

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Floating Drug Delivery Systems for Eradication of *Helicobacter pylori* in Treatment of Peptic Ulcer Disease

Yousef Javadzadeh and Sanaz Hamedeyazdan

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/57353>

1. Introduction

Peptic ulcer (gastric or duodenal ulcer) is one of the most common disorders affecting the gastrointestinal system. The lifetime cumulative incidence of peptic ulcer disease is more than 10% of adult population in western countries (Ofman et al., 2000). The pathophysiology of peptic ulcer disease is an imbalance between mucosal defense factors (bicarbonate, mucin, prostaglandin, nitric oxide and other peptides and growth factors) and injurious factors (acid and pepsin). The management and prevention of these acid-related disorder are possible either by decreasing the level of gastric acidity or by enhancing mucosal protection (Brunton et al., 2008). Various factors, including genetic, diet, pharmacologic and psychologic might contribute to peptic ulcers (Wyatt, 1989). *Helicobacter pylori* (*H. pylori*) is a prominent etiologic factor influencing peptic ulcer disease (Hauser et al., 2005). Regarding the fact that *H. pylori* play a dominant role in the majority of peptic ulcers, prevention of relapse is focused on eradication of this organism from the stomach.

Nowadays it is believed that, *H. pylori* and non-steroidal anti-inflammatory drugs (NSAID) are the two major contributing factors causing peptic ulcer disease (Graham, 1996). *H. pylori* is found in approximately 100% of chronic active antral gastritis cases; 90% to 95% of duodenal ulcer patients and 50% to 80% of gastric ulcer patients (Kluwer, 2004). Owing to the fact that chronic infection with *H. pylori* weakens the natural defenses of the lining of the stomach against the ulcerating action of acid, medications that neutralize stomach acid, antacids, and medications that decrease the secretion of acid in the stomach such as H₂-blockers and proton pump inhibitors (PPIs) have been used effectively for many years to treat ulcers. Obviously, antacids, H₂-blockers and PPIs not only would have no effect on *H. pylori* eradication from the stomach, but also the ulcers are frequently returned promptly after these medications are

discontinued. Accordingly, eradication of *H. pylori* also is important in the treatment of the pylori-related ulcers which could be achieved through the commonly used antibiotics.

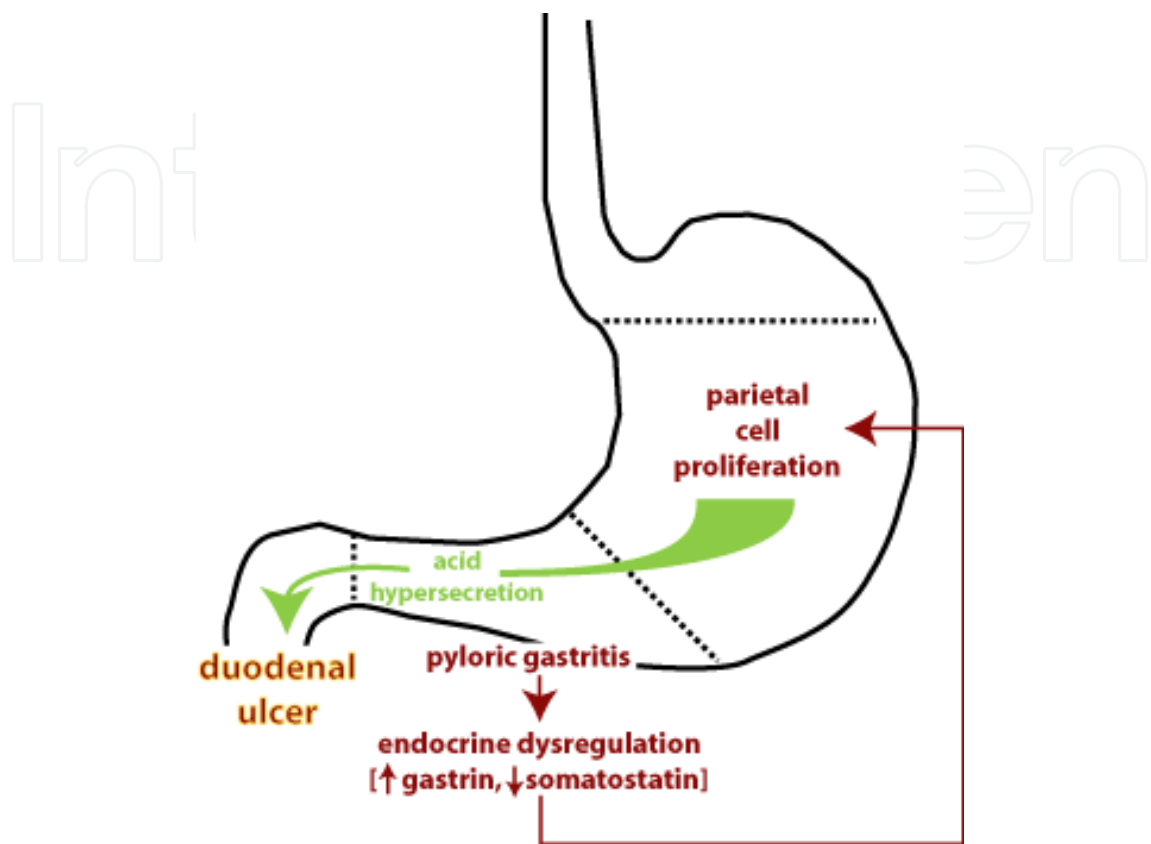


Figure 1. *H. pylori* in peptic ulcers.

Not surprisingly, the wide range of effective medicinal agents available today is one of the greatest scientific achievements. Regardless of the effectiveness and safety of the medicines embedded in dosage forms, the pharmaceutical concept of the latter is growing to be ever more eminent in the management of different diseases. The oral dosage forms of the medications available for *H. pylori* eradication, typically, possess several physiological restrictions such as non-uniform drug absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach (MotlekarYouan, 2006; Adibkia et al., 2011; GisbertCalvet, 2011). Rate of the transition for a dosage form through the gastrointestinal (GI) tract is highly affected by the physiological properties of the GI tract as well as the formulation properties (Bardonnnet et al., 2006a; Khobragade et al., 2009). Hence, suitable pharmaceutical dosage forms in *H. pylori* eradication is also an important basic principle of the drug delivery system dominating these constraints and offering a proper delivery strategy that would function independent of the digestive state, clinical condition, or GI motility of the individual. Since the bioavailability of drugs often depends on the GI transit rate of the dosage form, it appears necessary to establish an appropriate sustained release system for drug delivery (Hu et al., 2010; JavadzadehHamedeyazdan, 2012).

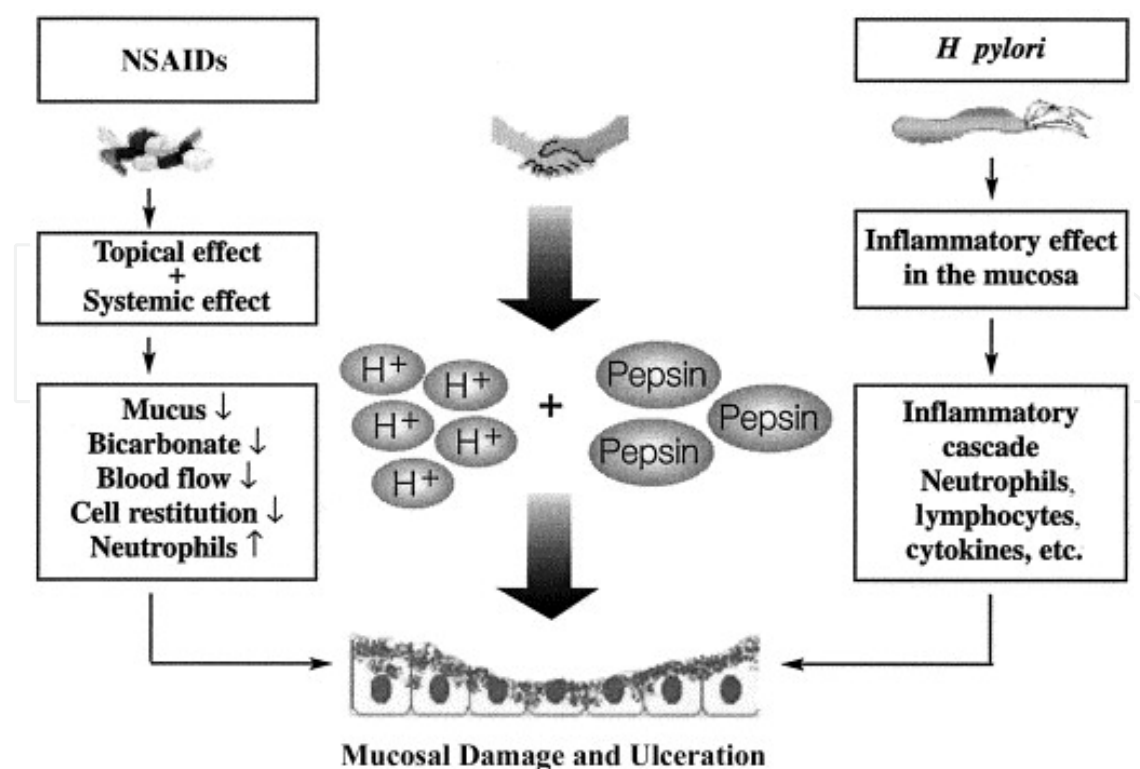


Figure 2. Major factors causing mucosal damage and ulceration (Peura, 2004).

2. Prolongation of GI retention

Scientific and technological advancements have been made in the research and development of different types of drug delivery systems. Keeping up with the rapid development in designing novel drug delivery systems, it is advisable to explore the existing delivery concept and new intra gastric delivery systems which would be expected to overcome the current medication limitations of the treatment of *H. pylori* associated peptic ulcer. It is obvious that formulating dosage forms that retained in the stomach for a prolonged and predictable period of time seem to be advantageous in *H. pylori* eradication.

The most feasible method for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by gastro retentive and sustained release dosage forms that have some beneficial in safety and efficacy over normal release systems. This method of application is especially helpful in delivery of sparingly soluble and insoluble drugs used in *H. pylori* eradication. It is acknowledged that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and so the transit time becomes an important factor affecting drug absorption in drugs with lower solubility. Other drug candidates suitable for gastroretentive drug delivery systems include those drugs that are locally active in the stomach, drugs with narrow absorption window in GI tract, drugs that are unstable in the intestinal or colonic environment, drugs that act locally in the proximal part of GI tract or disturb normal colonic microbes like antibiotics and also drugs that exhibit low solubility at high pH values. Concerning the pharmacotherapy of the stomach through local

drug release of gastroretentive dosage forms, bringing about high levels of drug concentrations at the gastric mucosa (eradication of *H. pylori* from the submucosal tissue of the stomach), and treating stomach and duodenal ulcers, gastritis and oesophagitis, the risk of gastric carcinoma would be drastically reduced. In contrast, there are drugs that do not fit in gastroretentive drug delivery systems; Drugs that have very limited acid solubility, drugs that suffer instability in the gastric environment, and drugs intended for selective release in the colon should follow other techniques of drug delivery to reach for their intended site of action. Hence, gastroretentive dosage forms despite providing rather constant drug concentrations in the bloodstream for longer periods of time do not fulfill this benefit with several groups of drugs (Javadzadeh-Hamedeyazdan, 2012; Pahwa et al., 2012b).

One of the advantages of the sustained release dosage forms is that medication is administered less often than other dosage forms reducing fluctuations of drug concentration in the bloodstream. As a result, the patient is not repeatedly subjected to different levels of drug which are less or more than adequate. Nor does the blood chemistry undergo frequent chemical imbalances, which might be risky to the patient's health. Additionally, through gastroretentive dosage forms not only the bioavailability and therapeutic efficacy of drugs are improved but also it may allow for a possible reduction in the dose because of the steady therapeutic levels of drugs. Drugs that have poor solubility in higher pH, absorption windows in stomach, requiring local delivery in stomach could be delivered ideally to the site of action by the gastroretentive formulations. On the other hand, drugs that cause irritation to gastric mucosa and the ones meet first-pass metabolism or have stability problems in gastric fluids are not appropriate for these kinds of drug delivery systems (Javadzadeh-Hamedeyazdan, 2012; Pahwa et al., 2012a; Pawar et al., 2012).

In brief, gastric retention is a means to enable a delivery strategy that will function irrespective of the digestive state, clinical condition, or GI motility of the individuals with longer drug residence time in the stomach being advantageous in superior drug bioavailabilities and also in certifying local action of some drugs in the upper part of the GI tract, that are used in *H. pylori* eradication (Bardonnet et al., 2006b; Nama et al., 2008; Badhan et al., 2009; Shah et al., 2009; Adebisi-Conway, 2013).

3. *H. pylori* associated peptic ulcer

3.1. Acidic condition of stomach

The human stomach can produce and secrete about 2.2 to 3 L of gastric acid per day with basal secretion levels being typically highest in the evening. Normally no bacteria or viruses can survive in this medium that is composed of digestive enzymes and concentrated hydrochloric acid. Consequently, stomach has been regarded as a sterile ingestion organ for its hostile and acidic environment that could be considered as a barrier for invasion of various microorganisms. However, this notion has been totally changed since *H. pylori* as a major cause of peptic ulcer disease and gastritis in human was firstly isolated by Marshall and Warren in 1983 (Yang et al., 1999). *H. pylori*, a spiral-shaped gram-negative rod, is classified as *Campylobacter*

pyloridis due to its similar histological and growth properties to the *Campylobacter* species. Based on the unique morphological and biochemical characteristics, *Campylobacter pyloridis* was regrouped into a new genus *Helicobacter* (Brooks et al., 2004).

3.2. Pathogenesis of *H. pylori*

H. pylori is associated with antral gastritis, peptic ulcer disease (gastric and duodenal ulcer disease) and gastric carcinoma, however, it initially induces chronic gastritis to develop peptic ulcer rather than directly causing the ulcer disease (Wyatt, 1989). Ever since, *H. pylori* grows optimally at a pH of 6-7, it would not grow at the pH of the gastric lumen. Gastric mucus is relatively impermeable to acid and has a strong buffering capacity so deep mucus layer near the epithelial surface where the pH is about physiologic of 7.4 is an appropriate place for *H. pylori* growth. The bacterium produces a protease modifying the gastric mucus to reduce the ability of acid to diffuse through the mucus. In addition, *H. pylori* also has potent urease activity, which yields production of ammonia and further buffering of acid, which may directly damage the cells, too (Brooks, Butel et al., 2004; Abe et al., 2011). Although, the mechanisms by which *H. pylori* causes mucosal inflammation and damage, are not well known but they may involve both bacterial and host factors. Compared to other infectious diseases, the *H. pylori* associated morbidity is relatively high, which is about 10% for peptic ulcer disease and 0.5% for gastric adenocarcinoma (Kusters, 2001). Once *H. pylori* eradication has been achieved, re-infection rates are less than 0.5% per year, and ulcer recurrence rates are dramatically reduced (Kluwer, 2004). Since, there is not any clear hypothesis about spread of *H. pylori*, prevention is rather difficult issue. Then in treatment of peptic ulcer disease, clinicians are logically focusing on the eradication of *H. pylori* (Ables et al., 2007; Yamaoka, 2010).

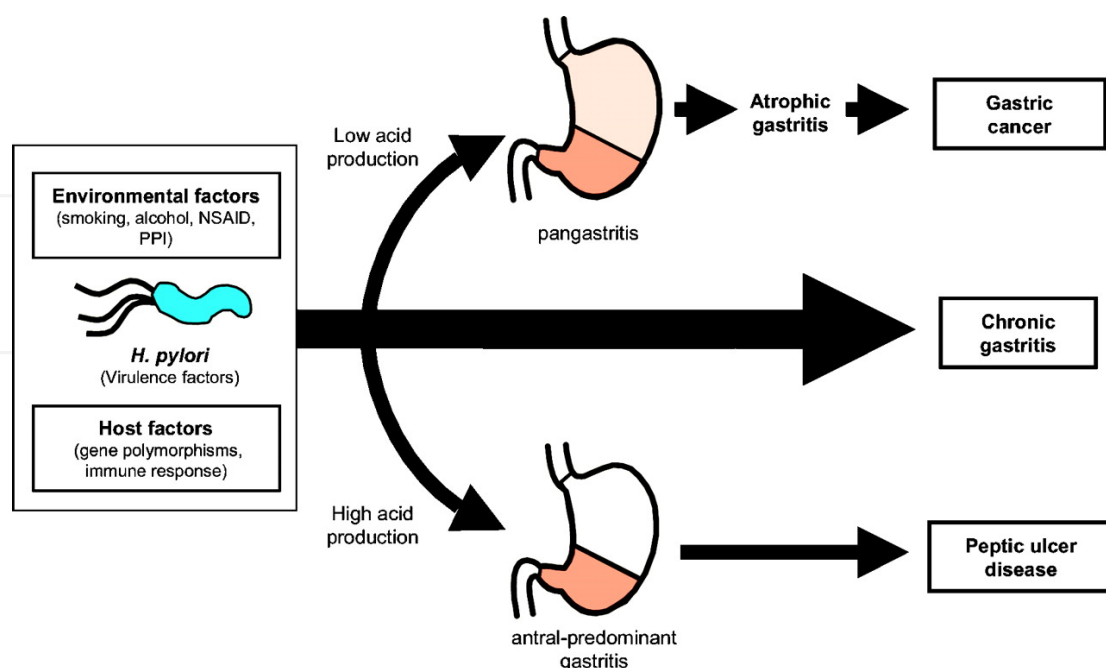


Figure 3. Pathogenesis of *H. pylori* (Kusters et al., 2006).

3.3. Treatments for *H. pylori* associated peptic ulcer disease

Basically, the goals for peptic ulcer treatments have been defined as: alleviation of symptoms, healing of the ulceration, prevention of recurrence of ulcer. Primarily, before the bacterium was found, it was believed that stomach ulcers occur when excess acid damaged the gastric mucosa so the treatment was based on reduction or neutralization of that acid (Gisbert et al., 2010; GisbertPajares, 2010). Patients were treated with long-term suppressive therapy by giving acid-blocking medications, for instance, H₂-blockers and, more recently, proton pump inhibitors (BreuerGraham, 1999). This kind of treatment could certainly relieve ulcer-related symptoms, heal gastric mucosal inflammation and even heal the ulcer. Unfortunately, it has a high recurrence rate just owing to the lack of basic treatment of the infection and eradication of the bacterium, *H. pylori* (Brunton, Parker et al., 2008). The identification of *H. pylori*, and understanding of *H. pylori* associated peptic ulcer disease have greatly changed therapeutic regimens covering peptic ulcer disease. Eradication of *H. pylori* is now recognized to be the correct approach in the treatment of the disease (Yang, Eshraghi et al., 1999; Chuah et al., 2011). The treatment of peptic ulcer with antibiotics is recognized as the choice treatment for patients (Beales, 2001). Savings of costs and time are the major benefits of this protocol to therapy with acid reducing medications. The same drug and dosage regimens could be applied to the treatment for both gastric and duodenal ulcer as there are no important differences between these two ulcer diseases (DzieniszewskiJarosz, 2006). Antibiotics and agents used to eradicate *H. pylori*, attack three main areas, i.e. the bacterium cell wall, the ribosome and nuclear DNA. For instance, metronidazole, a nitroimidazole antiprotozoal drug that also has potent antibacterial activity against anaerobes, including bacteroides and clostridium species, can disrupt the bacterial DNA helix preventing replication and interrupting gene expression, bismuth salt may disrupt bacterial cell wall or membrane (Malfertheiner, 1996).

3.3.1. Combination therapy

Although *H. pylori* is sensitive to many antibiotics *in vitro*, this sensitivity is not correlated with eradication of the organism *in vivo* (Drumm, 1990). Recurrence of the infection is common after treatment of *H. pylori* by bismuth alone or monotherapy antibiotic (Rauws et al., 1988; Oderda et al., 1989; Chang et al., 2009). It has been postulated that the failure of antibiotic monotherapy to clear *H. pylori in vivo* may be due to the lack of efficacy of the antibiotics in the acid environment of the stomach (Drumm, 1990). Other possible reason of failure could be the area that *H. pylori* colonized and resistance to bacteria. As a result of failure of single antibiotic therapies, combination regimens are suggested to increase the rate of *H. pylori* eradication. Nonetheless, many regimens for *H. pylori* eradication have been proposed, the ideal regimen in this setting should achieve a cure rate of >80% (Brunton, Parker et al., 2008).

3.3.2. Triple combination therapy

Triple combination therapy, using two antibacterial antibiotics and a proton pump inhibitor, had achieved a high eradication rate and seems to be the most effective regimens for *H. pylori* eradication (AxonMoayyedi, 1996; Ishizone et al., 2007). Proton pump inhibitors promote eradication of *H. pylori* through several mechanisms: direct antimicrobial properties (minor);

raising intra-gastric pH and lowering the minimal inhibitory concentrations of antibiotics against *H. pylori*. One of the principal treatment regimens consists of a 10–14 day regimen of "triple therapy": a proton pump inhibitor (standard dose, b.i.d.), clarithromycin, (500 mg, b.i.d.) and amoxicillin (1 g, b.i.d.). For patients who have allergy to penicillin, metronidazole, 500 mg twice daily, should be substituted for amoxicillin. Moreover, after completion of triple therapy, the proton pump inhibitor has been recommended to be continued once daily for a total of 4–6 weeks to ensure complete ulcer healing (Katzung, 2006). Other triple therapies that are being mentioned in other reference includes combinations of bismuth salts and various antibiotics (Rauws, Langenberg et al., 1988).

3.3.3. Quadruple combination therapy

In the case of *H. pylori* eradication quadruple therapy has been offered for 14 days: Proton pump inhibitor twice a day, metronidazole 500 mg three times daily, bismuth subsalicylate 525 mg, tetracycline 500 mg four times daily or H₂-receptor antagonist twice a day, bismuth subsalicylate 525 mg, metronidazole 250 mg, tetracycline 500 mg four times daily (Brunton, Parker et al., 2008). Antibiotics from systemic circulation have to traverse the epithelial layer (Malfertheiner, 1996; Hsu et al., 2011). Seeing as, in systemic administration of drugs the gastric emptying makes the effective local concentrations of drugs difficult to maintain, the effects of drug is not local and is through its systemic absorption, the frequent doses of oral antibiotics are required leading to higher drug dosages, lower patient compliance, and adverse drug effects.

3.4. Drug delivery systems for *H. pylori* eradication

3.4.1. Importance of drug delivery systems in treatment of diseases

It is judicious to be reminiscent of the GI tract being a primary site for the absorption of drugs with a variety of limitations making the *in vivo* performance of drug delivery systems uncertain. Despite tremendous advancement in drug delivery, the oral route still remains the preferred route for the administration of therapeutic agents in consequence of the low cost of therapy, and ease of administration, as well as patient compliance. However, oral dosage forms hold several physiological restrictions like non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach (Adibkia, Hamedeyazdan et al., 2011). Undoubtedly, rate of drug transition through the gastrointestinal (GI) tract is highly controlled by the physiological properties of the GI tract as well as the formulation properties. Since, bioavailability of drugs in this route of administration often depends on the GI transit rate of the dosage form it is of value to distinguish between an appropriate drug delivery system for an especial objective in treatment of diseases. Acquiring a clear notion of why certain medications are prone to problems in reaching the desired efficiency and bioavailability, to dominate the relative constraints offering successful medication therapy recalling some fundamental characteristics of the stomach would be of note.

3.4.2. Stomach and drug delivery systems

As far as we know, the stomach is a muscular, hollow, dilated part of the alimentary canal which functions as an important organ of the human body located between the esophagus and the small intestine. Surface epithelium of stomach retains its integrity throughout the course of its lifetime, even though it is constantly exposed to a high concentration of hydrochloric acid and powerful enzymes. This self protection mechanism is due to the fact that the specialized goblet cells located in the stomach and continuously secrete a large amount of mucus that remains closely applied to the surface epithelium (Chein, 1992). In general, stomach is an important site of enzyme production with small surface area, offering an imperfect site of absorption (Chein, 1992). The main function of stomach is to store food temporarily, grind it, and then release it slowly in to the duodenum. The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. Fasted state is characterized by an inter-digestive series of electrical events which cycle both through the stomach and small intestine every 2–3 h which is called the inter-digestive myoelectric cycle or migrating myoelectric complex (Fell, 1996). In the fed state, the gastric emptying rate is slowed since the feeding results in a lag time prior to the onset of gastric emptying, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 h. Alterations in gastric emptying occurs due to factors such as age, race, sex, and disease states, as they may seriously affect the release of a drug from the drug delivery system (SinghKim, 2000).

The complex and highly variable nature of gastric emptying process making the *in vivo* performance of conventional drug delivery systems uncertain draw researchers' attention to find a clue and dominate these constraints and present suitable drug delivery strategies that would serve independent of the digestive state, clinical condition, or GI motility of the individual. Conventional oral dosage forms provide a specific drug concentration in the systemic circulation without offering any control over the rate of drug delivery, whilst controlled-release drug delivery systems provide drug release at a predetermined, predictable, and controlled rate of drug release (Hwang et al., 1998). Nevertheless, in some cases the insufficient residency of drugs in the vicinity of absorption site for the life time of drug delivery restricts the use of controlled-release drug delivery systems. The inadequate drug residence in the vicinity of absorption site might arise from differences in GI transit time of drugs in individuals, and physical properties of the object ingested as well as the physiological conditions of the alimentary canal. Correspondingly, medications with sustained drug release forms have some benefits over normal release systems in safety and efficacy in reducing the frequency of drug dosage, together with the diminished incidence of adverse drug reactions. Hence, if medications used in *H. pylori* eradication therapy are used in terms of sustained release dosage forms some advantages are fulfilled seeing as the medications are administered less often than other dosage forms, fluctuations of drug concentration in the blood would be reduced, and the patient is not repeatedly subjected to amounts of the drug which are less or more than adequate, nor the blood chemistry experience frequent chemical imbalances, which might be detrimental to the patient's health (Klausner et al., 2003; Javadzadeh et al., 2007; Tang et al., 2007; Javadzadeh et al., 2009; Javadzadeh et al., 2012). Several methods have been

developed for extension of GI transit time via enhancing the residence time of drug delivery systems in the stomach.

3.4.3. Floating drug delivery systems

One of the approaches followed to extend the residency of medications in the stomach is floating dosage forms with lower density than the gastric fluids to be capable of floating on the gastric juice in the stomach (SinghKim, 2000; Adibkia, Hamedeyazdan et al., 2011). According to the mechanism of buoyancy, two evidently different technologies are applied in development of floating dosage forms, effervescent and non-effervescent systems. In general, the principle rule is indelible in all approaches and that is to float on gastric juice with a specific density of less than 1.004 g/cm of the gastric juice in the stomach.

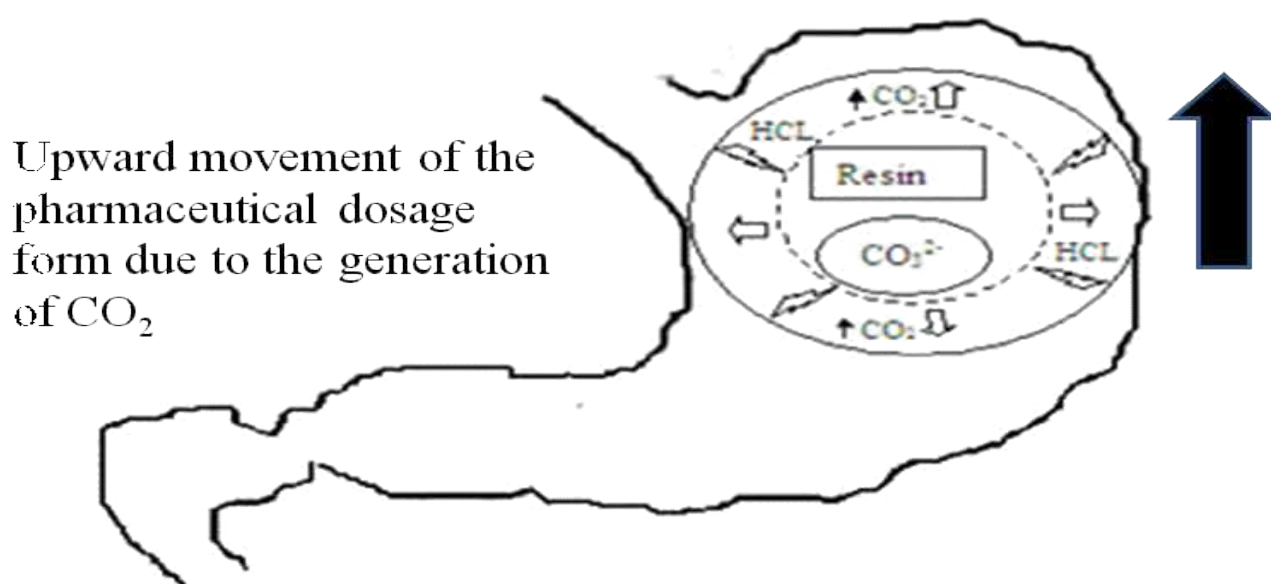


Figure 4. Effervescent floating drug delivery system in the stomach

Besides, multi-particulates of floating dosage forms consisting of small discrete units in which the active substance is offered as a number of small independent subunits are less reliant on gastric emptying, bringing about less inter and intra-subject variability in GI transit time. Moreover, they are also well distributed and less likely to cause local irritation. Nowadays, much emphasis is being laid on the development of multi particulate dosage forms rather than single unit systems due to potential benefits of them such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation as well as predictable gastric emptying (MohamadDashevsky, 2007; GuptaPathak, 2008).

A number of factors that affect gastric emptying of a dosage form, such as density, size, and shape of dosage form, concomitant intake of food and drugs such as anticholinergic agents (e.g., atropine, propantheline), opiates (e.g., codeine), prokinetic agents (e.g., metoclopramide,

cisapride), and biological factors like gender, posture, age, body mass index, and disease states (e.g., diabetes, Crohn's disease) could be controlled by these floating dosage forms providing a more convenient medication therapy (SinghKim, 2000).

These systems are also appropriate for drugs which are locally active to the gastric mucosa in the stomach, such as administration of metronidazole (MZ) as an antibiotic for *H. pylori* eradication in the treatment of peptic ulcer disease (Murata et al., 2000; Rajinikanth et al., 2007; RajinikanthMishra, 2007; RajinikanthMishra, 2008). Treatment of *H. pylori* infection by topical administration of antimicrobial agents has been reported. In order to avoid the side effects of standard triple therapy, Satoh used a technique of instilling a combination of bismuth subnitrate, amoxicillin and metronidazole into the stomach via a naso-gastric tube for 1 hour. He found that topical therapy was highly successful with high eradication rate of *H. pylori* and none-ulcer dyspepsia as well. Although this local administration successfully avoids some of the side effects of standard triple therapy, it is inconvenient and still complicated to patient when compared to oral dosage delivery system (Satoh, 1996). Elsewhere, the hydrodynamically balanced delivery system of Clarithromycin was developed which, after oral administration had the ability of prolonged gastric residence time with the desired *in vitro* release profile for the localized action in the stomach, in the treatment of *H. pylori* mediated peptic ulcer. In this study, wet granulation technique was applied for preparing of floating tablets of Clarithromycin. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. The formulation that developed using 66.2% Clarithromycin, 12% HPMC K4M polymer, 8% sodium bicarbonate gave floating lag time less than 3 min with a floating time of 12 h, and an *in vitro* release profile very near to the desired release. *In vivo* radiographic studies also suggested that the tablet had increased gastric residence time for the effective localized action of the antibiotic (Clarithromycin) in the treatment of *H. pylori* mediated peptic ulcer. The mechanism of release of Clarithromycin from the floating tablets was anomalous diffusion transport and followed by zero order kinetics (Nama, Gonugunta et al., 2008). In another study by Pornsak Sriamornsak, oil-entrapped calcium pectinate gel floating beads were prepared using selected oils that were floated immediately and remained floating for 24 hours. They concluded that this lasting intra-gastric buoyancy of a controlled release dosage form may also provide a suitable manner to deliver drugs that are locally active to the gastric mucosa in the stomach and, hence, achieve a site-specific therapeutic action (e.g., antibiotic administration for *H. pylori* eradication in the treatment of peptic ulcer disease (Sriamornsak et al., 2004). Then again, in another study Sriamornsak et al. evaluated the effects of some variables on release behavior of metronidazole from floating emulsion gel beads of calcium pectinate. They detected a notable prolongation drug release profile by coating the beads with Eudragit or by hardening with glutaraldehyde, whereas no clear effect on drug release was obtained using PEG10000, glyceryl monostearate and Eudragit as additives in the formulations (Sriamornsak, Thirawong et al., 2004; Sriamornsak et al., 2005).

Considering the fact that prolongation of the local availability of the antibacterial agents show positive effects of increasing in the effectiveness of *H. pylori* treatment ensuring a high drug concentration in the gastric mucosa, we had tried to formulate metronidazole in floating

pharmaceutical dosage forms to encounter higher concentrations of the antibacterial agent in the gastric mucosa and clarify the mechanism of the release obtaining a general kinetic model for drug release profiles. In our previously published papers, we had reported the use of two different mechanisms in preparation of metronidazole floating matrix tablets including: A low density producing agent (gas generating agent/porous agent) and hydrocolloid-forming polymer(s) (Asnaashari et al., 2011). Carbonate acted as the gas generating agent when it came into contact with an acidic environment of the stomach under fed condition which got entrapped inside the system, producing bubbles, decreasing the density of the formulation. Preparing a low-density system using calcium silicate a characteristically porous structure with many pores and a large pore volume which forms a porous buoyant system (Jain et al., 2005). The hydrocolloids such as HPMC, carbopol, psyllium in the metronidazole formulations were hydrated and formed a colloid gel barrier that controlled the rate of drug release, around its surface with thickness growing by time and increasing of volume due to hydration that in a bulk density less than 1 g/cm³ remaining buoyant on the gastric fluid. The established suitable release metronidazole floating matrix tablets could ensure a more localized drug concentration which might be useful for *H. pylori* eradication. In other survey, we had prepared alginate beads of metronidazole employing gas generating and porous agents followed by physicochemical evaluations for the prepared formulations (Javadzadeh et al., 2010). Alginates due to their high biocompatibility and nontoxic nature in oral administration that also demonstrate protective effect on the mucous membranes of the upper GI tract are a remarkable natural polymers found in brown algae that have been studied for a variety of biomedical applications. Sodium-Alginate beads (Na-Alg) have been developed in recent years as a unique vehicle for drug delivery. Alginates, which are naturally substances, are found in brown algae and can be considered as block polymers, which mainly consist of mannuronic acid (M), guluronic acid (G) and mannuronic-guluronic (MG) blocks. Alginate is known to be nontoxic when taken orally and also have protective effect on the mucous membranes of the upper gastrointestinal tract. The alginate beads with the structure of spherical gels are taken shape through dropwise addition of aqueous alginate solution to the aqueous solution containing calcium ions and/or other di and polyvalent cations (10). The pH dependent reswelling property of dried alginate beads let them to be administrated as controlled release system in gastrointestinal tract. The drug release from pharmaceutical dosage forms is a major determinant in their biological effect, thus evaluation of drug release kinetic is of paramount importance in the field. The findings of our study revealed high compatibility of the alginate beads in achieving a suitable floating pharmaceutical dosage forms which could control metronidazole release from the beads with a definite kinetic of drug release. Identifying drug release kinetics of a drug which is an important variable in obtaining one or two physically meaningful parameters in relating the drug release parameter with important parameters such as *in vivo* drug bioavailability is of substantial value in pharmaceutical manufacturing.

Hence, developing an efficient floating dosage form is reliant to a better understanding of the relation among the physiological properties of the GI tract, formulation variables and the performance of these floating systems *in vivo* and clinical stages, leading to a superior floating drug delivery system in special cases like *H. pylori* eradication.

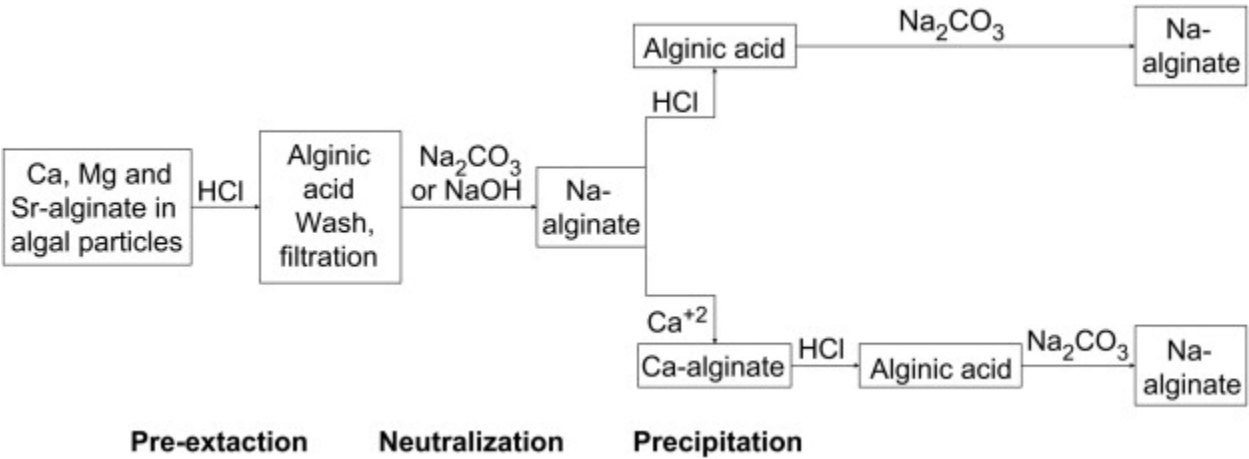


Figure 5. Alginates in floating drug delivery systems

4. Conclusion

Overall, developing an efficient floating dosage form for *H. pylori* eradication could be established by the combination of two buoyancy mechanisms, gas generating systems with swellable polymers, being advantages in view point of obtaining an appropriate floating lag time and duration of buoyancy which guarantees the optimum efficiency of the pharmaceutical dosage form. Nonetheless, further investigations may focus on the compatibility of the mentioned concepts in the interplay of the pharmacokinetic and pharmacodynamic parameters *in vivo* and also in clinical aspect to provide the effectiveness of the floating drug delivery systems in *H. pylori* eradication therapies.

Author details

Yousef Javadzadeh and Sanaz Hamedeyazdan

Biotechnology Research center, Tabriz University of Medical Sciences, Iran

References

[1] Abe, T., Kodama, M., Murakami, K., Matsunari, O., Mizukami, K., Inoue, K., Uchida, M., Okimoto, T., Fujioka, T., Uchida, T., Moriyama, M. & Yamaoka, Y. (2011). Impact of Helicobacter pylori CagA diversity on gastric mucosal damage: an immunohistochemical study of East-Asian-type CagA. *J. Gastroenterol. Hepatol.*, Vol.26, No.4, pp. 688-693.

- [2] Ables, A.Z., Simon, I. & Melton, E.R. (2007). Update on *Helicobacter pylori* treatment. *Am. Fam. Physician.*, Vol.75, No.3, pp. 351-358.
- [3] Adebisi, A.O. & Conway, B.R. (2013). Preparation and characterisation of gastroretentive alginate beads for targeting *H. pylori*. *J Microencapsul*, pp.
- [4] Adibkia, K., Hamedeyazdan, S. & Javadzadeh, Y. (2011). Drug release kinetics and physicochemical characteristics of floating drug delivery systems. *Expert Opin. Drug Deliv.*, Vol.8, No.7, pp. 891-903.
- [5] Asnaashari, S., Khoei, N.S., Zarrintan, M.H., Adibkia, K. & Javadzadeh, Y. (2011). Preparation and evaluation of novel metronidazole sustained release and floating matrix tablets. *Pharm. Dev. Technol.*, Vol.16, No.4, pp. 400-407.
- [6] Axon, A.T. & Moayyedi, P. (1996). Eradication of *Helicobacter pylori*: omeprazole in combination with antibiotics. *Scand. J. Gastroenterol. Suppl.*, Vol.215, pp. 82-89.
- [7] Badhan, A.C., Mashru, R.C., Shah, P.P., Thakkar, A.R. & Dobarra, N.B. (2009). Development and evaluation of sustained release gastroretentive minimatrices for effective treatment of *H. pylori* infection. *AAPS PharmSciTech*, Vol.10, No.2, pp. 459-467.
- [8] Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C. & Falson, F. (2006a). Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*. *J. Control. Release*, Vol.111, No.1-2, pp. 1-18.
- [9] Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C. & Falson, F. (2006b). Gastroretentive dosage forms: overview and special case of *Helicobacter pylori*. *J Control Release*, Vol.111, No.1-2, pp. 1-18.
- [10] Beales, I.L. (2001). Efficacy of *Helicobacter pylori* eradication therapies: a single centre observational study. *BMC Gastroenterol.*, Vol.1, pp. 7.
- [11] Breuer, T. & Graham, D.Y. (1999). Costs of diagnosis and treatment of *Helicobacter pylori* infection: when does choosing the treatment regimen based on susceptibility testing become cost effective? *Am. J. Gastroenterol.*, Vol.94, No.3, pp. 725-729.
- [12] Brooks, G., Butel, J., Morse, S., Melnick, J., Jawetz, E. & Adelberg, E. (2004). *Jawetz, Melnick, & Adelberg's Medical Microbiology*. United States of America, McGraw-Hill Professional.
- [13] Brunton, L., Parker, K., Blumenthal, D. & Buxton, L. (2008). *Goodman & Gilman's Manual of Pharmacology and Therapeutics*. United States of America, McGraw-Hill Companies.
- [14] Chang, W.L., Sheu, B.S., Cheng, H.C., Yang, Y.J., Yang, H.B. & Wu, J.J. (2009). Resistance to metronidazole, clarithromycin and levofloxacin of *Helicobacter pylori* before and after clarithromycin-based therapy in Taiwan. *J. Gastroenterol. Hepatol.*, Vol.24, No.7, pp. 1230-1235.
- [15] Chein, Y.W. (1992). *Novel Drug Delivery System*. New York, Marcel Dekker, Inc.

- [16] Chuah, S.K., Tsay, F.W., Hsu, P.I. & Wu, D.C. (2011). A new look at anti-*Helicobacter pylori* therapy. *World J. Gastroentero.*, Vol.17, No.35, pp. 3971-3975.
- [17] Drumm, B. (1990). *Helicobacter pylori*. *Arch. Dis. Child.*, Vol.65, No.11, pp. 1278-1282.
- [18] Dzieniszewski, J. & Jarosz, M. (2006). Guidelines in the medical treatment of *Helicobacter pylori* infection. *J. Physiol. Pharmacol.*, Vol.57 Suppl 3, pp. 143-154.
- [19] Fell, J.T. (1996). Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. *J. Anat.*, Vol.189 (Pt 3), pp. 517-519.
- [20] Gisbert, J.P. & Calvet, X. (2011). Review article: the effectiveness of standard triple therapy for *Helicobacter pylori* has not changed over the last decade, but it is not good enough. *Aliment. Pharm. Ther.*, Vol.34, No.11-12, pp. 1255-1268.
- [21] Gisbert, J.P., Calvet, X., O'Connor, A., Megraud, F. & O'Morain, C.A. (2010). Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J. Clin. Gastroenterol.*, Vol.44, No.5, pp. 313-325.
- [22] Gisbert, J.P. & Pajares, J.M. (2010). Treatment of *Helicobacter pylori* infection: the past and the future. *Eur. J. Intern. Med.*, Vol.21, No.5, pp. 357-359.
- [23] Graham, D.Y. (1996). Nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and ulcers: where we stand. *Am. J. Gastroenterol.*, Vol.91, No.10, pp. 2080-2086.
- [24] Gupta, R. & Pathak, K. (2008). Optimization studies on floating multiparticulate gastroretentive drug delivery system of famotidine. *Drug Dev. Ind. Pharm.*, Vol.34, No. 11, pp. 1201-1208.
- [25] Hauser, K., Longo, B. & Jameson, F. (2005). *Harrison's Principles of Internal Medicine*. United States of America, McGraw-Hill companies.
- [26] Hsu, P.I., Wu, D.C., Wu, J.Y. & Graham, D.Y. (2011). Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter*, Vol.16, No.2, pp. 139-145.
- [27] Hu, L.D., Xing, Q.B., Shang, C., Liu, W., Liu, C., Luo, Z.L. & Xu, H.X. (2010). Preparation of rosiglitazone maleate sustained-release floating microspheres for improved bioavailability. *Pharmazie*, Vol.65, No.7, pp. 477-480.
- [28] Hwang, S.J., Park, H. & Park, K. (1998). Gastric retentive drug-delivery systems. *Crit Rev Ther Drug Carrier Syst*, Vol.15, No.3, pp. 243-284.
- [29] Ishizone, S., Maruta, F., Suzuki, K., Miyagawa, S., Takeuchi, M., Kanaya, K., Oana, K., Hayama, M., Kawakami, Y. & Ota, H. (2007). *In vivo* bactericidal activities of Japanese rice-fluid against *H. pylori* in a Mongolian gerbil model. *Int. J. Med. Sci.*, Vol.4, No.4, pp. 203-208.

- [30] Jain, S.K., Awasthi, A.M., Jain, N.K. & Agrawal, G.P. (2005). Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and *in vitro* characterization. *J. Control. Release*, Vol.107, No.2, pp. 300-309.
- [31] Javadzadeh, Y., Asnaashari, S. & Hamedeyazdan, S. (2012). Recrystallization of Drugs: Significance on Pharmaceutical Processing Recrystallization. K. Sztwiertnia. Croatia, InTech.
- [32] Javadzadeh, Y. & Hamedeyazdan, S. (2012). Novel Drug Delivery Systems for Modulation of Gastrointestinal Transit Time Recent Advances in Novel Drug Carrier Systems. A. D. Sezer. Croatia, InTech: 393-418.
- [33] Javadzadeh, Y., Hamedeyazdan, S., Adibkia, K., Kiafar, F., Zarrintan, M.H. & Barzegar-Jalali, M. (2010). Evaluation of drug release kinetics and physico-chemical characteristics of metronidazole floating beads based on calcium silicate and gas-forming agents. *Pharm. Dev. Technol.*, Vol.15, No.4, pp. 329-338.
- [34] Javadzadeh, Y., Jafari-Navimipour, B. & Nokhodchi, A. (2007). Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). *Int J Pharm*, Vol.341, No.1-2, pp. 26-34.
- [35] Javadzadeh, Y., Mohammadi, A., Khoei, N.S. & Nokhodchi, A. (2009). Improvement of physicomechanical properties of carbamazepine by recrystallization at different pH values. *Acta Pharm*, Vol.59, No.2, pp. 187-197.
- [36] Katzung, B. (2006). *Basic and Clinical Pharmacology*. San Francisco, mc graw hill press-ed.
- [37] Khobragade, D.S., Parshuramkar, P.R., Ujjainkar, A.P., Mahendra, A.M., Phapal, S.M. & Patil, A.T. (2009). Conception and evaluation of sustained release polymeric matrix beads for enhanced gastric retention. *Curr. Drug. Deliv.*, Vol.6, No.3, pp. 249-254.
- [38] Klausner, E.A., Lavy, E., Friedman, M. & Hoffman, A. (2003). Expandable gastroretentive dosage forms. *J. Control. Release*, Vol.90, No.2, pp. 143-162.
- [39] Kluwer, W. (2004). *Drug Facts and Comparisons*. St. Louis, USA., Facts and Comparisons.
- [40] Kusters, J.G. (2001). Recent developments in *Helicobacter pylori* vaccination. *Scand. J. Gastroenterol. Suppl.*, No.234, pp. 15-21.
- [41] Kusters, J.G., van Vliet, A.H. & Kuipers, E.J. (2006). Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev*, Vol.19, No.3, pp. 449-490.
- [42] Malfertheiner, P. (1996). Management of *Helicobacter pylori*-positive peptic ulcer disease. *Scand. J. Gastroenterol. Suppl.*, Vol.215, pp. 69.
- [43] Mohamad, A. & Dashevsky, A. (2007). *In vitro* and *in vivo* performance of a multiparticulate pulsatile drug delivery system. *Drug Dev. Ind. Pharm.*, Vol.33, No.2, pp. 113-119.

- [44] Motlekar, N.A. & Youan, B.B. (2006). The quest for non-invasive delivery of bioactive macromolecules: a focus on heparins. *J. Control. Release*, Vol.113, No.2, pp. 91-101.
- [45] Murata, Y., Sasaki, N., Miyamoto, E. & Kawashima, S. (2000). Use of floating alginate gel beads for stomach-specific drug delivery. *Eur. J. Pharm. Biopharm.*, Vol.50, No.2, pp. 221-226.
- [46] Nama, M., Gonugunta, C.S. & Reddy Veerareddy, P. (2008). Formulation and evaluation of gastroretentive dosage forms of Clarithromycin. *AAPS PharmSciTech*, Vol.9, No.1, pp. 231-237.
- [47] Oderda, G., Dell'Olio, D., Morra, I. & Ansaldi, N. (1989). Campylobacter pylori gastritis: long term results of treatment with amoxycillin. *Arch. Dis. Child.*, Vol.64, No.3, pp. 326-329.
- [48] Ofman, J.J., Etchason, J., Alexander, W., Stevens, B.R., Herrin, J., Cangialose, C., Ballard, D.J., Bratzler, D., Elward, K.S., FitzGerald, D., Culpepper-Morgan, J. & Marshall, B. (2000). The quality of care for Medicare patients with peptic ulcer disease. *Am. J. Gastroenterol.*, Vol.95, No.1, pp. 106-113.
- [49] Pahwa, R., Saini, N., Kumar, V. & Kohli, K. (2012a). Chitosan-based gastroretentive floating drug delivery technology: an updated review. *Expert Opin Drug Deliv*, Vol.9, No.5, pp. 525-539.
- [50] Pahwa, R., Singh, M., Kumar, V. & Kohli, K. (2012b). Recent advances and patent perspectives in gastroretentive technology. *Recent Pat Drug Deliv Formul*, Vol.6, No.3, pp. 278-290.
- [51] Pawar, V.K., Kansal, S., Asthana, S. & Chourasia, M.K. (2012). Industrial perspective of gastroretentive drug delivery systems: physicochemical, biopharmaceutical, technological and regulatory consideration. *Expert Opin Drug Deliv*, Vol.9, No.5, pp. 551-565.
- [52] Peura, D.A. (2004). Prevention of nonsteroidal anti-inflammatory drug-associated gastrointestinal symptoms and ulcer complications. *Am J Med*, Vol.117 Suppl 5A, pp. 63S-71S.
- [53] Rajinikanth, P.S., Balasubramaniam, J. & Mishra, B. (2007). Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. *Int. J. Pharm.*, Vol.335, No.1-2, pp. 114-122.
- [54] Rajinikanth, P.S. & Mishra, B. (2007). Preparation and in vitro characterization of gelatin based floating beads of acetohydroxamic acid for eradication of H. pylori. *Acta Pharm.*, Vol.57, No.4, pp. 413-427.
- [55] Rajinikanth, P.S. & Mishra, B. (2008). Floating in situ gelling system for stomach site-specific delivery of clarithromycin to eradicate H. pylori. *J. Control. Release*, Vol.125, No.1, pp. 33-41.

- [56] Rauws, E.A., Langenberg, W., Houthoff, H.J., Zanen, H.C. & Tytgat, G.N. (1988). Campylobacter pyloridis-associated chronic active antral gastritis. A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. *Gastroenterology*, Vol.94, No.1, pp. 33-40.
- [57] Satoh, K. (1996). Treatment of Helicobacter pylori infection by topical administration of antimicrobial agents. *Scand. J. Gastroenterol. Suppl.*, Vol.214, pp. 56; discussion 57-60.
- [58] Shah, S.H., Patel, J.K. & Patel, N.V. (2009). Gastoretentive floating drug delivery systems with potential herbal drugs for Helicobacter pylori eradication: a review. *Zhong Xi Yi Jie He Xue Bao*, Vol.7, No.10, pp. 976-982.
- [59] Singh, B.N. & Kim, K.H. (2000). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J. Control. Release*, Vol.63, No.3, pp. 235-259.
- [60] Sriamornsak, P., Thirawong, N. & Puttipipatkachorn, S. (2004). Morphology and buoyancy of oil-entrapped calcium pectinate gel beads. *AAPS J.*, Vol.6, No.3, pp. e24 (21-27).
- [61] Sriamornsak, P., Thirawong, N. & Puttipipatkachorn, S. (2005). Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. *Eur. J. Pharm. Sci.*, Vol.24, No.4, pp. 363-373.
- [62] Tang, Y.D., Venkatraman, S.S., Boey, F.Y. & Wang, L.W. (2007). Sustained release of hydrophobic and hydrophilic drugs from a floating dosage form. *Int. J. Pharm.*, Vol. 336, No.1, pp. 159-165.
- [63] Wyatt, J.I. (1989). The role of Campylobacter pylori in the pathogenesis of peptic ulcer disease. *Scand. J. Gastroenterol. Suppl.*, Vol.157, pp. 7-11; discussion 21-12.
- [64] Yamaoka, Y. (2010). Mechanisms of disease: Helicobacter pylori virulence factors. *Nat. Rev. Gastroenterol. Hepatol.*, Vol.7, No.11, pp. 629-641.
- [65] Yang, L., Eshraghi, J. & Fassihi, R. (1999). A new intragastric delivery system for the treatment of Helicobacter pylori associated gastric ulcer: *in vitro* evaluation. *J. Control. Release*, Vol.57, No.3, pp. 215-222.

