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Recent Advances in the Development of Polymeric Floating Biomaterials for *Helicobacter pylori* Therapy: Current Status and Future Directions

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Abstract: *Helicobacter pylori (H. pylori)* infection is a common global health problem linked to peptic ulcers, gastric cancer, and other digestive problems. Current *H. pylori* eradication therapy must address issues such as antibiotic resistance, poor patient compliance, low stomach pH, and insufficient medication concentration at the infection site. With an emphasis on the present state and potential future directions in this developing field, this review attempts to give a broad overview of recent developments in the creation of such biomaterials for *H. pylori* therapy. This review examines the benefits of microballoon-based drug administration, utilizes the situation of *H. pylori* therapy, and covers several formulation and evaluation techniques for microballoon. Additionally, it discusses current studies and clinical trials using microballoon drug delivery techniques to treat *H. pylori*. Microballoon have the potential to improve drug delivery, reduce dose frequency, increase drug stability, and improve drug targeting. The assessment of challenges and opportunities in this burgeoning field provides insights into the evolving landscape of biomaterial-based *H. pylori* management, offering a roadmap for forthcoming research and clinical implementation.

Keywords: *Helicobacter pylori*; Microballoon; Hallow microsphere; Biomaterials; Gastro-retentive drug.

1. INTRODUCTION

Helicobacter pylori (H. pylori) infection is a typical bacterial infection that affects the stomach. About 50% of people worldwide have *H. pylori* infection, which is more prevalent in developing nations, according to the World Health Organization [1]. Infection with *H. pylori* can have serious effects. The infection is an important factor in peptic ulcer disease and has been associated with a higher risk of stomach cancer, which can be quite dangerous [2,3]. Non-ulcer dyspepsia, a disorder characterized by persistent or recurrent abdominal pain or discomfort as well as other digestive symptoms, can also be brought on by *H. pylori* infection. *H. pylori* can have considerable negative repercussions on the economy and society in addition to the direct effects of peptic ulcer disease treatment.

Biomaterials, defined as materials engineered to interact with biological systems, provide specific benefits in the treatment of *H. pylori*. Therapeutic agents can be transported by these materials, which offer precise delivery, controlled and prolonged release, and resistance to degradation by stomach acid. Several study endeavors have examined the possibility of biomaterials augmenting the effectiveness of *H. pylori* treatment. For example, in one study, antibiotic-loaded polymeric nanoparticles showed improved stability and extended release, which led to increased antibacterial activity against *H. pylori* [4]. The development of biomaterials with particular characteristics, like floating or mucoadhesive attributes, is

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required to overcome the particular difficulties presented by the acidic gastric environment and extend the duration of contact with the gastric mucosa. These characteristics may improve the therapeutic efficacy of medications administered locally. The application of floating microspheres containing antimicrobial agents showed enhanced antibacterial activity against *H. pylori* and a longer period of stomach residence [5].

1.1. Surveillance of *H. Pylori*

H. pylori colonizes the human and primate stomach mucosa. *H. pylori* thrives in an acidic environment that gastroenterologists traditionally believe to be sterile. *H. pylori* employs a two-pronged strategy to live in the harsh environment of the human stomach [6-8]. First, the bacteria possess several polar flagella, which allow them to travel through the mucus layer lining the stomach until they reach the cells at the bottom. Second, they create a microenvironment where the acidity and alkalinity balance is close to neutral, preventing direct contact with the hydrochloric acid produced by the stomach. Urease's enzymatic activity generates chemical compounds that neutralize the acidity in the mucus immediately surrounding the bacteria, thereby establishing a microzone that protects the bacteria. *H. pylori* is non-invasive, yet it colonizes the antral region and mucosal surfaces of the human stomach, releasing pathogenic proteins that induce cell injury and inflammation. These alterations make the stomach and duodenum more susceptible to damage by digestive fluids, such as stomach acid.

1.2. Pathogenesis of *H. Pylori* Infection

Although the precise methods by which H. pylori causes disease are not fully known, it is believed that they entail several elements, including the development of toxins and enzymes that harm the stomach lining and the ability of the bacteria to elude the immune system. [6] The ability of H. pylori to produce the enzyme urease, which converts urea into ammonia and carbon dioxide, is one of its primary virulence factors [9]. The ammonia aids in balancing the stomach's acidic environment, enabling the bacteria to persist and colonize the stomach lining. In addition, H. pylori secretes a variety of toxins and enzymes that can harm the stomach lining and aid in the growth of gastritis and ulcers. The inflammation brought on by the H. pylori infection and its progression are influenced by the immune system. Inflammation and tissue damage may result from H. pylori's ability to increase the production of cytokines and other immune mediators [10]. In addition, H. pylori produces chemicals that suppress the activity of immune cells as one of its many methods for evading the immune system and surviving in the stomach.

1.3. Current Status of *H. Pylori* Therapy

A proton pump inhibitor (PPI) in addition to antibiotics is the first-line treatment for *H. pylori* infection. While the PPI aids in lowering the amount of acid produced in the stomach, which helps the antibiotics function more effectively, the antibiotics are used to kill the bacteria. Depending on the patient and the exact strain of *H. pylori* implicated, different antibiotics and PPIs may be utilized. It is important to remember that a PPI is typically used together with a combination of two or three different antibiotics to treat *H. pylori* infections. Depending on how many antibiotics are taken, this is referred to as "triple therapy" or "quadruple therapy."

The American College of Gastroenterology and the European Helicobacter and Microbiota Study Group, among other medical organizations, have published guidelines outlining the recommended first-line treatment for *H. pylori* infection [11-16]. Alternative treatment alternatives may be taken into account if the first-line therapy for treating *H. pylori* infection is ineffective or if the patient cannot handle the drugs.

Second-line therapy: This typically involves a combination of different antibiotics and a PPI, or a bismuth-based quadruple therapy.

Sequential therapy: This involves taking a PPI and an antibiotic for the first week, followed by a PPI and two different antibiotics for the second week.

Concomitant therapy: This involves taking a PPI and two different antibiotics simultaneously for the entire treatment course.

Current treatment for *H. pylori* infection mainly uses antibiotic-based triple or quadruple therapy with acid-suppressing agents. However, rising antibiotic resistance challenges these treatments' efficacy. Alternative non-pharmacological methods being explored include probiotics, oxygen-rich environments, antibacterial photodynamic therapy, nanomaterials, antimicrobial peptide therapy, phage therapy, and modified lysins. The increasing antimicrobial resistance necessitates new strategies and continuous assessment of treatment regimens based on local resistance rates, eradication rates, and cost [17, 18]. Additionally, improved diagnostic methods, like rapid nucleic acid amplification tests, are crucial for guiding treatment based on resistance patterns.

1.4. Reasons for *H. Pylori* Eradication Failure

H. pylori eradication failure can occur due to several reasons (Fig. 1), including bacterial resistance to antibiotics, poor patient compliance, low stomach pH, and insufficient drug concentration.

Antibiotic resistance: *H. pylori* strains can become resistant to clarithromycin, metronidazole, and levofloxacin. Conventional antibiotic therapy for *H. pylori* is less effective because of increasing drug resistance [19].

Poor compliance: *H. pylori* eradication requires 7–14 days of antibiotics and acid-suppressants. Most physicians and investigators believe that patient compliance and antibiotic resistance are the primary challenges to generating the best *H. pylori* treatment regimens. To ensure compliance, patients must be informed and educated before starting *H. pylori* eradication medication, which can be complex and have negative effects [20].

Low stomach pH: *H. pylori* can adapt to acidic surroundings and become resistant to acid-suppressing treatments. Gastric acid secretion varies widely among people. Some people with normal gastrin levels have increased basal acid production. Lower eradication rates are observed in patients with hypersecretion, who most likely have more parietal cells. People can have weak, moderate, or extensive metabolizers due to gene polymorphism. Conventional PPI doses appear to be insufficient in patients who are extensive metabolizers to give enough pH inhibition to permit antibiotic activity in the stomach mucosa, leading to lower eradication rates despite some contradicting results [21].

Insufficient antibiotic concentration at the H. pylori site: Due to the synthesis of urease and the presence of flagella, *H. pylori* may survive in the gastrointestinal environment over a wide pH range, pass through the gastric mucous layer, and enter the gastric epithelium, where it can be found attached to and even inside of cells. Numerous antibiotics appear to have significantly reduced *in vivo* efficacy compared to their good *in vitro* performance because of poor mucous layer transport and low pH inactivation. After eradication from the antrum and gastric body, *H. pylori* may survive in the gastric cardia. Lack of antibiotic concentration at the *H. pylori* infection site is an important cause of treatment failure [22].

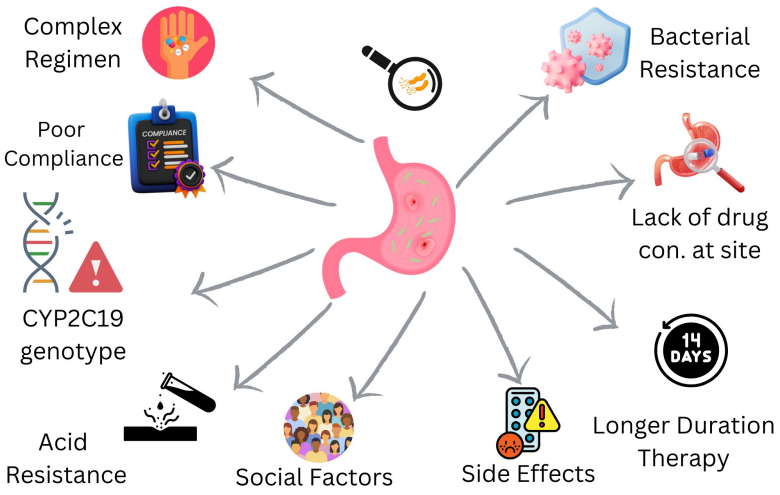

Fig 1. Reasons for *H. Pylori* Eradication Failure

2. NEED OF NOVEL DRUG DELIVERY

Because antimicrobial medications only stay in the stomach for a short time, they are unable to effectively concentrate on the gastric mucus layer or epithelial cell surfaces, which are home to *H. pylori.* Tablets and capsules are frequently used in eradication therapy, but they do not remain in the stomach long enough to reach the minimum inhibitory concentration in the gastrointestinal mucus where *H. pylori* thrives. Since *H. pylori* is still present in some people, new, more efficient medication regimens are required. Researchers tried many methods to eliminate *H. pylori* from the stomach in the 1980s. The stomach niche, bacterial load, and coccoid morphology require the medicine to persist in high concentration at the site of action to be therapeutic. Gastric retentive delivery methods may improve mucus penetration and medication concentration at the site of action. Higher antibiotic concentrations from gastroretentive drug delivery systems can eradicate *H. pylori* [23].

3. GASTRORETENTIVE DOSAGE FORMS

Gastroretentive dosage forms are drug delivery systems that are made to stay in the stomach for a long time and release the active pharmaceutical ingredient (API) gradually. As these systems can aid in increasing the bioavailability and duration of action of the API, they are frequently employed for drugs that are poorly absorbed in the small intestine or that have a short half-life. Gastroretentive dosage forms come in a variety of formats, such as floating systems, swellable systems, and high-density systems [24-29].

Floating systems: These systems are designed to remain buoyant in the stomach by incorporating a gas-generating agent or a hollow, air-filled structure. Examples of floating systems include floating tablets and capsules.

Swellable systems: These systems are made to inflate or expand in the stomach after intake, which aids in keeping them there for longer. Swellable systems can take the form of hydrogels and hydrocolloids, for instance.

High-density systems: These systems have been developed to have a higher density compared to gastric fluids, which helps to keep them in the stomach. Beads and microspheres are a few examples of high-density systems.

To address the issue, floating drug delivery devices with site-specific drug delivery are suggested among the gastroretentive drug delivery systems. By using floating drug delivery devices, a topical narrow-spectrum antibiotic may be able to completely eradicate bacteria in the stomach.

4. POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

Several types of polymeric materials are suitable for floating drug delivery systems, providing the buoyancy necessary for prolonged gastric retention [30,31]. Here are some commonly used types.

Hydroxypropyl Methylcellulose (HPMC): HPMC is a hydrophilic polymer that swells upon contact with gastric fluids, forming a gel barrier [31]. This gel enhances buoyancy, allowing sustained release of drugs. HPMC is often used in the formulation of floating microspheres or tablets for controlled drug delivery.

Polymethacrylates: Polymethacrylates, such as Eudragit polymers [32], can be designed to have pH-dependent solubility. This property allows them to remain intact in the acidic stomach environment, providing sustained drug release. Polymethacrylates are utilized in the development of floating dosage forms, particularly gastroretentive tablets.

Polyvinyl Acetate (PVA): PVA is a water-soluble polymer that can be used in combination with other polymers to create floating drug delivery systems [31]. It provides mechanical strength and stability to formulations. PVA is employed in the preparation of floating microspheres and matrices for controlled drug release.

Chitosan: Chitosan is a biodegradable and mucoadhesive polymer derived from chitin. It exhibits good floating properties and can adhere to the gastric mucosa. Chitosan is used in the formulation of floating drug delivery systems, particularly for its bioadhesive characteristics [31].

Ethylcellulose: Ethylcellulose is a hydrophobic polymer that provides resistance to gastric fluids [31]. It is commonly used in the coating of drug particles to achieve controlled release. Ethylcellulose-coated formulations are employed to create floating drug delivery systems, ensuring prolonged gastric residence time.

Poly (lactic-co-glycolic acid) (PLGA): PLGA is a biodegradable and biocompatible polymer that can be tailored for sustained drug release. It is often used in the preparation of microspheres or nanoparticles. PLGA-based formulations are employed for their controlled release properties in floating drug delivery systems [31].

Polyethylene Oxide (PEO): PEO is a water-soluble and hydrophilic polymer that can contribute to the buoyancy of drug formulations. It is often used in combination with other polymers. PEO is used in the development of floating dosage forms for controlled drug delivery [31].

Sodium Alginate: Sodium alginate is a natural polysaccharide derived from seaweed. It forms a gel in the presence of calcium ions, contributing to controlled drug release and buoyancy. Sodium alginate is often utilized in the formulation of floating microspheres and beads for oral drug delivery [31].

Starch-Based Polymers: Starch and its derivatives, such as hydroxypropyl starch, can be used to create floating drug delivery systems. These polymers can provide both buoyancy and controlled drug release. Starch-based polymers are employed in the development of gastroretentive formulations for sustained drug delivery [31].

Guar Gum: Guar gum is a natural polysaccharide with excellent swelling and gelling properties. It can contribute to the buoyancy and controlled release of drugs. Guar gum is used in the formulation of floating tablets and capsules for oral drug delivery [31].

Acrylic Acid Derivatives: Acrylic acid derivatives, such as carbomer, can be used to create mucoadhesive floating drug delivery systems [32, 33]. These polymers adhere to the gastric mucosa, prolonging drug release. Acrylic acid derivatives are employed in formulations designed for enhanced gastric retention and localized drug delivery.

Polymeric floating biomaterials and advanced drug delivery systems are vital in treating *H. pylori* infections. These technologies protect drugs from stomach acid, target lesions, control drug release, and disrupt biofilms, enhancing drug efficacy. Hydrophilic swellable polymers in bilayer tablets enable sustained drug release for up to 24 hours, while floating tablets with specific polymers ensure gastric retention, providing prolonged exposure to *H.*

pylori and effective eradication [34]. These systems leverage polymers' properties to overcome challenges like drug inactivation, intracellular bacteria, and biofilm formation, offering promising solutions for improved treatment outcomes.

5. MICROBALLOON DRUG DELIVERY SYSTEM

A microballoon or hollow microsphere drug delivery system is a pharmaceutical formulation that uses non-effervescent floating, or small spherical particles, to deliver drugs to the site. Because the relative density of these microballoons is less than 1, their sphere-shaped cavity, which is protected by a strong polymer shell, enables them to float on top of gastric acid. Microballoons with drug-loaded outer polymer shells are created by combining enteric acrylic polymers with the emulsion solvent diffusion method. This allows for controlled drug release and continuous floating for more than 12 hours *in vitro*. The drug is released gradually as the microballoons float over the stomach components [32,33,35]. The performance and potential advantages of microballoon drug delivery systems will be affected by various characteristics, like the size and shape of the microballoons, the composition of the microballoons, the drug loading and release profile, and the manufacturing process.

6. ADVANTAGES OF MICROBALLOON-BASED DRUG DELIVERY SYSTEMS

There are several advantages of microballoon-based drug delivery systems over other drug delivery methods [34,35], including:

Enhanced drug targeting: Microballoon-based drug delivery systems are designed to target specific areas of the gut, which may improve the local concentration of the drug and enhance its effectiveness.

Improved drug delivery: Microballoon drug delivery systems can reduce the frequency of dosing, which may improve compliance. To solve this problem, microballoon drug delivery systems were created, which prolong the duration that drugs remain in the stomach. Floating drug delivery systems, mucoadhesive drug delivery systems, and controlled-release drug delivery systems are a few examples of these systems. Gastroretentive drug delivery devices can increase the efficacy of *H. pylori* eradication therapy and lower the risk of treatment failure by enhancing eradication concentration in the stomach. To make the drug locally available and effective at eradicating infections, the stomach residence duration of the antibiotic must be extended.

Reduced dosing frequency: GRDDS can reduce the dosing frequency required for *H. pylori* eradication therapy. This can improve patient compliance and reduce the risk of treatment failure due to missed doses.

Improved safety: GRDDS can reduce the risk of systemic side effects by limiting drug absorption into the bloodstream. This can improve the safety profile of *H. pylori* eradication therapy.

Increased drug stability: Microballoon-based drug delivery systems can also improve the stability of drugs, which may be beneficial for drugs that are sensitive to pH or degradation. This can help to increase the shelf life of the drugs and improve their effectiveness.

7. FORMULATION OF MICROBALLOONS

Several methods can be used to prepare microballoons, which are small, spherical particles containing the active pharmaceutical ingredient [36-38]. These methods include:

Solvent evaporation: In this method, the drug is dissolved in a solvent, which is then sprayed into a drying chamber. The solvent is allowed to evaporate, leaving behind the drug in the form of small, spherical particles.

Emulsion solvent diffusion: In this method, the drug is dissolved in a solvent and then emulsified in an aqueous phase. The mixture is then poured into a non-solvent, causing the drug to form small, spherical particles as the solvent diffuses out.

Coacervation: In this method, two immiscible polymers are dissolved in a solvent to form a polymer solution. The drug is then added to the solution, and the solvent is gradually removed, causing the polymers to coacervate around the drug to form microballoons.

Spray drying: In this method, the drug is suspended in a solution or a suspension, which is then atomized and sprayed into a drying chamber. The solvent or water is evaporated, leaving behind the drug in the shape of small, spherical particles.

Solvent diffusion: Within this method, a solvent is used to dissolve the drug and a polymer, which are then mixed to form a solution. The solution is then poured into a non-solvent, causing the drug and polymer to form small, spherical particles as the solvent diffuses out.

Phase separation: In this method, the drug is mixed with a polymer and a solvent, and the mixture is then poured into a non-solvent. The non-solvent causes the drug and polymer to separate into small, spherical particles as the solvent diffuses out.

8. EVALUATION OF MICROBALLOONS

Several parameters can be used to evaluate microballoons, which are small, spherical particles containing the active pharmaceutical ingredient [39-42]. These parameters include:

Particle size: The size of the microballoons can affect the drug release profile and the long-term sustainability of the particles. Microscopy or laser diffraction are two methods that can be used to determine the particle size distribution.

Surface morphology: The stability of the particles and the drug release profile of the microballoons can both be impacted by their surface shape. Scanning Electron Microscopy (SEM) can be used to assess surface morphology.

Drug content: The drug content in the microballoons can be determined using analytical techniques such as spectrophotometry or chromatography.

Drug release: In vitro release tests, which can be carried out utilizing methods like dialysis or sink conditions, can be used to assess the drug release profile of the microballoons.

Stability: The stability of the microballoons can be evaluated by storing the particles under different conditions (e.g., different temperatures, and humidity levels) and analyzing their physical properties (e.g., particle size, drug content) over time.

Flow properties: The flow properties of the microballoons, such as their bulk density and angle of repose, can affect their handling and processing during manufacturing. These properties can be determined using techniques such as tap density measurements or the funnel method.

Surface charge: The surface charge of the microballoons can affect their stability and their interactions with other particles or surfaces. Surface charge can be evaluated using techniques such as zeta potential measurements.

In vitro drug release: The release profile of the drug from the microballoons can be assessed using *in vitro* drug release tests under various conditions (such as various pH levels and surfactant concentrations).

In vivo performance: *In vivo* studies can be used to evaluate the performance of the microballoons in an animal model or clinical trials. These studies can provide information on the bioavailability, pharmacokinetics, and safety of the drug delivered using microballoons.

Compatibility with excipients: The materials used to make the microballoons must be compatible with the drug and any excipients (inactive substances) that may be utilized in the formulation. Techniques like differential scanning calorimetry (DSC) or Fourier transform infrared spectroscopy (FTIR) can be used to assess compatibility.

Overall, the characterization of microballoons involves the evaluation of a range of physical and chemical properties, which can help to understand the performance of these particles and to optimize their formulation and manufacture.

9. CURRENT RESEARCH IN MICROBALLOON DRUG DELIVERY SYSTEMS FOR *H. PYLORI*

Designing targeted delivery systems: To increase the drug local concentration and efficacy, researchers are working on creating microballoon-based drug delivery systems that can target particular bodily regions, like the gastrointestinal tract. One way to extend the duration of drug residence in the stomach is to utilize floating dose forms, which have a lower density than gastric fluids and can float above the gastric juice in the stomach. The mechanism of buoyancy is used in the production of floating dosage forms for both effervescent and non-effervescent systems. There is no breaking down of the fundamental rule, which stipulates that things must float on gastric liquid that has a specific density of less than 1.004 g/cm of the gastric fluid in the stomach [43,44].

Ramachandran S (2010) *et al.*, Designed and characterized the floating drug delivery system using Eudragit L-100 polymer over the improvement of bioavailability of famotidine by prolonging the gastric residence time. Long-lasting release (>8 h) and buoyancy (>10 h) were both characteristics of the hollow microspheres [45]. In comparison to the control and standard groups of rats, the *in-vivo* study revealed strong antiulcer capabilities of famotidine-loaded microspheres. By employing the *pyloric* ligation method on rats, the hollow microsphere formulation showed strong antiulcer activity that was comparable to that of the common drug famotidine, showing its success as a potential formulation.

Awasthi R (2011) *et al.*, Created an *H. pylori* infection treatment using an amoxicillin gastroretentive floating system (GFS). The ratios of dichloromethane/ethanol/isopropyl alcohol, amoxicillin-Eudragit S100, and cellulose acetate phthalate were selected [46]. According to the study, the developed GFS is an efficient design for amoxicillin for targeted drug release in the gastric region, which can help treat *H. pylori* infection.

Sanjay Bansal (2014) *et al.,* With a quality-by-design (QbD)-based methodology, multiple-unit gastroretentive microballoons containing itopride hydrochloride (ITH) were created and improved [47]. Excellent floating qualities and acceptable drug release control could be seen in the optimized formulation. Experiments on the compatibility of drug excipients and SEM experiments validated the formulation's appropriateness. Studies using *in-vivo* X-ray imaging on rabbits verified the microballoons' buoyant properties for 8 hours in the upper GI tract. Overall, this work was successful in creating gastroretentive floating microspheres for ITH injection once a day.

Akash Jain (2015) *et al.,* Developed and evaluated Nizatidine-loaded microballoons for improved drug bioavailability and prolonged residence time in the gastrointestinal tract [48]. Eudragit S-100 and HPMC were used to make microballoons, which were then optimized for several formulation factors. SEM, drug entrapment, buoyancy, *in-vitro* drug release, and *in-vivo* floating efficiency experiments were used to characterize the optimised formulation. The drug-loaded microballoons demonstrated considerable ulcer prevention in comparison to free drug treatment in a mouse model of ethanol-induced ulcers. The improved formulation demonstrated sustained drug release for 12 hours and stayed afloat in the gastric contents for the same amount of time. These findings suggest that floating microballoons containing nizatidine extended a drug delivery system for the efficient treatment of stomach ulcers.

Sandeep Choudhary (2016) *et al.,* In a study designed for the treatment of peptic ulcer disease, a new gastroretentive floating system was created for the regulated delivery of rabeprazole sodium and amoxicillin tri-hydrate. Using Eudragit S-100 and hydroxypropyl methylcellulose along with various drugs, polymers, stirring speed, and time concentrations [49], low-density microballoons were created. The formulation factors had a big impact on

the drug release *in vitro*. In rabbits and a mouse model with ulcers, the gastro-retentive capacity of the microballoons was confirmed, with enhanced buoyancy and a decreased ulcer index compared to conventional drugs. According to the study's findings, these microballoons could enhance the treatment of ulcers by delivering drugs to the stomach in a targeted and sustained manner to get rid of *H. pylori*.

Ritesh Kumar (2018) *et al.,* Developed and optimised famotidine-loaded microballoons for prolonged gastric residence, sustained release, and improved bioavailability [50]. Utilizing HPMC K4M, microballoons were created, and their performance in terms of *in vitro* drug release, buoyancy, and drug entrapment was all assessed. The floating behavior and anti-ulcer activity of the optimized formulation were assessed *in vivo*. The mixture that was chosen demonstrated sustained release for more than 12 hours while remaining buoyant in the stomach. Studies conducted *in vivo* revealed a higher ulcer prevention index when compared to the commercial brand. According to the findings, famotidine-loaded microballoons extended the drug's stay in the patient's system when treating *H. pylori* infection.

Future research to combat *H. pylori* includes exploring probiotics, nanoparticles, plant-based natural products, and developing new vaccines such as multi-epitope and vector-based types. Studies focus on *H. pylori*-related gastric ulcer pathogenesis, oxidative stress mechanisms, competitive acid inhibitors, gut microbiota, probiotic adjuvant therapy, and neutrophil activator protein's immune protective effects [51]. Addressing antibiotic resistance in *H. pylori* also requires investigating clarithromycin resistance and alternative therapies. These diverse approaches offer promising strategies for future treatment.

10. CLINICAL TRIALS INVOLVING MICROBALLOON DRUG DELIVERY SYSTEMS

Sato Y (2004) *et al.,* Investigated the behavior of microballoon and nonfloating microspheres labeled with 99mTc in fasted and fed human subjects using gamma scintigraphy [33]. It also examined the pharmacokinetics of riboflavin released from these particles. According to the findings, microballoon dispersed in the upper stomach after feeding and stayed there for up to 300 minutes, whereas nonfloating progressively went to the lower stomach after 90 minutes. Microballoons floated for roughly 60 minutes in the fasting condition before being quickly eliminated through the inner digestive migrating motor complex, whereas nonfloating was gone after 60 minutes. The pharmacokinetic parameters excretion half-life time (t1/2) and total urinary excretion, as well as the stomach residence time as evaluated by gamma scintigraphy, were shown to be strongly correlated in the study. The study's overall conclusion is that microballoon can increase medication bioavailability, resulting in pharmacological benefits that last longer.

Sato Y (2003) *et al.,* Created floating controlled drug delivery systems using hollow microspheres known as microballoons. Enteric acrylic polymers were used to create these microballoons, and they were dissolved in a solution of dichloromethane and ethanol [52]. The riboflavin release profiles of non-floating microspheres and the floating characteristics of the microballoons were compared. In comparison to riboflavin powder and non-floating microspheres, the microballoons showed delayed urine excretion of riboflavin, especially under fed conditions. Additionally, both in the fed and fasted conditions, the microballoons showed greater total riboflavin urine excretion levels. The study concluded that the microballoons' ability to float in the stomach may contribute to the long-lasting pharmacological activity, improving drug absorption.

Hussein O Ammar (2016) *et al.,* Created as a gastro-retentive microballoon for cinnarizine continuous release. utilizing cellulose acetate butyrate as the hosting polymer and a solvent mixture of 100% ethanol and dichloromethane, the microballoon were created utilizing the emulsion solvent diffusion technique [53]. The formulation was improved using

a factorial experimental approach, producing an improved microballoon formulation with a particular drug loading capacity and release efficiency as well as a suitable size. The improved microballoon spherical form and porous structure were validated by SEM. The modified microballoon formulation outperformed traditional tablets in terms of bioavailability metrics, according to *in vivo* tests on human volunteers. Indicating prolonged stomach stay, this comprised quicker absorption, a larger area under the concentration-time curve, and a much longer mean residence duration.

Sato Y (2004) *et al.,* Study involving three healthy volunteers, orally administered riboflavin-containing microballoon were analyzed to investigate the pharmacokinetics of riboflavin [41]. The findings demonstrated that microballoon consumption under both water and "fed" circumstances prolonged riboflavin urine excretion. The buoyancy of the microballoon in the stomach, which extended gastric residence time, was credited for the prolonged excretion. Additionally, compared to microballoons with lesser buoyancy, those with increased buoyancy displayed longer excretion half-life (t1/2). An *in vivo* evaluation using an analysis of urine excretion showed that mixing microballoon with hydroxypropylmethylcellulose in various ratios improved riboflavin release qualities. Strong correlations between buoyancy and t1/2, as well as between the release of riboflavin from microballoon and total urine excretion, were found in the study, underlining the potential advantages of microballoon intragastric floating capabilities for achieving the sustained pharmacological effect.

Combining outcomes from *in vivo* and *in vitro* studies enhances the understanding of novel drug delivery systems for *H. pylori* therapy [54, 55]. *In vivo* studies with animal models like Mongolian gerbils and transgenic mice provide insights into *H. pylori*-related complications. *In vitro* studies on alternative treatments, such as lactic acid bacteria (LAB) and their secretions, show promising anti-*H. pylori* effects by inhibiting bacterial growth, reducing virulence, and suppressing pro-inflammatory responses. Additionally, research into advanced drug delivery systems like nano and microparticles highlights their potential to improve drug retention and release rates at the target site, offering solutions against antibiotic-resistant *H. pylori* strains [56]. Integrating data from these studies can lead to a comprehensive review of innovative therapeutic approaches for *H. pylori* infections.

CONCLUSION

Recent advances in biomaterials have led to innovative polymeric membranes from marine biopolymers for tissue engineering [57, 58]. These membranes, made from collagen, chitosan, and fucoidan, offer structural stability, suitable swelling ability, and mechanical properties similar to native articular cartilage, making them ideal for tissue regeneration. Sustainable polymers from renewable sources are also being emphasized, focusing on environmentally friendly processing and end-of-life considerations [59, 60]. An interdisciplinary approach has resulted in diverse polymeric biomaterials for wound care therapies, addressing the challenges of complex, chronic wounds. These advancements highlight the ongoing importance of research and innovation in developing biomaterials for biomedical applications.

The development of novel biomaterials, especially polymeric floating biomaterials, presents a promising avenue for targeted and sustained drug delivery to the gastric mucosa is a novel approach to combat *H. pylori*. These particles can be made using a variety of materials, including polymers, proteins, and natural polysaccharides, and can be used to deliver a wide range of drugs. The use of microballoons in treating *H. pylori* infection, a common cause of peptic ulcer disease, has been investigated. The use of microballoon-based extended drug delivery systems in *H. pylori* therapy possesses the potential to enhance the effectiveness and safety of the treatment. Microballoons may assist in addressing some of the issues with conventional methods of treating *H. pylori*, such as low bioavailability and the

emergence of antibiotic resistance, by regulating the release rate of the drug and lengthening its duration of action. Microballoons may also be useful for delivering prodrugs, natural products, gene therapies, and vaccines over the treatment of *H. pylori* infection. In general, research into the application of microballoon-based extended drug delivery systems for *H. pylori* therapy is ongoing, and more research is required to fully grasp their potential and optimize their formulation and use.

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