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Review on: Gastro-Retentive Floating Drug Delivery System for the Treatment of *H.Pylori* Infection

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ABSTRACT:

Helicobacter pylorus (H. pylori) is one of the most common pathogenic bacterial infections and is found in the stomachs of approximately half of the world's popula- tion. It is the primary known cause of gastritis, gastro- duodenal 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 ob- stacles 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. Gastro- retentive 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.

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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, gastro-duodenal 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 gastro- duodenal 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. Gastro-retentive dosage forms are one of the oral site-specific drug delivery systems that have been proposed.

Stomach patho-physiology 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].

Gastro-retentive Drug Delivery Systems (Floating system): Floating systems, first described by Davis in 1968, are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period[29, 30]. While the system floats over the gastric contents, the drug is released slowly at the desired rate [31, 32] which results in increased GRT and reduces fluctuation in plasma drug concentration[33]. Floating systems can be classified as effervescent and non-effervescent systems.

These are single unit dosage forms, containing one or more gelforming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC) is the most common used excipient, although hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), sodium carboxymethyl cellulose (NaCMC), agar, carrageenans or alginic acid are also used[34,35].The polymer is mixed with drug and usually administered in a gelatine capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass. Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy.

ADVANTAGES OF GRDDS:

- Increased gastric retention time of the drug delivery system.
- Reduced fluctuations of plasma drug levels.
- Better local delivery to specific region like stomach.
- Improved bioavailability
- Better therapeutic effect due to prolonged gastric retention.
- Controlled release of the drug from the dosage from can be obtained.

RECENT ADVANCES IN GRDDS FOR THE TREATMENT OF *H.PYLORI* INFECTION:

Singh et al. studied that gastro-retentive tablet of an anti-bacterial drug Clarithromycin can be formulated as an approach to increase gastric residence time and thereby improving its bioavailability. Formulation containing HPMCK100M prolonged the release(88.3% upto 10hours) of the drug.

Sriamornsak et al. prepared oil-entrapped calcium pectinate gel floating beads 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.

Yang et al prepared a triple layer tablet based on 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.

Prajapati et al formulated Domperidone floating matrix tablet to prolong gastric retention time. Release retardant such as HPMC K4M, carbopol, sodium alginate is used either alone or in combination. Major evaluation parameters were in vitro buoyancy and floating time. The formulation by using all the three polymers and along with small quantity of PEG400 showed 24hr floating time.

Ashmawy et al demonstrated the feasibility of prolonging the gastric residence time of anti-H. pylori drugs via oral administration of the proposed floating t ablets. Furthermore, sustained release of the model drugs (metronidazole and AmoxTH) from such floating tablets ca n be achieved over a period of at least 6.0 h.

Jain et al. prepared metronidazole floating matrix tablet using gas generating agent. . 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

Asnaashari et al. demonstrated preparation of metronidazole floating matrix tablets using hydrocolloid forming polymers. . The hydrocolloids such as HPMC, carbopol, psyllium in the metronidazole formulations were hydrated and formed a colloid gel barrier that controled 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.

Shah et al. developed a gastric floating drug delivery system (GFDDS) containing Levofloxacin against the H.pylori infection using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like Hydroxypropyl ethylcellulose (HPMC) and Carbopol 974P. The prepared tablets were evaluated in terms of their pre compression parameters, physical characteristics, in vitro release, buoyancy, floating lag time (FLT), total floating time (TFT) and swelling index. The formulations were optimized for the different viscosity grades of HPMC, Carbopol 974P and its concentrations and combinations. Stability study was also performed after storage at 40°C/75% RH for three months. All the formulations showed good floating lag time i.e. less than 3 mins. The batch containing combination of HPMC K4M, HPMC K100M and Carbopol 974P (i.e. L12) showed total floating lag time more than 24 hrs. The batch L12 showed the highest swelling index among all the prepared batches (i.e. 95%). The batch L12 was chosen as the optimized batch since it was also stable for three months during stability study.

Rajnikant et al : Gellan gum based floating beads containing clarithromycin (FBC) were prepared by iontotropic gelation method for stomach-specific drug delivery against Helicobacter pylori. The scanning electron microscope photograph indicated that prepared beads were spherical in shape with rough outer surface. Formulation variables such as concentrations of gellan, calcium carbonate and drug loading influenced the in vitro drug release characteristics of prepared beads. In vitro release rate of clarithromycin was corrected using first order degradation rate constant which is degraded significantly during the release study in simulated gastric fluid pH 2.0. Further, the absence of interactions between drug and polymer was confirmed by differential scanning calorimetry analysis. Kinetic treatment of the in vitro drug release data with different kinetic equations revealed matrix diffusion mechanism. Prepared beads showed good anti-microbial activity against isolated H. pylori strain. The prepared beads have shown good in vivo floating efficiency in rabbit stomach. The stability studies of beads did not show any significant changes after storage of beads at 40 degrees C/75% relative humidity for 6 months. The preliminary results from this study suggest that floating beads of gellan can be used to incorporate antibiotics like clarithromycin and may be effective when administered locally in the stomach against H. pylori.

Ranade et al. performed a project work with a view to retain the drug in stomach for better antiulcer activity and substituting one of the synthetic drugs in this therapy with a herbal alternative. Hence, aim of the present work was to design and develop a bilayer floating tablet of amoxicillin and Aloe vera gel powder for the treatment of peptic ulcer. A. vera gel powder is used for its cytoprotective action. Bilayer floating tablets were prepared by applying direct compression technique. The proportion of sodium bicarbonate and citric acid was adjusted to get the least possible lag time with good matrix integrity and total floating time. Polymer concentration was adjusted to get the maximum release in 8 h. The formulation was developed using hydroxypropyl methyl cellulose (HPMC) K4M and HPMC K100M in a ratio of 85:15 along with 1:4 ratio of effervescent agents was found to give floating lag time of less than 1 min with total floating time of more than 8 h and 97.0% drug release in 8 h. In vivo study in rats meets the requirement of antiulcer activity for bilayer tablet in comparison to single amoxicillin as standard.

MARKETED PRODUCTS:

1. **Cipro® XR 500mg, Bayer HealthCare Pharmaceuticals**
2. **Valrelease®, Hoffmann- LaRoche, USA**
3. **Cifran OD®, Ranbaxy, India**
4. **Madopar® HBS, Roche Products, USA**
5. **Cytotech®, Pharmacia, USA**

CONCLUSION:

A novel floating controlled-release drug delivery system was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastroretentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Thus, this approach can be used effectively to treat h.pylori infections.

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