagus by serving as a protective barrier between the stomach and the esophagus. (Bunlung et al. 2021)

IV. EVALUATION PARAMETERS FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Evaluation of Floating Systems:

To assess floating systems, a six-stage dissolution test apparatus is employed. Dissolution media consists of 0.1N, 900 ml HCl. Critical parameters measured include the time needed for the system to surface on the medium, referred to as the Floating Lag Time, and the total duration of the floating time. In-vitro studies are performed at a temperature of 37 degrees Celsius for a specified duration, approximately 8 hours.

Evaluation of Mucoadhesive Systems:

The measurement of bio-adhesive strength is vital for evaluating mucoadhesive systems. A cellophane membrane, which is analogous to the stomach's mucosa, or intact mucosa derived from rabbits, is employed in this process. When the bio-adhesive polymer comes in contact with the mucosa, it adheres to it. The force required to separate this bond is then measured, which provides a measure of the polymer's adhesive strength.(Reddy Donthi and Dudipala 2015)

Evaluation of Swellable Systems:

Assessment parameters for swellable systems involve examining water uptake, which gives an indication of the swelling index. Additional checks include monitoring changes in weight, diameter, and thickness. A dissolution test is conducted using 0.1N HCl as the dissolution fluid. The swelling index (S.I) is calculated using the formula:
Swelling Index (S.I) = (Wt - Wo / Wo) x 100
where, Wt refers to the final weight after water uptake and Wo indicates the initial weight.(Pradhan et al. 2015)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

Micro balloons:

Fourier Transform Infrared Spectroscopy (FTIR) Analysis: FTIR analysis is utilized to study potential interactions between the drug and the polymer. The FT-IR spectra of pure drug, Eudragit RS 100, HPMC, and floating microballoons are recorded with a Shimadzu 8700 FTIR spectrophotometer.

Micromeritic Properties: Microballoons are characterized based on their micromeritic properties, including particle size, bulk density, tapped density, compressibility index, and flow properties.

Morphological Examination: The morphology of the microballoons is investigated by preparing the dried microballoons with a gold film coating under vacuum conditions using a sputter coater. The surface of the microballoons is then observed under a scanning electron microscope (Joel JSM-1600, Tokyo, Japan).

Evaluation of Floating Behaviour: The floating behavior of the microballoons is assessed by placing fifty milligrams of floating microballoons in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v% Tween 20. The mixture is stirred at 100 rpm using a magnetic stirrer. After six hours, the floating and settled portions of the microballoons are separated by filtration, dried, and weighed. The buoyancy is determined by comparing the weight ratio of floating particles to the sum of floating and sinking particles.

The buoyancy percentage is determined using the formula:

$$\text{Buoyancy (\%)} = (Wf / (Wf + Ws)) \times 100$$

Here, Wf and Ws are the weights of floating and settled microparticles respectively. (Ramachandran et al. 2010)

In Vitro Drug Release Study:

The drug release rate from the microballoons is ascertained utilizing a USP XXIII basket type dissolution apparatus. A quantity of hollow microspheres equivalent to 20 mg of drug is encapsulated and placed in the basket. The dissolution medium, simulated gastric fluid (SGF, pH-1.2) containing Tween 20 (0.02 w/v %), is maintained at 37± 0.5° C at a rotation speed of 100 rpm.

Throughout the drug release studies, perfect sink conditions are maintained. At each 1-hour interval, a 5 ml sample is withdrawn, filtered through a 0.5µm membrane filter (Millipore), and analyzed spectrophotometrically at 296 nm to determine the concentration of drug present in the dissolution medium. After each withdrawal, the initial volume of the dissolution fluid is maintained by supplementing with 5 ml of fresh dissolution fluid. All experiments are conducted in triplicate. (Vardakou et al. 2011)

Stability Testing:

The most efficacious floating microballoon formulation, selected based on buoyancy and drug release percentage, is subjected to stability testing. The formulation is placed in borosilicate screw-capped glass containers and stored at various temperatures - ambient (27±2°C), oven temperature (40±2°C), and refrigerated conditions (5-8°C) for a period of 90 days. At regular intervals, the samples are assayed for drug content (drug entrapment). (Gao et al. 2019)

CONCLUSION

Based on an extensive literature review, we can affirm that gastroretentive drug delivery systems present significant potential benefits, especially for drugs with restricted absorption to the upper gastrointestinal tract (GIT) leading to suboptimal bioavailability. These innovative systems promise to enhance drug delivery efficiency, thereby optimising drug absorption and improving overall bioavailability.

However, the intricate nature of pharmacokinetic and pharmacodynamic parameters necessitates further in vivo studies to establish the optimal dosage form for specific drugs. In addition, individual physiological variations, including stomach physiology and the timing of drug administration in relation to meals, must be taken into account when designing these systems.

Designing an efficient gastroretentive dosage form poses a significant challenge to pharmaceutical technology. The system must remain in the stomach for an adequate duration, which contrasts with the stomach's natural physiology designed for progression of its contents. Gastroretentive drug delivery systems encompass a variety of forms such as high density, floating, expandable, unfoldable, swelling, superporous, bioadhesive, and magnetic systems. Each of these systems holds its own unique advantages and limitations.

Currently, substantial efforts are underway to develop an array of gastroretentive delivery systems for various drugs. We anticipate these

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2949-2961 www.ijprajournal.com ISSN: 2249-7781

systems will become increasingly important in the future, contributing to enhanced efficiencies of various types of pharmacotherapies. The success of these technologies holds immense potential to revolutionise drug delivery and patient outcomes, marking a pivotal shift in the field of pharmaceutical science.

REFERENCES

[1]. Arza, Ramji Anil Kumar, Chandra Sekhara Rao Gonugunta, and Prabhakar Reddy Veerareddy. 2009. 'Formulation and Evaluation of Swellable and Floating Gastroretentive Ciprofloxacin Hydrochloride Tablets'. AAPS PharmSciTech 10 (1): 220–26. https://doi.org/10.1208/s12249-009-9200-y.

[2]. Auriemma, Giulia, Andrea Cerciello, Francesca Sansone, Aldo Pinto, Silvana Morello, and Rita P. Aquino. 2018. 'Polysaccharides Based Gastroretentive System to Sustain Piroxicam Release: Development and in Vivo Prolonged Anti-Inflammatory Effect'. International Journal of Biological Macromolecules 120 (December): 2303–12. https://doi.org/10.1016/j.ijbiomac.2018.08.140.

[3]. Bhosale, Aishwarya Rajendra, Jitendra V Shinde, and Rajashree S. Chavan. 2020. 'A Comprehensive Review on Floating Drug Delivery System (FDDS)'. Journal of Drug Delivery and Therapeutics 10 (6): 174–82. https://doi.org/10.22270/jddt.v10i6.4461.

[4]. Birajdar, Anuradha A., Madhuri T. Deshmukh, and Rajkumar V. Shete. 2021. 'A Review on Gastro-Retentive Floating Microspheres'. Journal of Drug Delivery and Therapeutics 11 (1-s): 131–38. https://doi.org/10.22270/jddt.v11i1-s.4518.

[5]. Braeckmans, Marlies, Joachim Brouwers, ImkeMasuy, Cécile Servais, Jan Tack, and Patrick Augustijns. 2020. 'The Influence of Gastric Motility on the Intraluminal Behavior of Fosamprenavir'. European Journal of Pharmaceutical Sciences 142 (January): 105117. https://doi.org/10.1016/j.ejps.2019.105117.

[6]. Bunlung, Suputra, TeerapatNualnoi, OusaneeIssarachot, and RuedeekornWiwattanapatapee. 2021. 'Development of Raft-Forming Liquid and Chewable Tablet Formulations Incorporating Quercetin Solid Dispersions for Treatment of Gastric Ulcers'. Saudi Pharmaceutical Journal 29 (10): 1143–54. https://doi.org/10.1016/j.jsps.2021.08.005.

[7]. Charoenying, Thapakorn, PrasopchaiPatrojanasophon, TanasaitNgawhirunpat, TheerasakRojanarata, PrasertAkkaramongkolporn, and PraneetOpanasopit. 2020. 'Fabrication of Floating Capsule-in- 3D-Printed Devices as Gastro-Retentive Delivery Systems of Amoxicillin'. Journal of Drug Delivery Science and Technology 55 (February): 101393. https://doi.org/10.1016/j.jddst.2019.101393.

[8]. Chauhan, Yashpal Singh, UdichiKataria, and Ashok Dashora. 2018. 'Importance of Floating Drug Delivery System'. Research Journal of Pharmaceutical Dosage Forms and Technology 10 (4): 220. https://doi.org/10.5958/0975-4377.2018.00034.4.

[9]. Cheng, Chun-sheng, Ting-ji Sun, and Hou-de Zhang. 2019. 'Human Gastric Magnet-Controlled Capsule Endoscopy Conducted in a Standing Position: The Phase 1 Study'. BMC Gastroenterology 19 (1): 184. https://doi.org/10.1186/s12876-019-1101-2.

[10]. Cheng, Lisa, and Harvey Wong. 2020. 'Food Effects on Oral Drug Absorption: Application of Physiologically-Based Pharmacokinetic Modeling as a Predictive Tool'. Pharmaceutics 12 (7): 672. https://doi.org/10.3390/pharmaceutics12070672.

[11]. Cvijic, Sandra, Svetlana Ibric, Jelena Parojcic, and Jelena Djuris. 2018. 'An in Vitro - in Silico Approach for the Formulation and Characterization of Ranitidine Gastroretentive Delivery Systems'. Journal of Drug Delivery Science and Technology 45 (June): 1–10. https://doi.org/10.1016/j.jddst.2018.02.013.

[12]. Emara, Laila H., Aya R. Abdou, Ahmed A. El-Ashmawy, Rania M. Badr, Nesrin F. Taha, and Nadia M. Mursi. 2013. 'In Vitro Release Evaluation of Gastroretentive Amoxicillin Floating Tablets Employing a Specific Design of the Flow-Through Cell'. Dissolution Technologies 20 (1): 27–34. https://doi.org/10.14227/DT2000113P27.

[13]. Gao, Zongming, Cindy Ngo, Wei Ye, Jason D. Rodriguez, David Keire, Dajun Sun, Hong Wen, and Wenlei Jiang. 2019. 'Effects of Dissolution Medium PH and Simulated Gastrointestinal Contraction on Drug Release From Nifedipine Extended-Release Tablets*'. Journal of Pharmaceutical Sciences 108 (3): 1189–94. https://doi.org/10.1016/j.xphs.2018.10.014.

[14]. Han, Guang, Shuming Wen, Han Wang, and Qicheng Feng. 2020. 'Selective Adsorption Mechanism of Salicylic Acid on Pyrite Surfaces and Its Application in Flotation Separation of Chalcopyrite from Pyrite'. Separation and Purification Technology 240 (June): 116650. https://doi.org/10.1016/j.seppur.2020.116650.

[15]. Heissam, Khaled, Nichola Abrehart, Caroline L. Hoad, Jeff Wright, Alex Menys, Kathryn Murray, Paul M. Glover, et al. 2020. 'Measurement of Fasted State Gastric Antral Motility before and after a Standard Bioavailability and Bioequivalence 240 ML Drink of Water: Validation of MRI Method against Concomitant Perfused Manometry in Healthy Participants'. PLOS ONE 15 (11): e0241441. https://doi.org/10.1371/journal.pone.0241441.

[16]. Hens, Bart, ImkeMasuy, Eveline Deloose, Raf Mols, Jan Tack, and Patrick Augustijns. 2020. 'Exploring the Impact of Real-Life Dosing Conditions on Intraluminal and Systemic Concentrations of Atazanavir in Parallel with Gastric Motility Recording in Healthy Subjects'. European Journal of Pharmaceutics and Biopharmaceutics 150 (May): 66–76. https://doi.org/10.1016/j.ejpb.2020.02.014.

[17]. Iglesias, Nieves, Elsa Galbis, Lucía Romero-Azogil, Elena Benito, Ricardo Lucas, M. Gracia García-Martín, and M.-Violante de-Paz. 2020. 'In-Depth Study into Polymeric Materials in Low-Density Gastroretentive Formulations'. Pharmaceutics 12 (7): 636. https://doi.org/10.3390/pharmaceutics12070636.

[18]. Kumar, Pramod, Sanjay Singh, and Brahmeshwar Mishra. 2008. 'Floating Osmotic Drug Delivery System of Ranitidine Hydrochloride: Development and Evaluation—A Technical Note'. AAPS PharmSciTech 9 (2): 480–85. https://doi.org/10.1208/s12249-008-9065-5.

[19]. Lopes, Carla M., Catarina Bettencourt, Alessandra Rossi, Francesca Buttini, and Pedro Barata. 2016. 'Overview on Gastroretentive Drug Delivery Systems for Improving Drug Bioavailability'. International Journal of Pharmaceutics 510 (1): 144–58. https://doi.org/10.1016/j.ijpharm.2016.05.016.

[20]. Mandal, Uttam Kumar, Bappaditya Chatterjee, and FariaGiasSenjoti. 2016. 'Gastro-Retentive Drug Delivery Systems and Their in Vivo Success: A Recent Update'. Asian Journal of Pharmaceutical Sciences 11 (5): 575–84. https://doi.org/10.1016/j.ajps.2016.04.007.

[21]. Maraie, Nidhal K, Zeina D Salman, and Nora Zawar Yousif. 2018. 'DESIGN AND CHARACTERIZATION OF OROSLIPPERY BUOYANT TABLETS FOR RANITIDINE HYDROCHLORIDE'. Asian Journal of Pharmaceutical and Clinical Research 11 (1): 143. https://doi.org/10.22159/ajpcr.2018.v11i1.21982.

[22]. More, Swapnil, Kaustubh Gavali, Onkar Doke, and Prasad Kasgawade. 2018. 'GASTRORETENTIVE DRUG DELIVERY SYSTEM'. Journal of Drug Delivery and Therapeutics 8 (4). https://doi.org/10.22270/jddt.v8i4.1788.

[23]. Niharika, Mirmeera Girish, Kannan Krishnamoorthy, and Madhukar Akkala. 2018. 'OVERVIEW ON FLOATING DRUG DELIVERY SYSTEM'. International Journal of Applied Pharmaceutics 10 (6): 65. https://doi.org/10.22159/ijap.2018v10i6.28274.

[24]. Porat, Daniel, Julie Vaynshtein, Roni Gibori, Opal Avramoff, Gad Shaked, Oleg Dukhno, David Czeiger, Gilbert Sebbag, and Arik Dahan. 2021. 'Stomach PH before vs. after Different Bariatric Surgery Procedures: Clinical Implications for Drug Delivery'. European Journal of Pharmaceutics and Biopharmaceutics 160 (March): 152–57. https://doi.org/10.1016/j.ejpb.2021.01.016.

[25]. Pradhan, Roshan, Hee-Hyun Lee, Jung-Ok Kim, Sung-Ok Moon, Hye-Min Choi, Jong-Bum Kim, Chul Soon Yong, Hwa-Dong Lee, and Jong Oh Kim. 2015. 'Preparation and Evaluation of Gastroretentive Effervescent Floating Drug Delivery System of Samchulkunbi-Tang'. Journal of Pharmaceutical Investigation 45 (5): 423–31. https://doi.org/10.1007/s40005-015-0187-y.

[26]. Ramachandran, S., S. Shaheedha, G. Thirumurugan, and M. Dhanaraju. 2010. 'Floating Controlled Drug Delivery System of Famotidine Loaded Hollow Microspheres (Microballoons) in the Stomach'. Current Drug Delivery 7 (1): 93–97. https://doi.org/10.2174/156720110790396436.

[27]. Reddy Donthi, Mahipal, and NarendharDudipala. 2015. 'Design and Evaluation of Floating Multi Unit Mini Tablets (MUMTS) Muco Adhesive Drug Delivery System of Famotidine to Treat Upper Gastro Intestinal Ulcers'. Journal of Pharmacovigilance 03 (05). https://doi.org/10.4172/2329-6887.1000179.

[28]. Salehi, Niloufar, GislaineKuminek, Jozef Al-Gousous, David C. Sperry, Dale E. Greenwood, Nicholas M. Waltz, Gordon L. Amidon, Robert M. Ziff, and Gregory E. Amidon. 2021. 'Improving Dissolution Behavior and Oral Absorption of Drugs with PH-Dependent Solubility Using PH Modifiers: A Physiologically Realistic Mass Transport Analysis'. Molecular Pharmaceutics 18 (9): 3326–41. https://doi.org/10.1021/acs.molpharmaceut.1c00262.

[29]. Schol, Jolien, Lucas Wauters, Ram Dickman, Vasile Drug, AgataMulak, Jordi Serra, Paul Enck, et al. 2021. 'United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) Consensus on Gastroparesis'. United European Gastroenterology Journal 9 (3): 287–306. https://doi.org/10.1002/ueg2.12060.

[30]. Stillhart, Cordula, Katarina Vučićević, Patrick Augustijns, Abdul W. Basit, Hannah Batchelor, Talia R. Flanagan, Ina Gesquiere, et al. 2020. 'Impact of Gastrointestinal Physiology on Drug Absorption in Special Populations—An UNGAP Review'. European Journal of Pharmaceutical Sciences 147 (April): 105280. https://doi.org/10.1016/j.ejps.2020.105280.

[31]. Teaima, Mahmoud, Magdi M. Abdel Hamid, Nabil A. Shoman, Bhaskara R. Jasti, and Mohamed A. El-Nabarawi. 2020. 'Promising Swellable Floating Bupropion Tablets: Formulation, in Vitro/in Vivo Evaluation and Comparative Pharmacokinetic Study in Human Volunteers'. Drug Design, Development and Therapy Volume 14 (July): 2741–57. https://doi.org/10.2147/DDDT.S258571.

[32]. Tripathi, Thapa, Maharjan, and Jeong. 2019. 'Current State and Future Perspectives on Gastroretentive Drug Delivery Systems'. Pharmaceutics 11 (4): 193. https://doi.org/10.3390/pharmaceutics11040193.

[33]. ———. 2019b. 'Current State and Future Perspectives on Gastroretentive Drug Delivery Systems'. Pharmaceutics 11 (4): 193. https://doi.org/10.3390/pharmaceutics11040193

[34]. Uemura, Karime Lucas, Dalton Chaves, Wanderley M. Bernardo, Ricardo Sato Uemura, DiogoTurianiHourneaux de Moura, and Eduardo GuimarãesHourneaux de Moura. 2020. 'Peroral Endoscopic Pyloromyotomy for Gastroparesis: A Systematic Review and Meta-Analysis'. Endoscopy International Open 08 (07): E911–23. https://doi.org/10.1055/a-1119-6616.

[35]. Vardakou, Maria, Annalisa Mercuri, Susan A. Barker, Duncan Q. M. Craig, Richard M. Faulks, and Martin S. J. Wickham. 2011. 'Achieving Antral Grinding Forces in Biorelevant In Vitro Models: Comparing the USP Dissolution Apparatus II and the Dynamic Gastric Model with Human In Vivo Data'. AAPS PharmSciTech 12 (2): 620–26. https://doi.org/10.1208/s12249-011-9616-z.

[36]. Verma, Anurag, Juhi Dubey, Rahul Rama Hegde, Vaibhav Rastogi, and J. K. Pandit. 2016. 'Helicobacter Pylori : Past, Current and Future Treatment Strategies with

Gastroretentive Drug Delivery Systems'. Journal of Drug Targeting 24 (10): 897–915. https://doi.org/10.3109/1061186X.2016.1171326.

[37]. VINCHURKAR, Kuldeep, Jitendra SAINY, Masheer Ahmed KHAN, Sheetal MANE, Dinesh K MISHRA, and Pankaj DIXIT. 2022. 'Features and Facts of a Gastroretentive Drug Delivery System-A Review'. Turkish Journal of Pharmaceutical Sciences 19 (4): 476–87. https://doi.org/10.4274/tjps.galenos.2021.44959.

[38]. Vrbanac, Helena, JurijTrontelj, Sandra Berglez, BoštjanPetek, JernejaOpara, RebekaJereb, DejanKrajcar, and Igor Legen. 2020. 'The Biorelevant Simulation of Gastric Emptying and Its Impact on Model Drug Dissolution and Absorption Kinetics'. European Journal of Pharmaceutics and Biopharmaceutics 149 (April): 113–20. https://doi.org/10.1016/j.ejpb.2020.02.002.

[39]. Wickham, M. J. S., R. M. Faulks, J. Mann, and G. Mandalari. 2012. 'The Design, Operation, and Application of a Dynamic Gastric Model'. Dissolution Technologies 19 (3): 15–22. https://doi.org/10.14227/DT190312P15.

[40]. Wu, Yujia, Wen Zhang, Jianyu Huang, Zichen Luo, Junsong Li, Lingchong Wang, and Liuqing Di. 2020. 'Mucoadhesive Improvement of Alginate Microspheres as Potential Gastroretentive Delivery Carrier by Blending with BletillaStriata Polysaccharide'. International Journal of Biological Macromolecules 156 (August): 1191–1201. https://doi.org/10.1016/j.ijbiomac.2019.11.156.