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Gastroretentive drug delivery systems for the treatment of *Helicobacter pylori*

Shan Zhao, Yan Lv, Jian-Bin Zhang, Bing Wang, Guo-Jun Lv, Xiao-Jun Ma

Shan Zhao, Yan Lv, Jian-Bin Zhang, Bing Wang, Guo-Jun Lv, Xiao-Jun Ma, Laboratory of Biomedical Material Engineering, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning Province, China

Shan Zhao, Yan Lv, Jian-Bin Zhang, Bing Wang, University of Chinese Academy of Sciences, Beijing 100049, China

Author contributions: Zhao S designed and wrote the paper, Lv Y, Zhang JB and Wang B provided the images, contributed to literature research and drafted the article; Lv GJ and Ma XJ revised the manuscript critically.

Correspondence to: Xiao-Jun Ma, Professor, Laboratory of Biomedical Materials Engineering, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, Liaoning Province, China. maxj@dicp.ac.cn
Telephone: +86-411-84379139 Fax: +86-411-84379096

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Abstract

Helicobacter pylori (*H. pylori*) is one of the most common pathogenic bacterial infections and is found in the stomachs of approximately half of the world's population. It is the primary known cause of gastritis, gastroduodenal ulcer disease and gastric cancer. However, combined drug therapy as the general treatment in the clinic, the rise of antibiotic-resistant bacteria, adverse reactions and poor patient compliance are major obstacles to the eradication of *H. pylori*. Oral site-specific drug delivery systems that could increase the longevity of the treatment agent at the target site might improve the therapeutic effect and avoid side effects. Gastroretentive drug delivery systems potentially prolong the gastric retention time and controlled/sustained release of a drug, thereby increasing the concentration of the drug at the application site, potentially improving its bioavailability and reducing the necessary dosage. Recommended gastroretentive drug delivery systems for enhancing local drug delivery include floating sys-

tems, bioadhesive systems and expandable systems. In this review, we summarize the important physiological parameters of the gastrointestinal tract that affect the gastric residence time. We then focus on various aspects useful in the development of gastroretentive drug delivery systems, including current trends and the progress of novel forms, especially with respect to their application for the treatment of *H. pylori* infections.

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Key words: *Helicobacter pylori*; Gastroretentive systems; Floating systems; Bioadhesive systems; Expandable systems

Core tip: *Helicobacter pylori* (*H. pylori*) is one of the most common pathogenic bacteria. It is the primary known cause of gastritis, gastroduodenal ulcer disease and gastric cancer. In addition to triple therapies, oral site-specific drug delivery systems (especially gastroretentive dosage forms) prolong the gastric retention time and can increase the concentration of the drug at the target site, thereby improving the therapeutic effect. This review focuses on gastroretentive drug delivery strategies and their application to the eradication of *H. pylori*.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common

pathogenic bacteria and is found in the stomachs of more than half of the world's population. *H. pylori* infections are the primary known cause of gastritis, gastroduodenal ulcer disease and gastric cancer^[1]. Even after 30 years of experience in *H. pylori* treatment, clinicians and researchers are still exploring the ideal regimens for clinical application^[2].

Although *H. pylori* has been shown to be highly sensitive to a single antimicrobial agent in many antibacterial *in vitro* trials, in clinical the eradication rate of *H. pylori* is still low^[3]. There are three explanations for this finding: first, many antibiotics are unstable in the low pH of gastric acid; second, the concentration of the drug in the deep gastric mucus where the bacterium lives is too low and third, the amount of time that the antibiotic resides in the stomach is too short^[4]. Triple therapies consisting of the combined use of antibiotics are frequently used in the clinical treatment of *H. pylori* associated with gastroduodenal disease. However, the high level of antibiotic resistance by *H. pylori*, drug side effects and poor patient compliance are major drawbacks of multidrug therapy.

For these reasons, prolonging the gastric residence time of the drug while improving its stability in gastric acid is a logical approach to overcome these issues. Gastroretentive dosage forms are one of the oral site-specific drug delivery systems that have been proposed. Research into gastroretentive drug delivery systems has resulted in the development of several formulations such as floating systems, mucoadhesive/bioadhesive systems, expandable systems and magnetic systems, all of which could prolong gastrointestinal (GI) residence time to improve drug effectiveness against *H. pylori*^[5-7].

H. PYLORI AND TREATMENT STRATEGIES

H. pylori

H. pylori is a spiral gram-negative bacterium commonly found in the stomach. It was discovered and identified in 1982 by the Australian scientists Barry Marshall and Robin Warren. More than half of the world's population harbors *H. pylori* in their GI tract, including up to 70% of people in developing countries and 25%-50% in developed countries^[8]. *H. pylori* is well known to also cause several GI diseases, such as peptic ulcers and gastric carcinoma. In some countries, *H. pylori* infection has been shown to increase the risk of gastric cancer four-fold and even higher^[9-12]. In gastric biopsy specimens, *H. pylori* bacteria are 2.5-5.0 μm long and 0.5-1.0 μm wide and have four to six unipolar sheathed flagella^[13,14].

Most *H. pylori* localize deep in the less acidic region of the gastric mucus layer, which is more hospitable for survival, and do not directly interact with host cells^[15]. *H. pylori* secretes urease, which hydrolyzes urea to ammonia and carbonic dioxide. These products can neutralize the acidic environment of the stomach and result in the release of toxins^[16].

Although immune cells can normally recognize *H. pylori* and induce immune responses, *H. pylori* exert resistance to local immune responses by reducing the recognition of immune sensors and interfering with the uptake of antigens, as well as by other genetic mechanisms^[17-19].

Stomach pathophysiology following *H. pylori* infection

H. pylori is highly adapted to colonize the human stomach, whereas most other bacteria cannot persist in the low pH environment. *H. pylori* secretes toxins and other effector molecules^[20] and stimulates numerous signaling pathways^[21]. The primary pathogenic factors of *H. pylori* are altered local acid homeostasis, disruption of the gastric mucosal barrier, induction of gastric inflammation and resistance to the immune response^[22,23]. Some studies have found that the secretion of vacuolating toxin A and γ -glutamyl transpeptidase both contribute to *H. pylori* persistence in the gastric niche and to immune tolerance^[24].

Recent findings observed abnormalities in the tight junction complexes in patients with *H. pylori* infections^[25-27], which indicated that *H. pylori* infection can increase gastric mucosal permeability and result in disruption of the gastric mucosal barrier. Acid secretion studies demonstrated that increased acid secretion occurred upon *H. pylori* infection, resulting in local inflammation^[28,29].

First-line therapy of treating *H. pylori*

The recommended *H. pylori* treatment is a combination therapy with a proton pump inhibitor and two of the following antibiotics for 7, 10 or 14 d: clarithromycin, amoxicillin and metronidazole. However, in clinical practice, at least 20% of the patients might relapse^[5,30,31], and in some Western countries, the cure rate is only 25%-60%^[32]. Drug resistance is considered the primary reason for the observed ineffectiveness^[33-35]. Currently, sequential therapy and non-bismuth quadruple therapy are the trends in the treatment of *H. pylori*. Several studies have shown that these novel treatment schedules are superior to triple therapy with regard to antibiotic resistance and the clinical eradication rate^[36-41].

Recently, a "hybrid" therapy that combines sequential and concomitant therapies has been considered as a novel innovation^[42-44]. Hsu *et al.*^[42] observed that the eradication rate using hybrid therapy was greater than 95%.

Although there is a high rate of eradication of *H. pylori* in clinical practice, bacterial resistance, side effects and poor patient compliance are major drawbacks of the multidrug therapies.

Based on *H. pylori* pathophysiology and the problems in clinical practice, oral site-specific drug delivery systems that can prolong the residence time at the reaction site are considered to be an ideal strategy. Gastroretentive dosage forms as a novel site-specific system could potentially improve the stability of antibiotics in gastric acid by employing different formulation strategies and allowing the antibiotic to localize to the target site in the stomach by increasing residence time^[45].

PHYSIOLOGICAL AND PHYSICAL ASPECTS OF GASTRORETENTIVE DOSAGE FORMS

Physiological factors affecting the gastric retention of oral drugs

There are several factors that affect the gastric retention time of oral drugs, including physiological problems and pharmaceutical factors.

Gastric emptying is a brief but key factor associated with the physiological problems. One of the primary functions of the stomach is to digest food, which involves the process of gastric emptying. To understand the influence of oral dosage gastric retention, the factors that control gastric emptying should be known. Table 1 shows the primary influential factors of gastric emptying.

Physical properties of the oral dosage form and gastric retention

Two important features that affect the oral dosage gastric residence time are the density and size of the drug. The density of the dosage determines the location and amount of time the drug resides in the stomach. Low-density systems can float on top of the gastric juice, where as high-density systems sink to the bottom of the stomach. Both positions could prolong the gastric retention time.

Size is important in designing an oral dosage form. The diameter of the human pyloric sphincter is 12 ± 7 mm^[53]. Although there is no unified standard regarding dependence of the dosage size on gastric emptying, many scientists have studied the relationship between gastric emptying and tablet size. Khosla *et al*^[54] and Coupe *et al*^[55] observed that the tablets greater than 13 mm in diameter were more difficult to disintegrate and less likely to be emptied from a full stomach in humans. Recent studies showed that micro- or nano-sized delivery systems are a more efficient form for targeting agent. In addition to dosage density and size, the physiochemical properties of the active agent, *e.g.*, the molecular weight and lipophilicity of the drug^[56], are important parameters. Shah *et al*^[4] showed that gastric mucus is more permeable to small molecules. Larhed *et al*^[57] demonstrated that a high lipophilicity drug has more difficulty in crossing the hydrophilic mucus layer.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS AGAINST *H. PYLORI*

Floating systems

Floating drug delivery systems were first described by Davis in 1968 and are low-density systems that can prolong the gastric retention time and increase bioavailability by floating on top of the gastric contents^[58]. The desired formulation of floating systems should comply with the following requirements: (1) maintaining a lower density or higher buoyancy than that of the gastric contents

Table 1 Primary factors that influence gastric emptying

Influence factors	Gastric emptying	
Disease	Chronic renal failure	Delay ^[46]
	Diabetes	Delay ^[47]
	<i>H. pylori</i> infection with non-ulcer dyspepsia	No association ^[48]
The form of the food	Liquid food is faster than solid food ^[49]	
Carbohydrate or fat	Slow ^[50,51]	
Dosage form	Liquid dosage is faster than solid form ^[52]	

(1.004-1.010); (2) providing a sufficient barrier to protect the stability of the active agent from gastric acid; and (3) releasing the drug in a controlled or sustained manner to achieve the therapeutic effect.

Usually, floating formulations are prepared using hydrophilic matrices that either have a lower density (Figure 1A) or float on the top of the gastric fluid after absorbing water and swelling (Figure 1B). Cellulose ether polymers are used as the hydrophilic matrices, and low-density fatty acids are also used to increase the buoyancy. Hydrodynamically balanced systems (HBSs), gas-generating systems and low-density systems are the primary approaches used in designing intragastric floating systems^[59].

HBSs are a single-unit dosage form containing a mixture of drugs, a gel barrier comprising hydrophilic polymers and other excipients. Hydroxypropyl methyl cellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, agar, carrageenans and alginate acid are commonly used excipients. After oral administration, the hydrocolloid is dissolved by either hydration or swelling and maintained at a low density, which allows for controlled drug release from the swollen gel matrix (Figure 2)^[6,60].

Gas-generating systems achieve their buoyant properties by the generation of gas bubbles. For example, CO₂ can be generated from sodium bicarbonate at an acidic pH. Thus, acids are required in the formulation. These systems include single- and multi-unit forms^[61,62].

Low-density systems are made of low-density materials, entrapping oil or air. Multi-unit systems such as microparticles are the most common type^[63,64]. The low-density materials that are commonly used include empty hard gelatin capsules, polystyrene foams and pop-rice grains. The external surface of the low-density materials comprises EC and cellulose acetate phthalate and is coated with drugs, with the entrapped oil and air providing the desired buoyancy.

In the last decade, the emulsification solvent evaporation method for the preparation of low density systems achieved tremendous popularity. A large number of studies have employed this method, and different anti-bacterial agents were encapsulated in these systems for the treatment of *H. pylori* (*e.g.*, metronidazole^[65,66], tetracycline^[67] and amoxicillin^[68]). A number of commercialized floating dosage products exist in the market, one of which targets *H. pylori*, and they are listed in Table 2^[6].

Yang *et al*^[67] prepared a triple layer tablet based on

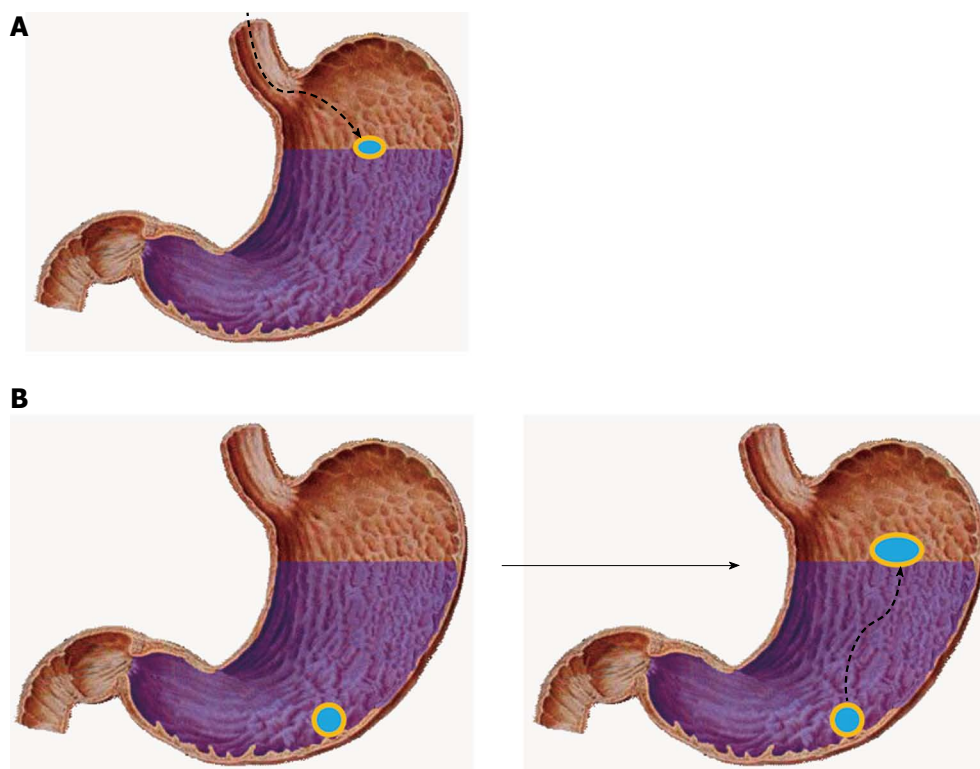


Figure 1 Floating systems. Low-density floating dosage (A) and the density of dosage can be lowered after administration (B).

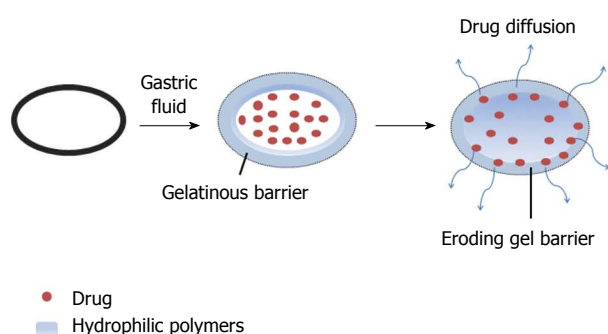


Figure 2 Hydrodynamically balanced system.

HBSs, which was composed of a rate-controlling polymer matrix and a drug core. Hydroxypropyl methylcellulose and poly (ethylene oxide) comprised the polymer layers, and tetracycline and metronidazole were encapsulated in the core. The *in vitro* evaluation demonstrated the sustained delivery of the antibiotics over 6-8 h while the tablet remained afloat. Rajinikanth *et al.*^[68] developed an intragastric in situ gelling system that floated for the controlled delivery of amoxicillin in the treatment of *H. pylori* infections. The *in vivo* *H. pylori* clearance efficacy was 10 times higher than the effects in an *in vivo* gerbil model because of the prolonged GI residence time of the formulation.

Bioadhesive systems

Bioadhesive/mucoadhesive drug delivery systems are a dosage form that can stick to the mucosal surface by dif-

Table 2 Different marketed products of floating systems

Product	Remarks	Active ingredient	Company
Topalkan	Loading liquid alginate	Aluminum magnesium Antacid	Pierre Fabre Medicament, France
Almagate flatcoat	Floating liquid form		
proQuin XR	AcuformTM	Ciprofloxacin	Depomed, United States

ferent mechanisms. This formulation involves a mucous coating or an adhesive polymer and is considered to be a bioadhesive form^[69]. The adhesive polymers primarily used for bioadhesive materials are listed in Table 3^[70]. Micro- and nanoparticles, which have higher mucosal permeability and drug delivery efficiency, are thought to be an ideal bioadhesive carrier^[71]. Once this dosage form is orally administered, it is dissolved in the gastric liquid and firmly sticks to the mucosal surface, which is predicted to prolong the residence time of the drug. The electronic theory, adsorption theory, wetting theory and diffusion theory are invoked to explain the adhesive mechanisms^[72,73].

Despite the bioadhesive properties of these polymers, they are difficult to maintain because of the turnover of gastric mucosa and gastric emptying. Despite these difficulties, several studies have shown promising results.

Liu *et al.*^[81] published a study on amoxicillin bioadhesive microspheres that use an emulsion-solvent evaporation technique, with Carbopol-934p as the mucoadhesive polymer and EC as the matrix. The *in vitro* release test

Table 3 Classification of bioadhesive polymers

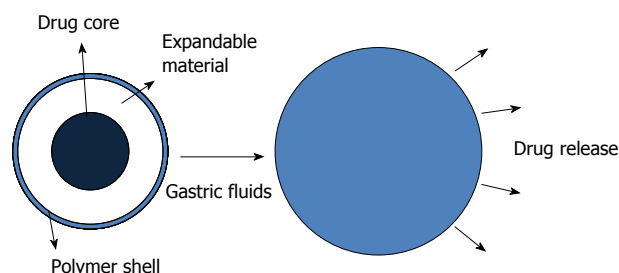
Anionic	Cationic	Neutral
Alginate ^[74]	Poly-L-lysine ^[75]	Polyethylene glycol ^[76]
Chondroitin sulfate ^[77]	Polybrene ^[78]	Polyvinylpyrrolidone ^[78]
Carboxymethylcellulose	Chitosan ^[79]	Polyethylene oxide
Carrageenan		Dextran
Pectin		
Poly (acrylic acid) (Carbopol®) ^[80]		

showed that approximately 90% of the amoxicillin was released in the pH 1.0 HCl solution after 4 h. *In vitro* and *in vivo* mucoadhesive tests showed that mucoadhesive microspheres adhered more strongly to the gastric mucous layer than non-adhesive amoxicillin microspheres. Amoxicillin mucoadhesive microspheres were retained in the GI tract for an extended period of time^[81]. Jayvadan KP and Jayant RC also formulated mucoadhesive amoxicillin microspheres for the treatment of *H. pylori* infections. They prepared the microspheres using a similar method and carrier polymer. The amoxicillin microspheres showed a high efficiency of drug entrapment. The *in vitro* adhesive test showed that mucoadhesive microspheres adhered more strongly to the gastric mucous and that more than 50% of the microspheres were retained in the GI tract after 12 h. Furthermore, *in vivo* tests were performed by orally administering amoxicillin powder and mucoadhesive microspheres in an *H. pylori* infection animal model under fed conditions at single and multiple doses. The results indicated that the mucoadhesive microspheres had a better clearance than the powder^[82].

Floating-bioadhesive systems

Although significant advances have been made in both floating and bioadhesive systems, there are still many challenges. First, the floating systems are unable to release the drug at the intended site. Second, gastric emptying may reduce the buoyancy of the floating systems in the stomach. Third, the turnover of the gastric mucosa and gastric emptying reduce the adhesive force of bioadhesive systems. Therefore, a dual working system would overcome the drawbacks associated with bioadhesive and floating systems and would have a significant effect on improving the therapeutic outcomes.

Zheng *et al.*^[83] designed floating-bioadhesive microparticles to increase the efficacy of antibiotics against *H. pylori*. The formulation containing clarithromycin was prepared by the method of emulsification/evaporation and internal gelation with EC, sodium alginate and chitosan. *In vitro* buoyancy and drug release tests showed that approximately 74% of the microparticles floated in an acetate buffer solution for 8 h and 90% of the clarithromycin was released in a sustained manner within 8 h. An *in vivo* mucoadhesive test demonstrated that 61% of the microparticles were retained in the stomach after 4 h. Rajinikanth *et al.*^[84] developed stomach-specific floating-bioadhesive microspheres of clarithromycin for

**Figure 3** Drug release from expandable systems.

the treatment of *H. pylori* infections. The microspheres were prepared by the emulsification-solvent evaporation method using EC as the matrix polymer and Carbopol-934P as the bioadhesive material. The microspheres showed strong mucoadhesive properties and good buoyancy during the *in vitro* evaluation and a significant anti-*H. pylori* effect after oral administration to Mongolian gerbils infected with *H. pylori*.

Expandable systems

The dosage size in the stomach is one of the influential factors of gastric retention time. Expandable drug delivery systems are small for easy swallowing and expand to a larger size after contact with gastric juices, which can prolong the gastric retention time (Figure 3)^[85,86]. Thus, an optimal expandable dosage requires the following properties: convenience for oral ingestion, expandable upon contact with the gastric contents, controlled drug release and either a degradable nature or a reduction in size enabling safe evacuation after drug release^[85,87,88]. Superporous hydrogels that are pH and temperature sensitive, are fast-swelling and have a high swelling capacity are considered to be a novel material for swellable systems^[89]. Chen *et al.*^[90] synthesized superporous hydrogels that used cross-carmellose sodium (AC-Di-Sol®) as a composite material, and its addition resulted in a significant improvement in the properties of the superporous hydrogels. Park *et al.*^[91] prepared chitosan-based superporous hydrogels using freeze drying and gas blowing techniques. *In vitro* tests showed that the superporous hydrogels were highly sensitive to the pH of the swelling media. These swelling behaviors and degradation kinetics are important variables in determining the gastric retention time.

Novel drug delivery systems for the treatment of *H. pylori* infection

Diseases of the GI tract present challenging targets for drug delivery, particularly for oral formulations. Recently, advances in micro- and nanotechnology research opened up a vast potential for the development of GI-targeted drug delivery systems. Liposomes, a type of nanoparticle, became a focal point of GI-targeted delivery systems^[92,93]. Liposomes are microscopic phospholipid bubbles with a bilayer membrane^[94]. They are nontoxic, nonhemolytic and nonimmunogenic^[95]. Singh *et al.*^[96] prepared double liposomes that encapsulated two drugs: the inner liposome

was first loaded with one drug (amoxicillin) by thin film hydration and then was enveloped with a thin lipid film containing the second drug (ranitidine bismuth citrate). This formulation showed prolonged, sustained drug release, efficient binding to *H. pylori*, increased inhibition of bacterial growth, reduced bacterial secretion and an ulcer protective ability in an *in vitro* test. Jain *et al.*^[97] designed a gastroretentive polyelectrolyte-coated multilayered liposome containing amoxicillin and metronidazole. The system was prepared by alternative coatings of polyanionic poly (acrylic acid) and polycationic poly (allylamine hydrochloride), using liposomes as the core. Compared with conventional liposomes, the multilayered liposomes showed prolonged drug release in simulated gastric fluid. *In vitro* and *in vivo* evaluations indicated the bacterial clearance activity and binding propensity of the system were good.

CONCLUSION

Over the past two decades, there have been significant advances in the development of gastroretentive drug delivery systems for the treatment of *H. pylori* infections. The literature has shown that gastroretentive dosage forms are effective at not only prolonging retention time in the stomach but also targeting *H. pylori*. However, we still lack sufficient *in vivo* data, especially in humans. Although some studies have indicated that the gastroretentive delivery systems work well in animal models (*e.g.*, rats and Mongolian gerbils), these results may not translate to humans because of the differences among species. Therefore, screening and synthesizing new active agents and developing efficient targeted drug delivery systems are drawing more focus in the field, with one example being ligand-targeted drug formulations based on specific interactions^[98,99]. However, with the development and study of natural products, many traditional herb extracts, such as *ascardole*, *Mexican tea herbs* and *Pterocarpus santalinus*, have exhibited anti-*H. pylori* activity and may serve as potential treatment options^[100-102].

Progress in developing an efficient gastroretentive form for the eradication of *H. pylori* is closely linked to the development of pharmaceutical technology and functional polymer materials and to an increased understanding of the mechanisms of *H. pylori* pathogenicity.

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