5. AIMS AND OBJECTIVES

The therapeutic area in which gastroretentive floating drug delivery system (FDDS) can be explored is the eradication of *Helicobacter pylori* (*H. pylori*), which is now believed to be the causative bacterium for chronic gastritis and peptic ulcers. Although the bacterium is highly sensitive to most antibiotics, its eradication from patients requires high concentrations of drug be maintained within the gastric mucosa for a long duration.

Recommended treatments for first line *H. pylori* eradication are short term proton pump inhibitor (PPI) or ranitidine, bismuth citrate-based triple therapies consisting of clarithromycin (CL) and amoxicillin or a nitroimidazole.

Pantoprazole sodium sesquihydrate (PSS) is a prodrug that inhibits the proton pump and, consequently, the acid release in gastric lumen. This prodrug is used in the treatment of digestive ulcers, gastro esophageal reflux disease and as auxiliary in the eradication of the *H. pylori*. This prodrug reacts in acid medium. When this conversion occurs in the parietal cell canalicular lumen, it is activated by conversion to a cyclic sulfonamide, which is the active form. This conversion must occur inside the gastric parietals cells, so PSS should be absorbed intact by the intestinal tract, needing an enteric drug delivery system to be administered. When the PSS reacts with acid in the stomach lumen before absorption, the substance is degraded and no activity is observed.

The mean clearance of PSS has ranged from 0.7 to 1.3 L kg\(^{-1}\) h\(^{-1}\), and the elimination half life has ranged from 0.9 to 1.9 h. At pH 4.0, PSS exerted bactericidal activity against *H. pylori* at concentrations of 0.06 to 0.25 mg L\(^{-1}\), suggesting that an acid environment may be necessary to activate the drug (Fitton and Wiseman, 1996).

Clarithromycin is a macrolide, orally absorbed, broad-spectrum antibiotic. It is widely used in a standard eradication treatment of gastric *H. pylori* infection combined with a second antibiotic and an acid-suppressing agent like proton pump inhibitors. CL has highest rate of eradication of *H. pylori* in monotherapy *in vivo*, though it is unstable and rapidly undergo degradation in low pH of gastric acid.
There are many reasons for the failure of *H. pylori* eradication with conventional dosage forms of antibiotics. One of the reasons for incomplete eradication may be the degradation of CL by gastric acid. In an effort to overcome this problem, concomitant administration of antimicrobial agents and drugs which inhibit gastric acid secretion such as H$_2$ receptor antagonists and proton pump inhibitors have been tried.

As 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. These conventional delivery systems are single unit dosage forms and they do not remain in the stomach for prolonged period of time. Therefore, in the present study an attempt has been made to design multiparticulate drug delivery systems that not only alleviate the shortcomings of conventional delivery vehicles but also deliver the antimicrobials to the infected cell lines. The absorption of antibiotics into the mucus through the mucus layer (from the gastric lumen) is believed to be more effective for *H. pylori* eradication than absorption through the basolateral membrane, i.e. from blood.

Floating and gastroretentive drug delivery system have been gaining more attention due to its ability to deliver the antibacterial locally at stomach site and enhances local antibiotics concentration and prolongs the residence time of formulation. Majority of the research was focused on floating delivery systems based on CO$_2$ gas generation. The main disadvantage of this delivery system is that the carbon dioxide production gives a hostile environment for the bacterium.

The major objective of this project is to formulate a floating and gastroretentive delivery system of CL for the effective treatment of *H. pylori* based on a multiple floating delivery system using natural polymers and the freeze drying technology to aid floating of the dosage form. The usage of gas forming technique is avoided here for the development of floating delivery system. Freeze drying technology is utilized here to produce floating beads.
The acid suppression by PPI is highly essential to attain maximum efficacy for CL locally in the gastric mucosa. So an attempt is made here to develop an enteric coated delayed release dosage form of PSS for the purpose.

Product optimization tools were effectively utilized to develop formulations in a systematic way. A $3^2$ randomized full factorial design, a statistical tool is being used in this project to optimize the formulations. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed using all possible 9 combinations.

The main objectives of the present study are listed below:

A. To develop a stomach specific multi particulate formulation of CL, this floats in the stomach and releases the antibiotic for longer period of time.
   1. To retain the formulation in the gastric region for longer time by the principle of buoyancy the maximum efficacy of CL.
   2. To enhance the efficacy of CL by providing less degradation in the acidic environment by proton pump inhibition by PSS.
   3. To formulate CL as a multiple unit dosage form for better efficacy than single unit dosage form.

B. To formulate a Eudragit S100 enteric coated PSS formulations using mainly natural polymers such as sodium alginate and low methoxy pectin.
   1. To evaluate the formulation for its physicochemical properties.
   2. To study the drug release characteristics in the alkaline pH and final selection of the best formulation.
   3. To study the enhancement of CL concentration in the gastric mucosa by co-administration of PSS formulation

I. To effectively utilize the $3^2$ full factorial design tool for development and optimization of both CL and PSS formulations.

II. Avoid/ minimize the usage of organic solvents in the formulations to reduce the toxicity of the product.
III. To study the enhancement of CL concentration *in situ* by the formulation of PSS using *Wistar* rats.

IV. To study the gastroretentive property of CL formulation for adequate time for better efficacy by *in situ* gastro retention studies on *Wistar* rats.

V. To study the Pharmacokinetics of CL and *PSS* from the formulations using *albino* rabbits.
SCHEMATIC REPRESENTATION OF THE WORK DONE

Fig. 5.1. Schematic representation of the work done