GASTRORETENTIVE FLOATING TECHNOLOGY FOR ERADICATION OF HELICOBACTER PYLORI: AN INSIGHT VIEW

RAKESH PAHWAI*, BIGUL YOGESHVER BHARDWAJ1, ARCHANA SHARMA1, MONA PIPLANI2, MANISH KUMAR3

1Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, 136119 India, *School of Pharmacy, Maharaja Agrasen University, Baddi, Dist, Solan, Himachal Pradesh, 174103 India, 2M M College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana, Haryana, 133207 India

Email: rakesh_pahwa2407@yahoo.co.in

Received: 12 Aug 2020, Revised and Accepted: 13 Feb 2021

ABSTRACT

Helicobacter pylori is a virulent human pathogen infecting about 50% of the population worldwide. Being a leading cause of gastric ulcer, duodenal ulcer, gastritis, dyspepsia, gastric tumorigenesis etc., this organism has been the focus of concerted study to establish uncertainty of its genetics, immunopathogenesis and cell biology. Scientists have tried to effectively eradicate this pathogen from the gastrointestinal tract in various manners. Inquest of this venture, gastroretentive drug delivery systems including floating dosage forms have emerged as a boon and offer significantly improved therapeutic effects of different antimicrobial drugs. This article presents an evocative review of the structural features, epidemiological evidences and various pharma therapeutic vistas. In addition, various novel gastroretentive dosage forms developed so far to combat Helicobacter pylori infection are also discussed. Comprehensive literature review has been performed for this manuscript by utilizing relevant databases like PubMed, SCOPUS, Web of Science, Science Direct, Google Scholar etc., from 1997 up to the year 2020.

Keywords: Helicobacter pylori, Gastric ulcer, Pharmacotherapeutic vistas, Gastroretentive technology, Floating dosage forms

INTRODUCTION

Helicobacter pylori (H. pylori) is a spiral-shaped, micro-aerophilic and gram-negative bacterium. Campylobacter pyloridis is the earlier name of this pathogen; however, a new class has been introduced and currently, H. pylori is included in the family Helicobacteraceae, Helicobacter genus [1, 2]. Helicobacter pylori bacterium was initially identified in human populations in 1906 and successfully cultured in 1982 by Marshall and Warren, who jointly received 2005 Nobel Prize for their research on Helicobacter pylori [3-7]. This pathogen exists in the gastric mucosus overlying the epithelium of the stomach, in more than 50 percent population of the entire world [8-12]. Colonization of H. pylori in the gastric region causes chronic gastric inflammation in all infected persons, with the clinical indication in 10-20 percent [1].

Helicobacter pylori infection associated ailments

Infection associated with H. pylori includes peptic ulcers (duodenal ulcers and gastric ulcers), severe, recurrent and atrophic gastritis, gastric B cell lymphoma, gastric adenocarcinoma, intestinal metaplasia, mucosa-associated lymphoid tissue (MALT)-associated lymphoma etc [1, 13-19]. Typhoid fever has also independently associated with H. pylori [20]. Earlier epidemiologic evidence indicates that H. pylori infection increases the risk of gastric cancer. It has also been investigated that bacterium Helicobacter pylori-induced infection is carcinogenic to human population [19, 21-26]. DNA damage caused by this bacterium may lead to the cancer development in the stomach. Earlier studies revealed that genomic regions demonstrate more susceptibility to H. pylori induced DNA disruption and are substantially associated with chromosomal modifications in stomach cancer [27, 28]. Some virulence factors are also responsible for chromosomal changes. Two of the main significant virulence factors include cytotoxin-associated gene A (CagA) and vacuolating cytotoxin (VacA) [5, 29-32]. Multiple findings suggest that Helicobacter pylori infection is correlated with a substantially higher risk of stomach cancer and longer the time interval between detection of Helicobacter pylori and diagnosis of stomach cancer, greater the risk of developing carcinoma [33]. Flagella and spiral structure of H. pylori allows selective adherence to the epithelium through gastrointestinal mucus gel [11, 13, 34]. Drinking water can also be a risk factor for bacterial transmission [35]. Moreover, H. pylori have also been cultured through vomitus, diarrheal stool and saliva [36]. Aliments related to Helicobacter pylori infection is presented in fig. 1.

Immunological defence mechanisms against bacterial proliferation

Several factors produced by mucosa of the stomach inhibit bacterial proliferation. Antibacterial peptides are active against several specific types of bacteria, which include LL37 and β defensins 1 and 2. Lactoferrin also hampers bacterial development. Lactoferrin, a lactoferrin-derived peptide, also has antimicrobial qualities. Lysozyme can also be responsible for bacterial peptidoglycan degradation [37]. By diminishing inflammation grades and bacterial population, the antimicrobial peptide cathelicidin may serve as a natural antibiotic against H. pylori. Another proposed method of managing Helicobacter pylori infection is to use fatty acids, as numerous experiments have demonstrated their antibacterial activity [27]. The binding of H. pylori to

Fig. 1: H. pylori associated various ailments
gastrointestinal epithelial cells leads to triggering activation of various signalling mechanisms, which enables the effective transmission of toxic substances or other contaminants into gastric epithelium cells [37]. Findings in various animal models suggest that \textit{H. pylori}'s attachment to gastric epithelial cells affects the growth of inflammation in gastric mucosa, production of autoantibodies, partial cell diminution etc [37]. Urease and flagella are two crucial virulence factors for colonization of \textit{Helicobacter pylori} successfully into the stomach [38]. Urease enzyme produced by \textit{Helicobacter pylori} is responsible for mononuclear phagocytes activation along with enhancement in production of inflammatory cytokine, which creates favourable environment for bacteria to colonize [39, 40]. Diagnosis of infection is usually performed by diagnostic tests such as stool antigen test, urea breath test, blood antibody test etc [41, 42]. These tests determine whether a bacterial infection may induce ulcer or inflammation of stomach lining and also establish the effectiveness of the treatment strategies [43].

\textbf{Treatment strategies}

Several years ago, dual therapies which combined a proton pump inhibitor with either clarithromycin or amoxicillin were common. A large number of triple or quadruple treatments have also been reported. Triple therapy to eradicate \textit{Helicobacter pylori} infection includes a metronidazole (or tinidazole), proton pump inhibitor along with clarithromycin. Few probiotic strains may minimize the probability of adverse effects and thus enhance the eradication rate of \textit{Helicobacter pylori} [15, 24, 44-48]. In between 10-20 percent of cases, the most utilized medication regimens may also struggle. Quadruple therapy based on bismuth remains the primary choice for second-line treatment if not used as first-line therapy [15, 43, 47, 49-53]. Recently, many researchers have an ultimate aim for considering \textit{H. pylori} genetics for the development of new therapies. One example of this includes developing targeted interventions that eliminate \textit{H. pylori} without disrupting commensal human bacteria. For example, recent work has identified HtrA and BioV (a synthetic biotin enzyme) as specific to \textit{H. pylori}. These have potential for allowing the treatment of \textit{H. pylori} without affecting the host or the resident microbiota [54]. It was also found that eating broccoli sprouts daily for two month can reduces \textit{H. pylori} infection into the stomach [55]. It was reported that a Korean vegetable Kimichi may also eradicate \textit{H. pylori} [56].

Sometimes, several therapies to eradicate \textit{H. pylori} are difficult and complex. Increased and indiscriminate utilization of antibiotics has led to significant failures in treatment [43]. Owing to high antibiotics resistance and inadequate patient compliance, new medications with enhanced efficacy in addition to simpler regimens are desired for the eradication of \textit{Helicobacter pylori} [53]. Therefore, to attain a high wipeout rate of \textit{H. pylori} from the stomach, it's obligatory that delivery of antibiotic to the whole surface of the abdomen is achieved and consequently, drug should reach in the desired amount for adequate time to destroy the bacterium. Gastrectroentire drug delivery system is employed as a promising technology to provide advantageous results in site-specificity of antibiotics delivery. Retention of the delivery system is also ensured at a particular part of the gastrointestinal tract, wherever it is needed for local delivery and action at specific site [39].

\textbf{Gastrectroentire drug delivery systems}

The oral route is recognized as the most preferred route for drug delivery. This route has many inherent advantages like convenience, cost-effectiveness, non-invasiveness, safety and patient compliance [57-59]. However, bioavailability of medicaments delivered through this route can change considerably, particularly if pharmacotherapeutic substances are delivered utilizing conventional types. Such constraints are usually due to inter-and intra-subject variability in the physiology of the gastrointestinal tract, gastrointestinal tract transit period and in certain instances to region-specific (narrow absorption window) of drug [60]. However, modern technical development has resulted into various emerging pharmaceutical strategies, especially controlled release systems to effectively resolve this issue [61, 62]. Due to tremendous therapeutic benefits, orally controlled dosage forms have been developed in the previous few years [63-65]. Gastrectroentire technology is one illustration where characteristics such as prolonged gastric retention combined with controlled-release medication dramatically increased patient compliance [61, 66-68].

Extent of drug absorption from duodenum and jejunum is minimal, as transit through this area is fast. This phenomenon drastically limits the success of conventional delivery system [69, 70]. The failure of conventional approaches in gastric retention has contributed to the production of gastrectroentire technologies. These delivery systems have been engineered to maintain an extended interval of time in the upper gastrointestinal tract, after which drugs are released into a controlled manner. Prolonged interaction of gastrectroentire devices with absorption layer permits improved bioavailability of medicament [39, 71-73]. Such devices are especially useful for drugs predominantly absorbed in the regions of the duodenum and upper jejunum [69]. Various technical strategies have been explored in order to establish delivery systems that can be retained into the stomach. These methods have been suggested for improving retention in upper section of the gastrointestinal tract [74]. These gastrectroentire dosage forms are classified into various approaches as shown in fig. 2, such as floating systems [75-77], expandable systems [78, 79], bioadhesive systems [80-83], high-density systems [84, 85], superporous hydrogels [78, 86], magnetic systems [86, 87], dual working systems [88, 89] etc.

\textbf{Advantages of gastrectroentire strategies}

Gastrectroentire technologies are gaining popularity due to numerous advantages and patient compliance benefits. Some significant benefits of this system are mentioned in the subsection section. Various narrow absorption window drugs may show advantageous results after compounding into gastrectroentire dosage forms. Maximum drug utilization with limited negative consequences, low dosing frequency thus improved patient compliance besides controlled drug release behavior present the benefits of continuous and uniform blood drug level. The medication concentration variability is also significantly reduced. In addition, side effects based on dosage may also be minimized [90-95].

\textbf{Salient benefits}

Following are some important benefits of gastrectroentire delivery systems [95-98].

- Enhancing bioavailability as well as the therapeutic efficacy of molecules with narrow absorption window in the upper gastrointestinal tract.
- Enhanced utilization of medicaments with limited side effects.
- Low dosing frequency thus improved patient comfort and compliance.
• Controlled drug release behavior provides uniform and consistent blood level of medication.
• Variations in drug concentration are reduced. Hence, concentration-dependent side effects may be minimized.
• Avoiding gastric irritation due to sustained release profile.
• Site specificity.
• Uniform release of the drug without risk of dose dumping.
• Reduced inter-and intra-subject variability.
• Increased stomach retention period owing to buoyancy principle, circumventing the invariable and inadequate absorption of drugs.
• Versatility in the design of dosage form.
• Extended patent rights along with emerging newer market prospect.

Current viewpoint on gastroretentive approaches

Various gastroretentive drug delivery systems have been investigated for successful gastric retention. However, alteration in gastric retention time, especially in fed as well as fasted state, is still one of the major challenges for the scientists. Therefore, it is advantageous to explore suitable innovative gastroretentive approaches by overcoming the drawbacks of a particular approach. Various combined approaches might be a beneficial strategy for reducing the irregularity of gastric retention time. Also, coupled working system is less affected due to physiological state of the gut for instance, as in fed and fasting conditions. These advanced systems may ensure delayed gastric emptying. Therefore, a study on gastroretentive drug delivery systems in the near future should be with major concern of combining various strategies to achieve desired stomach retention of dosage forms also in fasted condition [39, 89, 99, 100]. The use of newer techniques such as extrusion and amalgamation of various approaches will further create interest in gastroretentive drug delivery systems and it will continue to create interest among pharmaceutical industries and researchers [57]. Various gastroretentive floating drug delivery systems investigated for Helicobacter pylori eradication are portrayed in fig. 3.

CONCLUSION

H. pylori is a global pathogen and its infection causes various clinical and pathological effects involving chronic gastritis, peptic ulcer, malignant stomach tumours etc. Development of an efficient gastroretentive dosage form is a real challenge for the eradication of bacteria by delivering suitable antibiotic in the stomach. The present review provides an insight of different aspects of this spiral gram-negative bacterium along with various antibiotic regimens available for the treatment of infection prevailing in all classes of people around the world. Immense potential of promising gastroretentive technologies for eradication of this prevalent contagion are highlighted in the current manuscript. Various research endeavours in the avenue of gastroretentive drug delivery

| S. No. | Drug Name          | Dosage form                     | Authors          | Year | Ref. |
|-------|--------------------|---------------------------------|------------------|------|------|
| 1.    | Levofloxacin hydrochloride | Gastroretentive wafers          | Li et al.        | 2020 | [101]|
| 2.    | Amoxicillin trihydrate        | Floating mucoadhesive alginate beads | Dey et al.       | 2016 | [102]|
| 3.    | Metronidazole             | Floating pH-sensitive chitosan hydrogel | ElMahrouk et al.| 2016 | [103]|
| 4.    | Amoxicillin and clarithromycin | Floating assembled modules      | Rossi et al.     | 2016 | [104]|
| 5.    | Amoxicillin trihydrate       | Floating mucoadhesive beads      | Thombre et al.   | 2016 | [105]|
| 6.    | Clarithromycin             | Floating mucoadhesive alginate beads | Adebisi et al.   | 2015 | [106]|
| 7.    | Clarithromycin             | Floating fine granules           | Aoki et al.      | 2015 | [107]|
| 8.    | Clarithromycin             | Floating tablets                 | Igrulu et al.    | 2014 | [108]|
| 9.    | Clarithromycin             | Floating mucoadhesive beads      | Gattani et al.   | 2010 | [109]|
| 10.   | Metronidazole             | Floating alginate beads          | Javadzadeh et al.| 2010 | [110]|
| 11.   | Clarithromycin             | Gellan gum-based floating beads  | Rajnikanth et al.| 2009 | [111]|
| 12.   | Amoxicillin               | Gastroretentive minimatrices     | Badhan et al.    | 2009 | [112]|
| 13.   | Clarithromycin             | Mucoadhesive microspheres        | Jain et al.      | 2009 | [113]|
| 14.   | Clarithromycin             | Floating gelling system          | Rajnikanth et al.| 2008 | [114]|
| 15.   | Acetyloxydoxamic acid      | Floating gelling system          | Rajnikanth et al.| 2008 | [115]|
| 16.   | Metronidazole             | Floating alginate beads          | Ishak et al.     | 2007 | [116]|
| 17.   | Amoxicillin               | Intra gastric floating gelling system | Rajnikanth et al.| 2007 | [117]|
| 18.   | Acetyloxydoxamic acid      | Gellan based floating beads      | Rajnikanth et al.| 2007 | [118]|
| 19.   | Amoxicillin               | Mucoadhesive microspheres        | Patil et al.     | 2007 | [119]|
| 20.   | Metronidazole             | Floating emulsion gel beads      | Sramonrouk et al.| 2005 | [120]|
| 21.   | Acetyloxydoxamic acid      | Floating microspheres            | Umamaheishwari et al.| 2003 | [121]|
| 22.   | Acetyloxydoxamic acid      | Floating mucoadhesive microspheres | Umamaheishwari et al.| 2002 | [122]|
| 23.   | Ampicillin                | Floating sustained release liquid | Katayama et al.  | 1999 | [123]|
| 24.   | Tetracycline and metronidazole | Floating tablets             | Yang et al.      | 1999 | [124]|

Miscellaneous research considerations on eradication of Helicobacter pylori through gastroretentive techniques have been published. Few of these findings are presented in table 1.

Fig. 3: Various floating dosage forms for eradication of H. pylori
ensuring maximal absorption of the antibiotic for eradication of the bacterium have also been discussed.

FUTURE PERSPECTIVES

Advancements are needed on technical and scientific aspects in this area for the development of novel and versatile gastroreinfective dosage forms so as to eradicate the bacterium efficiently and successfully. It is also emphasized that sophisticated research based on enhanced stability profile and prolonged residence time of dosage forms should be investigated to achieve better penetration of antibiotics through the stomach mucus layer to act on H. pylori. Progress in synergistic approaches utilizing superior drug delivery technologies may prove a useful prospect for improved pharmacotherapy of this complex infection. In addition, further additional in vivo studies are required to establish the suitability of gastroreinfective formulations for targeting actives to the gastric wall. Moreover, studies regarding antibiotics delivery to target receptor sites on H. pylori or circumvent the adhesion of bacteria to the gastric wall should also be focused.

FUNDING
Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

All the authors have contributed equally.

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