Chapter II

AIM, BACKGROUND CONCEPT AND OBJECTIVES
2.1. Aim
To formulate and evaluate sunflower oil entrapped chitosan coated polymeric gel beads for stomach specific delivery of amoxicillin trihydrate for the effective treatment of *Helicobacter Pylori* (*H. pylori*) infection.

2.2. Background Concept

*H. pylori* is a small, spiral, microaerophilic, gram-negative bacteria with a 4-6 bulbous tipped unipolar-sheathed flagella at one end (Fig. 2.1), which helps it to penetrate the gastric mucosa and to colonize on the gastric antrum [1,2]. Infection with *H. pylori* is universally accepted as the main threat for chronic gastritis and gastric carcinogenesis at present, and was classified as a carcinogen by the World Health Organization (WHO) in 1994 [3].

![Fig.2.1. (a) Helicobacter pylori, (b) Colonization of the gastric mucosa by Helicobacter pylori (Giemsa stain).](image)

Estimates from the WHO in 1994 claimed that about half of the world’s population was infected with *H. pylori* and although most infections are silent, a portion of the infected population will subsequently present with associated disease including chronic gastritis, peptic and duodenal
ulcers (Fig. 2.2). About 550,000 new cases a year of gastric cancer—about 55% of the worldwide total—were attributed to *H. pylori*, and it was predicted that by 2020 to enter the top ten of leading causes of death worldwide [4,5].

Fig. 2.2. Duodenal ulcer and gastric ulcer produced by *Helicobacter pylori*

Amoxicillin ($\alpha$-amino-hydroxybenzylpenicillin) is a semisynthetic, orally absorbed, broad-spectrum antibiotic. It is now widely used in a standard eradication treatment of gastric *H. pylori* infection combined with a second antibiotic and an acid-suppressing agent [6-8]. These triple therapies are proved to be effective in clinical application. However, some other reports and clinical trials indicate that the therapies cannot bring out complete eradication of *H. pylori* and suggest that the therapeutic effect needs more investigation [9, 10].

One reason for the incomplete eradication of *H. pylori* is probably due to the short residence time of antimicrobial agents in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces where *H. pylori* exists [11, 12]. Because conventional drug delivery systems do not remain in the stomach for prolonged periods,
they are unable to deliver the antibiotics to the site of infection in effective concentrations and in fully active forms. It is, therefore, necessary to design drug delivery systems that cannot only alleviate the shortcomings of conventional delivery vehicles but also deliver the antimicrobials to the infected cell lines (Fig. 2.3). The absorption of an antibiotic into the mucus through the mucus layer (from the gastric lumen) is believed to be more effective for \textit{H. pylori} eradication than absorption through the basolateral membrane (from blood).

![Fig. 2.3. Schematics of targeted drug delivery approach for \textit{Helicobacter pylori} eradication located within the stomach [13].](image)

Various strategies those are currently available for the development of improved amoxicillin trihydrate loaded formulations include the formation of floating tablets, mucoadhesive tablets, mucoadhesive beads, etc., in order to retain these in the gastrointestinal tract (GIT) for an extended time to offer increased effectiveness [14-16]. Since last decade, the strategy for effective delivery of antibiotics to \textit{H. pylori} has shifted to the use of mucoadhesive microspheres to extend the residence time in the stomach, but their drug loading capacities are poor [17,18]. On the other hand, use of biodegradable polymeric blend composites coated with a biopolymer holds a great promise to increase drug loading efficiency achieves sufficient therapeutic
concentration for the treatment of gastric disease, such as peptic ulcers [19-22]. In addition, the polymeric bead formulations using vegetable oils can have a lower bulk density than gastric fluids, thereby causing the beads to float and be retained in the stomach [23, 24]. The extended retention of the drug can maintain a higher antibiotic concentration in the gastric region where *H. pylori* exists and thereby improve the therapeutic efficacy.

Based on this concept, we have made an attempt to develop sunflower oil entrapped buoyant gel beads of amoxicillin trihydrate using sodium alginate and hydrophilic polymer hydroxypropyl methyl cellulose (HPMC) as matrix polymers and chitosan as coating polymer. The objective of the work was to develop gel beads those will remain floated for a long time inside the stomach, delivers the drug into the gastric mucosa locally, provide a sustained action and hence increase the efficiency of the drug towards the effective treatment of *H. pylori* infection.

The polymer used, sodium alginate is an inexpensive, nontoxic product extracted from kelp. Literature reports widespread use of sodium alginate for achieving sustained release of drugs [25], targeting gastric mucosa [26] and increasing the bioavailability of drugs [27]. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Another polymer HPMC, is a widely accepted pharmaceutical excipient, because HPMC is available in a wide range of molecular weights and the effective control of gel viscosity is easily possible. HPMC has been reported to enhance the sustained-release properties of alginate by providing a denser inner matrix [28]. Sunflower oil, the non-volatile oil compressed from sunflower (*Helianthus annuus*) seeds, also greatly aids the buoyancy of the formulation [29]. Chitosan, a polysaccharide derived from chitin by alkaline deacetylation, has been proposed as a useful coating excipient for control release of water-soluble drugs [22, 30].
2.3. Objectives

The objectives of the present work are as follows:

i. To formulate the floating beads by ionotropic gelation technique using sodium alginate and HPMC as core polymers, chitosan as coating polymer and sunflower oil as floating aid.

ii. To evaluate the formulated beads for their following physicochemical and in-vitro properties:
   - Preliminary compatibility studies between amoxicillin trihydrate and polymers using FTIR spectroscopy,
   - Appearance,
   - Bead size and % swelling,
   - Weight uniformity,
   - Drug entrapment efficiency (DEE),
   - Surface morphology study by Scanning Electron Microscope,
   - In-vitro floating study,
   - In-vitro evaluation of mucoadhesiveness,
   - In-vitro drug release,
   - In-vitro stability of amoxicillin trihydrate in simulated gastric fluid,
   - In-vitro H. pylori growth inhibition study of the selected formulations,

iii. To evaluate the selected formulations for in-vivo floating.
2.4. References


