MICROBALLOON: GASTRORETENTIVE DRUG DELIVERY SYSTEM FOR THE ERADICATION OF HELICOBACTER PYLORI

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Abstract

*Helicobacter pylori* is a spiral gram negative bacteria responsible for the development of chronic active gastritis, peptic ulcer disease, gastric mucosal-associated lymphoid tissue, lymphoma and gastric carcinoma. The primary route of infection is not known, but several routes have been proposed and they include gastric-oral, oral-oral, faecal-oral, zoonotic and water/food–borne. Contamination of food by human faecal material was the main risk factor for *H.pylori* infection. Acquired resistance developed against the commonly used antibiotics in the eradication of *H.pylori* as this has been suggested to be a major cause of the treatment failure. So a gastroretentive drug delivery system was developed in order to overcome the disadvantages of conventional dosage form. Microballoons are the gastro-retentive drug delivery system based on non-effervescent approach. These are the low density system that have sufficient buoyancy to float over the gastric contents and release the drug for prolonged period of time in a controlled manner. This article mainly reviewed about *H.pylori*, preparation of microballoons and applications of microballoons in floating drug delivery system.

Key words: Gastroretentive drug delivery system, *helicobacter pylori*, microballoon

Introduction

*Helicobacter pylori* is the main etiologic factor in the development of gastric ulcer and gastric carcinoma. The complete eradication of *helicobacter pylori* from the deep gastric mucosa has remained a challenge due to the
drawbacks of currently available conventional dosage forms. There are three explanations for these findings; first, many antibiotics are unstable in the low ph. of gastric acid; second, the concentration of drug in the deep gastric mucosa where the bacterium lives is too low and third, the amount of time that the antibiotics resides in the stomach is too short. Triple therapies consisting of the combined use of antibiotics are frequently used in the clinical treatment of H. pylori associated with gastroduodenal disease.

The major drawbacks of multidrug therapy are the high level of antibiotic resistance by H. pylori, drug side effects and poor patient compliance. Helicobacter pylori infections can be successfully treated if antibiotics are retained in the stomach for more than 1hr. Eradication of H. pylori result in ulcer healing and prevention of peptic ulcer recurrence.

Oral controlled release dosage forms suffer from the drawback of inability to retain in the gastrointestinal tract due to fluctuations in the gastric emptying. This result in non-uniform absorption pattern, inadequate medication release and shorter residence time of dosage form in the stomach. To overcome these difficulties a gastroretentive drug delivery system based on non-effervescent approach was developed. Microballoons are the gastroretentive drug delivery system based on non-effervescent approach and have a size range of less than 200µ. Aetiology of H.Pylori Infection

H. pylori is a spiral gram negative micro-aerophilic bacterium, with two to six unipolar, sheathed flagella, which provide motility and the ability to penetrate the gastric mucosa and resist gastric rhythmic contractions and remain in the gastric mucosa. It is 2.4 to 4.0µm long and 0.5-1.0 µm wide. This bacterium was firstly identified in autopsied dogs in 1893, described in humans in 1906 and successfully isolated in 1983. H. pylori Infection is silent. H. pylori is also responsible for the development of chronic active gastritis, peptic ulcer disease, gastric mucosal-associated lymphoid tissue lymphoma and gastric carcinoma. H. pylori infection has also been associated with coronary artery and ischaemic heart disease. H. pylori was classified as class 1 carcinogen in humans by the world health organization (WHO) International agency for research on cancer.
Mechanism of H.Pylori Infection

H. pylori infection may occur from childhood, between the ages of 1 to 5 years. The primary route of infection is not known, but several routes have been proposed and they include gastric-oral, oral-oral, faecal-oral, zoonotic and water/food–borne. Contamination of food by human faecal material was the main risk factor for H. pylori infection. In developing countries the major route of transmission is through intra-familial transmission. Acute infection occurs as a result of ingestion of the organism which is commonly asymptomatic, but may be associated with epigastric burning, abdominal distention or bloating, belching, nausea, flatulence, and halitosis. Stomach is the principal reservoir for H. pylori infection, especially the antrum. H. pylori attaches to the gastric epithelial cells and one of the major features of its infection is that it causes progressive injury to the gastric mucosa. Vacuolating cytotoxin VacA production enhances the injurious effect of bacterium. H. pylori is a very diverse species and cancer risks may be increased with strains having virulence–associated genes (cytotoxin–associated gene, CagA), host genetics and environmental factors. The enzymes produced by the H. pylori have a high urease activity. In the acidic environment of the stomach, urea (CH4N2O) breaks down into bicarbonate (CHO3) and ammonia (NH3) that shields the bacterium in the acidic environment of the stomach. The ammonium ions are more toxic to the gastric superficial epithelial cells, thereby causing further injury. Urease enhances inflammatory cytokine production and activates mononuclear phagocytes. On colonization, the host immune system is stimulated and there is an increase in secretory IgA (sIgA) detected in the gastric mucosa; raised specific IgG and the host is unable to rid itself of the bacterium. This colonization leads to persistent gastric inflammation; but the clinical course of the bacterial infection varies from patient to patient.[7]
Pathogenesis of *H. Pylori*

*H. pylori* is mainly responsible for antral gastritis, peptic ulcer disease (gastric and duodenal ulcer disease) and gastric carcinoma. It initially induces chronic gastritis which then leads to peptic ulcer rather than directly causing the ulcer disease. The optimum growth of *H. pylori* at pH of 6-7, it would not grow at the pH of the gastric lumen. Acids are impermeable through gastric mucus and has a strong buffering capacity. Deep mucus layer near the epithelial surface have a pH 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. *H. pylori* also has urease activity, which results in production of ammonia and further buffering of acid, which may directly damage the cells too. Although, the mechanisms by which *H. pylori* causes mucosal inflammation and damage, are not well known but they involve both bacterial and host factors. Compared to other infectious diseases, the morbidity rate is relatively high which is about 10% for peptic ulcer disease and 0.5% for gastric adenocarcinoma. Once *H. pylori* eradication has been achieved, re-infection rates are less than 0.5% per year, and ulcer recurrence rates are dramatically reduced. There is no clear hypothesis about spread of *H. pylori*, prevention is rather difficult issue. For the treatment of peptic ulcer disease, clinicians are logically focusing on the eradication of *H. pylori*. [8]

![Figure 2: Pathogenesis of *H. pylori*.](image-url)
Floating Drug Delivery System against H. Pylori

The oral route is the preferred route for the administration of therapeutic agents due to the low cost of therapy, and ease of administration, as well as patient compliance. Non-uniform absorption profile, incomplete drug release and shorter residence time of dosage form in the stomach are the major drawbacks of conventional oral dosage forms. The rate of drug transition through the gastrointestinal (GI) tract is highly controlled by the physiological properties. Bioavailability of drugs through oral route of administration depends on the GI transit rate of the dosage form.

Floating Drug Delivery System

Classification\[11\] : Floating system can be classified into two systems:

1. Effervescent system
   - Volatile liquid containing system
   - Gas generating system

2. Non-effervescent system
   - Colloidal gel barrier system
   - Alginate beads
   - Hollow microspheres

Treatment\[9\]

![](Recommended Treatment Strategy for the Eradication of Helicobacter pylori.png)
Resistance of H. Pylori to Antimicrobials

Acquired resistance developed against the commonly used antibiotics in the eradication of *H.pylori* as this has been suggested to be a major cause of the treatment failure. The standard triple regimens showed eradication rates of 40-80% in southern European countries. The prevalence rate of clarithromycin (CMN) (17.2%), metronidazole (MET) (26.7%), amoxicillin (11.2%) and levofloxacin (16.2%) resistance increased from Europe to Asia, America and Africa. Just as *H.pylori* infection is associated with geographical areas, so also the prevalence of the resistance rates appears to be partly determined by geographical factors. An analysis of 59 independent studies (56 in adults, 2 in children and 1 in both groups in Latin America) published from 1988 till October 2013, showed prevalence of antimicrobial primary resistance among adults varied by antibiotic. Resistance varied from 12% for CMN (35studies, to 53% for MET 93studies), to 4% for amoxicillin (28studies) to 6% for tetracycline (20studies) to 3% for furazolidone (6studies), to 15% for fluroquinolones (5studies) and 8% for dual CMN and MET (10 studies).

Elevated primary resistance to CMN (20 to >40%) and quinolones (20 to 33%) has been observed in developed countries, while high primary resistance to MET (≥76%), tetracycline (≥15%) and amoxicillin (>30%) has been found in developing countries. The secondary resistance is more common. The prevalence of CMN and MET resistance in China has both increased from 12.8 to 23.8% and 12.8 to 56.6% respectively between 2000 to 2009.

An increase in the duration of treatment and combination of different antibiotics with different mechanisms of actions has been used to reduce the prevalence of resistance. CMN is effective and is the key component of most combination therapies and resistance to CMN has become one of the main reasons for eradication failures. Resistance strains to CMN are emerging, but the instances are comparatively lower than MET. Resistance to CMN has been detected more in patients living in the south (up to 20%) than those of living in the north of Europe.

Spain has one of the highest levels of CMN resistance of about 35.6% observed in the antral mucosa and the mucus layer. In cases where CMN therapies fail, this drug should not been used in second line therapies and a
A regimen containing amoxicillin, MET and a PPI can be used or a levofloxacin – based triple therapy which has proven to be a superior therapy to quadruple therapy and fewer side effects.

A high dose of amoxicillin is required in either dual therapy or in second line treatment regimens as a result of the low local concentrations of amoxicillin at its site of action. An example is seen in a case where levels above the minimum inhibitory concentration have been detected for CMN in gastric juice, mucosa and serum after 6hrs following oral dosing with a triple therapy regimen of omeprazole CMN and amoxicillin.[10]

**Gastroretentive Applications in the Treatment of Peptic Ulcer Microballoons**

**Advantages**[11,12]

- Improves patient compliance by decreasing dosing frequency
- A desirable plasma drug concentration is maintained by continuous drug release and hence bioavailability can be enhanced.
- Gastric retention time is increased because of buoyancy
- Absorption of drugs can be enhanced which solubilize only in stomach
- Drug release in controlled manner for prolonged period of time
- Site specific delivery to stomach can be achieved
- Superior to single unit floating dosage forms such as microballoons releases drug uniformly and there is no risk of dose dumping
- Avoidance of gastric irritation, because of sustained release effect

**Floating Microballoons**[13,14]

After oral administration the microballoons will come in contact with gastric fluid the gel formers, polysaccharides, and polymers undergo hydration to form a colloidal gel barrier which will controls the fluid penetration rate into the device and subsequent drug release. The exterior surface of the dosage form dissolves and the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The swollen polymer will trap the air which will lowers the density and confers buoyancy to the microballoons. Minimum amount of gastric content is needed for proper achievement of buoyancy.
Formation of Microballoons\[^{15}\]\n
![Diagram of steps and mechanism of microballoons formation](image)

**Figure 3: Steps and Mechanism of Microballoons Formation.**

Techniques Used in the Preparation of Microballoons\[^{16,17}\]

Different methods are used for the preparation of microballoons and is depends on route of administration, duration of drug release and particle size. The various methods of preparations are;

**Emulsion solvent evaporation technique**

In this, the drug is dissolved in chloroform and then dissolved in polymer. The resulting solution is added to aqueous phase containing 0.2% sodium of PVP, which is used as emulsifier. This mixture was then stirred at 500 rpm. After the evaporation of the solvent microballoons are formed. The formed microballoons were collected by filtration and washed with demineralized water and desiccated at room temperature for 24 hrs. In this techniques, there are basically two systems which include oil-in-water (o/w) and water-in-oil (w/o) type.

**Oil in water solvent evaporation technique**

In this, both the drug and the polymer should be insoluble in water and a water immiscible solvent is needed for the polymer. The polymer is dissolved in an organic solvent like dichloromethane, methanol and chloroform. The drug is either dissolved or dispersed into polymer solution and this solution is emulsified into an aqueous phase to make an oil-in water emulsion using an emulsifying agent. After that the organic solvent is decanted and the micro particles are separated by filtration.
Water-in-oil emulsification solvent evaporation technique

This technique is also known as non-aqueous emulsification solvent evaporation. Drug and polymers are co-dissolved at room temperature, then this drug and polymer agitated vigorously to form uniform drug–polymer dispersion. This mixture was then poured into the dispersion medium consisting of light / heavy liquid paraffin in the presence of oil soluble surfactant such as Span. The mixture is then stirred using propeller agitator at 500 rpm over a period of 2–3 h to ensure complete evaporation of the solvent. The liquid layer is decanted and micro particles are separated by filtration through a Whatsman filter paper, washed with n-hexane and dried for 24 h and subsequently stored in desiccators.

Emulsion-solvent diffusion technique

In this technique the drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1). Then the mixture was added drop wise to sodium lauryl sulphate solution. The solution was stirred with mechanical stirrer equipped with propeller at room temperature at 150 rpm for 1 hour and formed floating microballoons were washed and dried in a desiccator at room temperature.

Ionic gelation technique

The drug was added to 1.2% (w/v) aqueous solution of sodium alginate and continuously stirred for complete solubility. It is then added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid. Microballoons were kept in original solution for 24 hr. for internal gelification followed by filtration for separation. The maximum release of the drug was obtained at pH 6.4-7.2.

Single emulsion technique

Micro particulate carriers of natural polymers (proteins and carbohydrates) are prepared by this technique. The natural polymers (proteins and carbohydrates) are dispersed in aqueous media followed by dispersion in non-aqueous medium such as oil with the help of cross linking agent.

Double emulsion technique

Double emulsion technique is the formation of the multiple emulsions or the double emulsion such as w/o/w.
Coacervation phase separation technique

It is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase known as co-acervates. The drug was dispersed in a solution of the polymer and to this an incompatible polymer is added, which makes first polymer to phase separate and engulf the drug particles.

Polymerization technique

The polymerization techniques conventionally are mainly classified as:

a. **Normal polymerization**: It is carried out using different techniques of polymerization such as bulk, suspension, precipitation, emulsion and micellar polymerization processes.

b. **Interfacial polymerization**: It involves the reaction of a range of monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed.

c. **Spray drying and spray congealing**: It is based on the principle of drying of the mist of the polymer and drug in the air. The polymer is dissolved in a suitable volatile organic solvent like dichloromethane, acetone and methanol etc. The solid form of drug is then dispersed in the polymer solution under high speed homogenization. This mixture is then atomized in a stream of hot air. Atomization results in the formation of small droplets or the fine mist from which the solvent evaporates to form microballoons in a size range 1-100μm. Depending upon the removal of the solvent or cooling of the solution are named spray drying and spray congealing respectively.

**Amoxicillin Loaded Floating Microballoons For Treatment of Helicobacter Pylori Induced Gastric Ulcer**

Amoxicillin loaded floating microballoons were evaluated based on micrometric properties and minimum inhibitory concentration test (MIC). Emulsion Solvent diffusion method is used for the preparation of amoxicillin loaded floating microspheres. Scanning electron microscopy (SEM) was used to determine the morphology of prepared microballoons.

Drug polymer compatibility study was carried out by using Fourier transformed infrared spectroscopy (FTIR). The relationship between the in vitro buoyancy and their physical properties like density and porosity were elucidated. Morphological characterization was done by using FTIR spectroscopy which reveals the absence of
any drug polymer interactions. Scanning electron microscopy was done to detect the spherical shape of microballoons with hollow internal cavity. The in vitro MIC study was carried out to detect the sustained drug effect from the microballoons. Based on this result we can conclude that the developed amoxicillin loaded microballoons are effective in the treatment of *helicobacter pylori* induced gastric ulcer.[18,19,20]

**Clarithromycin floating microspheres for eradication of H. Pylori**

The main aim of this study was to formulate floating microspheres of clarithromycin for eradication of *Helicobacter pylori*. Clarithromycin loaded floating microspheres were prepared by using different concentration of ethyl cellulose and HPMC is used as secondary polymer. Polyvinylpyrrolidone (PVP) or polyvinyl alcohol (PVA) is used as emulsifier.

The prepared microspheres were evaluated for buoyancy, drug entrapment and drug release, particle size, shape and surface morphology. The drug polymer interactions were studied by FTIR, physical state of microspheres confirmed by using DSC and X-ray diffraction studies carried to determine the physical state of drug in the floating microspheres. The floating microspheres were in micron range and their particle size can be reduced by replacing PVP with PVA.

The secondary polymer HPMC will reduce further particle size. The entrapment efficiency can be increased at high EC concentration especially in presence of HPMC. Immediate floatation was seen with at least 56% of the particles remaining on the surface after 8 hours. Higuchi matrix kinetic model revealed the release pattern in most formulations. [21,22,23]

**Conclusion**

Gastro retentive dosage forms which prolong the residence time of drugs in the stomach and improve their bioavailability. Microballoons are the gastroretentive drug delivery system based on non-effervescent approach. These are the low density system that have sufficient buoyancy to float over the gastric contents and release the drug for prolonged period of time in a controlled manner. *Helicobacter pylori* eradication is possible only if the antibiotics are retained in the stomach for more than 1 hr. Eradication of *H.pylori* result in ulcer healing and prevention of peptic ulcer recurrence.
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