Chapter 1

Introduction

1.1 INTRODUCTION

Oral route is considered as the most effective route of drug delivery due to ease of administration and better patient compliance. The techniques involved in manufacturing of oral dosage forms are also cost effective. Physiological factor such as gastric motility, pharmaceutical factor such as drug release from the dosage form, physicochemical property of a drug moiety such as solubility at specific pH environment and permeability at specific region of gastrointestinal tract (GIT) are the determinative factors in effectiveness of oral drug delivery system.

The drug absorption pattern along the GIT is determined by the interplay between physicochemical properties of drug and the physiological conditions, which affect the permeation properties of the drug within the different parts of the GIT. Once the drug is given orally, GI motility tends to move the drug through the alimentary canal. For drugs that are given orally, an anatomic "absorption window" may exist within the GIT in which the drug can be efficiently absorbed (Zhou, 2003). An elegant and simple way to improve drug absorption is to hold a drug delivery system above the absorption window and release drug at an appropriate rate. Because most absorption windows are thought to be located in the proximal small intestine, the obvious strategy will be to hold the formulation in the stomach (Talukdar and Fassihi, 2004).

Orally administered conventional dosage form remains for shorter duration in stomach. There are many therapeutic moieties which are intended for local action in stomach (e.g antibiotics against H.Pylori), primarily absorbed in stomach or upper part of small intestine (e.g. Levodpa, furosemide, riboflavin), have poor solubility in an alkaline pH (e.g. diazepam, chlordiazepoxide) and unstable in intestinal and colonic environment (e.g Captopril). Such moieties if delivered through conventional drug delivery system can not remain at the desired site for sufficient duration and may lead to therapeutic failure (Deshpande et al, 1996; Rocca et al., 2003; Conway, 2005; Davis, 2005; Streubel et al., 2006).

Since its discovery in 1982 by Warren and Marshall (leading to their recent Nobel Prize in Medicine) and its confirmation as a pathogen at the end of the 1980s, researchers have attempted in several ways to efficiently eradicate *Helicobacter*

pylori (H. pylori) from the stomach. It is well known that long lasting *H. pylori* infections can lead to severe diseases such as gastric cancers and mucosa associated lymphoid tissue lymphomas (Fischbach et al., 2005). In most countries, *H. pylori* infection is associated with a four to six fold increased risk of gastric cancer. This means that the majority of gastric carcinomas in the world are related to *H. pylori* infection (Warren, 1983; Marshall, 2002). Since 1994, the International Agency for Research on Cancer and the World Health Organization have been considering that *H. pylori* infection is carcinogenic to humans (group 1 carcinogen). Because of the high level of antibiotic resistance to *H. pylori* and the poor patient compliance, new medicines with better effectiveness and simpler regimens are required. It has been suggested that prolonged local availability of antibacterial agents may augment their effectiveness in treating *H. pylori* infection (Cooreman et al, 1993). In particular, *H. pylori* lives deep within the gastric mucus layer and prolonged local application of drug is needed for its sufficient diffusion to the bacteria (Emami et al., 2006). A logical way to improve the effectiveness of therapy is to develop a drug delivery system which can reside in the stomach for longer duration and release drug as long as possible in the ecological niche of the bacterium (Bardonnet et al., 2006). And Gastroretentive Drug Delivery System (GRDDS) is an ultimate remedy.

Gastroretentive formulations have been designed in large part based on various approaches which include low density (Singh and Kim, 2000) and high density dosage forms (Talukdar and Fassihi, 2004); bioadhesive formulations (Moes, 1993; Durig and Fassihi, 2000); formulations which can expand or unfold to a large size and limits its emptying through the pyloric sphincter (Klausner et al, 2003). Gastroretentive formulations can be developed as single unit as well as multiple unit formulations. Multiple unit formulations based on subunits such as minitablets, granules or pellets show numerous advantages over single unit systems such as higher degree of dispersion in the GI tract and reduced risk of systemic toxicity due to dose dumping (Behcgerd and Nielsen, 1978; Follonier and Doelker, 1992). As associated with single unit systems, multiple unit systems do not have drawback of "all or none" emptying pattern from the stomach which is observed due to unpredictable gastric emptying associated with migrating myoelectric complex motility pattern (Whitehead et al., 1998; Talukdar and Fassihi, 2004; Jain et al., 2005). Minimatrices can be manufactured with higher

reproducibility and cost effective approach as compared to other multiple unit systems such as microspheres and pellets (Brabander et al, 2000).

1.2 ANATOMY AND PHYSIOLOGY OF STOMACH

The stomach is divided into four parts namely fundus, body, pyloric antrum and pyloric canal. Fundus forms the upper convex part of the stomach, and body lies between the fundus and pyloric antrum, which can distend enormously along the greater curvature of the stomach. Pyloric antrum is separated from duodenum by the narrow and tubular pyloric canal. The mucosa of empty stomach contains longitudinal folds known as gastric rugae. The stomach is supplied by sympathetic nerves derived from T_6-T_{10} segments of the spinal cord, and parasympathetic nerves derived from vagi. Stimulation of parasympathetic nerves results in increased motility of stomach and secretion of gastric juice containing hydrochloric acid and pepsin (Tortora, 2003)

The physiological behavior of stomach varies, when it is empty or contains food. The nature of the gastrointestinal motor functions is determined mainly by the stimulating effects of food in the GIT. When food enters the stomach, due to vagovagal reflex the muscular tone of the body wall of stomach reduces enabling it to expand outward and accommodating more quantities of food. Weak peristaltic constrictor waves initiated by the basic electrical rhythm, begin in the mid portion of the stomach wall and move towards the antrum at every 15-20s. These constrictor waves intensify as they proceed towards antrum, providing powerful constrictor rings which force the antral contents towards the pylorus at a high pressure. Because of these stomach contractions, the partially digested food is discharged into the small intestine and the undigested food is retropelled into the main part of the stomach for further digestion.

At the end of digestion process, the stomach enters fasting state and begins a cycle called the Interdigestive Myoelectric Motor complex (IMMC). It causes the peristaltic waves to sweep slowly and rhythmically downward along the stomach and small intestine approximately every 2 h, sweeping the excess digestive secretions into the colon and preventing their accumulation in the upper GIT. The IMMC could be divided into four phases.

Phase I: It is a quiescent period lasting from 30 to 60 minutes with no contractions.

Phase II: It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as "house-keeper wave," sweep gastric contents down the small intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between last part of phase III and quiescence of phase I.

The stomach also experiences rhythmic peristaltic contractions known as hunger contractions, when empty. These contractions are powerful in young and healthy individuals with high gastrointestinal tone. The gastric emptying is regulated by neural and hormonal reflexes of the body. Vagal tone, gastrin, cholecystokinin and motilin enhance the gastric motility, while glucagon, secretin, gastric inhibitory peptide and vasoactive intestinal peptide inhibits the distal stomach contractions and there by inhibiting the gastric emptying.

1.3 H.PYLORI INFECTION

1.3.1 Pathophysiology of *H.Pylori* Infection

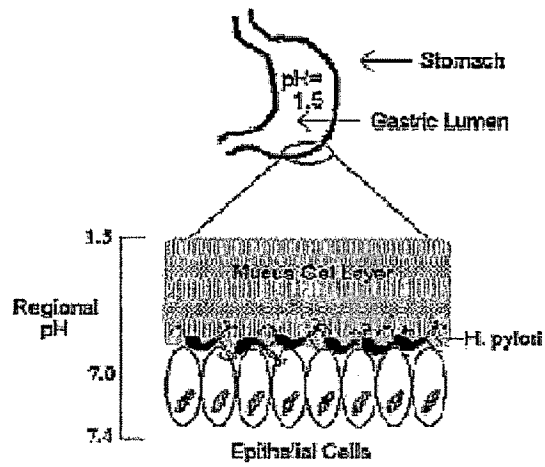


Fig 1.1 H.Pylori infection site in stomach

H. pylori is a Gram-negative, microaerophilic, spiral and flagellated bacterium, with a unipolar-sheathed flagella that provides motility. Its spiral shape and high

motility allow it to penetrate mucus, resist gastric emptying and remain in the host gastric mucosa (Chakraborty, 2001)

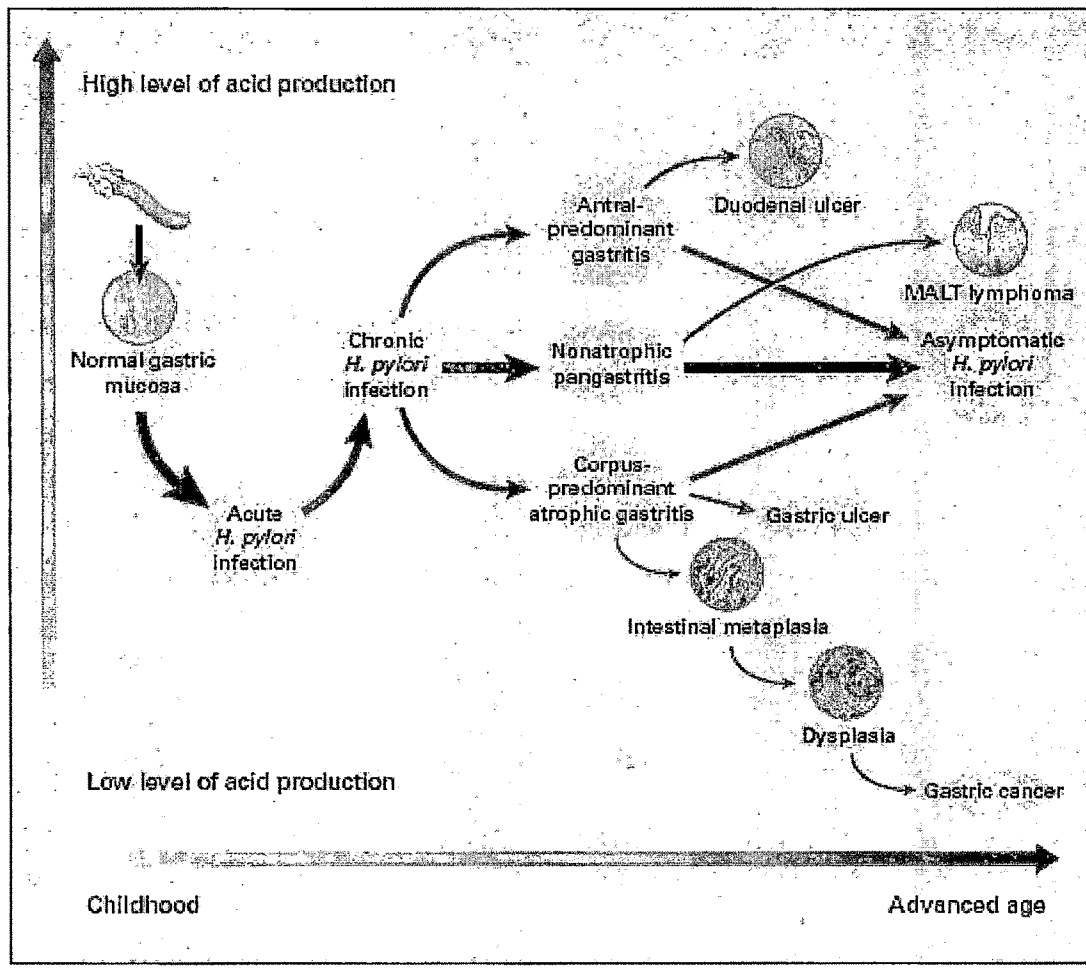


Fig.1.2 Pathophysiological consequences of H.Pylori infection

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 ulcer disease and gastric cancer (WHO report, 1996). About 5,50,000 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 (Murray and Lopez, 1997). *H. pylori* is a very diverse species and cancer risks may be increased with strains having virulence-associated genes, host genetics and environmental factors. Infection with H. pylori occurs predominately in childhood mainly between via oral ingestion of the bacterium.

The major feature of H.pylori infection is progressive injury to the gastric structure and function (Graham, 2000). The bacterium adheres to the gastric epithelial cell, producing a direct injurious effect that is then amplified by production and release of a vacuolating cytotoxin. *H. pylori* produces a variety of enzymes and is characterised by a high urease activity. Urea is broken down into bicarbonate and ammonia that protect the bacterium in the acid environment of the stomach. The levels of ammonium ions produced can be toxic to the gastric superficial epithelial cells and cause epithelial injury. H. pylori urease stimulates inflammatory cytokine production and activates mononuclear phagocytes (Dunn et al., 1997). Although, after colonisation, the host immune defences are stimulated, there is increased secretory IgA detected in the gastric mucosa and raised specific IgG, the infected host is not able to eliminate the organism. Colonisation results in persistent gastric inflammation but the clinical course of infection can be very variable and is influenced by microbial and host factors (Suerbam and Machetti, 2002).

Infection of the stomach with *H. pylori* can be diagnosed by endoscopic biopsy of the gastric mucosa or with noninvasive methods. Selection of an appropriate test depends on the clinical situation. Noninvasive methods available for the diagnosis of *H. pylori* infection include serologic tests and breath tests for urea. Chronic infection results in a circulating antibody response that can be detected by enzyme linked immunosorbent assay or other rapid serologic tests. Serologic testing is the least expensive method for the diagnosis of infection in an untreated patient, but it is not useful for early follow up testing after treatment (Walsh and Peterson, 1995).

1.3.2 Treatment of H.Pylori Infection

Use of triple therapy is regarded as a gold standard in *H. pylori* eradication and has been so verified in various reports. First-line *H. pylori* eradication therapy should be a 7-day triple therapy using a proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC), combined with clarithromycin and amoxicillin or metronidazole. Second-line therapy should be with a 7-day quadruple therapy using a PPI (b.i.d.), bismuth (120 mg q.i.d.), metronidazole (500 mg t.i.d.) and tetracycline (500 mg q.i.d.). Pronase is used as an adjuvant treatment, a mucolytic agent, had a significant additive effect in curing *H. pylori* infection when administered with other therapeutic agents. Although pronase has no *in vitro*

bactericidal activity, it could improve the gastric mucosal delivery of antibiotics by removing or disrupting the surface mucous gel layer of the stomach (Perri et al., 2003).

Failure of primary anti H.Pylori therapy results in a high rate of antimicrobial resistance. This necessitates a search for new regimens to cure *H. pylori* infection. Antos et al (Antos et al., 2006) have carried out the study to evaluate the efficacy and tolerability of a new levofloxacin-containing 7-day triple therapy and to compare it with that of standard triple therapy in patients with known *H. pylori* susceptibility to metronidazole and clarithromycin. Results of this study suggest that the new levofloxacin triple therapy may also be an option in patients with metronidazole and clarithromycin resistant *H. pylori* strains.

H. pylori is very sensitive - in vitro and in vivo – to amoxicillin. It acts by inhibiting the synthesis of bacterial cell walls, it has topical or intraluminal activity, and although stable in an acid environment, it is most active at a neutral pH. Unlike ampicillin, a related compound, amoxicillin is actively secreted from blood into the gastric juice, and intravenous amoxicillin can therefore eradicate *H. pylori* infection. Bacterial resistance to amoxicillin has not been reported. The side effects of amoxicillin include diarrhea, allergic reactions, and pseudomembranous colitis (Walsh and Pterson, 1995) .

Clarithromycin is a macrolide antibiotic that inhibits bacterial protein synthesis. Its antibacterial spectrum is similar to that of erythromycin, but it is more acid-stable, better absorbed, and more effective against *H. pylori* (Walsh and Pterson, 1995)

Stool antigen tests have been extensively evaluated in pre and post treatment settings. Urea breath test has been used as predictor of bacterial load, severity of gastric inflammation and response to eradication treatment. Several serological markers have also been used as indicator of gastric mucosa status (Dzierzanowska-Fangrat et al., 2006).

Levofloxacin and ranitidine bismuth citrate based regimen was evaluated and proved as an alternative to quadruple therapy in patients with previous omeprazole-clarithromycin-amoxicillin failure (Gisbert et al., 2007).

1.4 APPROACHES TO PROLONG GASTRIC RESIDENCE TIME OF A DOSGE FORM

Gastric residence time of a dosage form can be prolonged by various ways (Talukdar and Fassihi, 2004; Bardonnet et al., 2006). Depending on the principle which impart gastroretentive feature, the dosage forms can be categorized as:

1.4.1 High-density systems

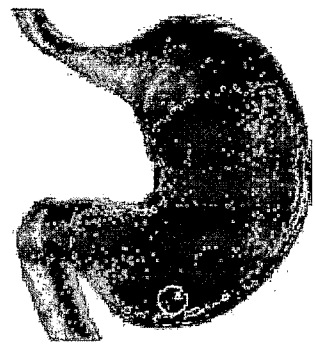


Fig 1.3 Principle of high density system

Density of a drug delivery system is an important factor influencing its gastric residence time. High-density devices use their weight as a retention mechanism. When the density of the system is larger than that of the gastric juice, the device settles down to the bottom of the stomach. However, so far, no successful approach has been described for a gastroretentive system being based only on high density. In contrast, it has been reported that such devices did not significantly extend the gastric residence time (Streubel et al., 2006).

1.4.2 Floating systems

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug candidate (Bardonnet et al 2006). Floating phenomenon may be based on effervescent or non effervescent principle.

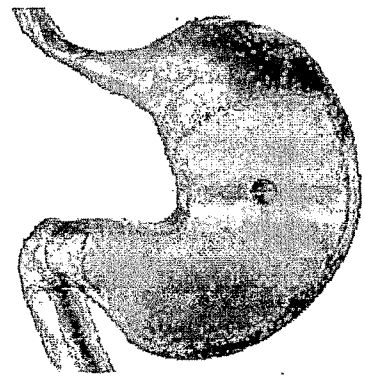


Fig 1.4 Floating formulation in stomach

1.4.3 Hydrodynamically balanced systems (HBS)

The architecture of designing HBS is based on the principle that devices with specific gravity less than that of the gastric juice will float in the stomach and retain the drug over there for an extended period thereby increasing the total residence time in the GIT. The reduction of specific gravity of the system can be obtained by incorporating fillers of low density within the system (Khan, 2001).

These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. HPMC is the most commonly used. Also hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, agar, carrageenans or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin 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 (Bardonnet et al 2006).

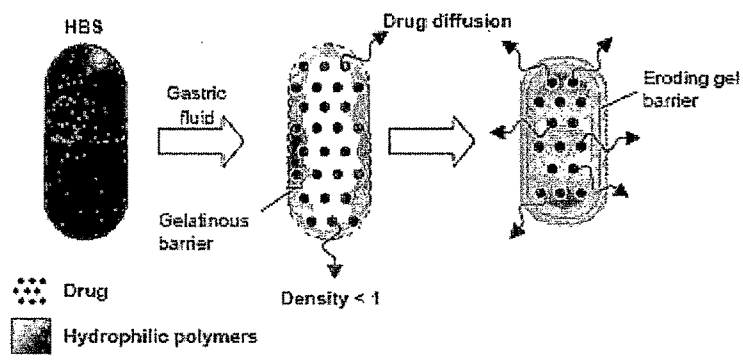


Fig 1.5 Hydrodynamically balanced system

1.4.4 Raft-forming systems

In this system a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2 bubbles on contact with gastric fluid. Formulations also typically contain antiacids such

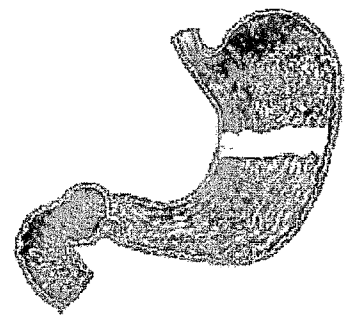


Fig 1.6 Raft forming system

as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment (Bardonnet et al 2006).

1.4.5 Low-density systems

Drug delivery systems having capability to float immediately following contact with gastric fluids are highly desirable. Immediate floating can only be achieved if the low density of the device is provided from the beginning. Compared with systems initially settling down, the risk of premature emptying from the stomach is greatly reduced. Low density feature is provided by entrapment of air (e.g. hollow chambers) or by incorporation of low-density materials, such as fatty substances or oils or foam powder (Streubel et al., 2006).

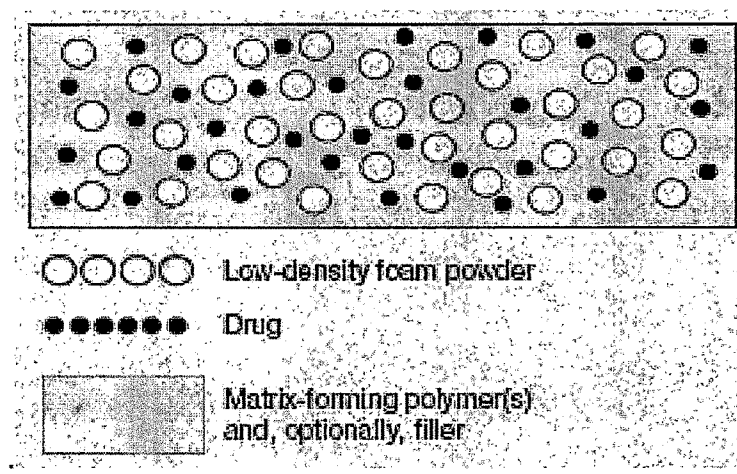


Fig 1.7 Low density system

1.4.6 Expandable systems

One of the approach to retain a dosage form in the stomach is by increasing its size above the diameter of the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release (Bardonnet et al., 2006). Approximately, the dosage form should be > 13 mm. In order to facilitate swallowing, dosage forms should be designed with an initially small size which after coming in contact with gastric fluid significantly increase in size. The expanded state should be achieved fairly quickly, in order to prevent premature emptying through the pylorus. On the other hand, the systems should also guarantee their clearance from the stomach after predetermined time intervals, in order to avoid accumulation following multiple administrations (Streubel et al., 2006).

Fig 1.8 Gastroretentive mechanism for swelling formulation

The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occurs because of osmosis. Unfolding takes place due to mechanical shape memory i.e. the GRDF is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake. In the stomach, the carrier is dissolved and the GRDF unfolds or opens out, to achieve extended configuration (Klausner et al., 2003)

1.4.7 Superporous hydrogels

Superporous hydrogels swell within minutes to the equilibrium swollen state regardless of their size. The fast swelling property is based on water absorption through open porous (>100 micrometer) structure by capillary force. Superporous hydrogels swell faster but have weak mechanical strength. For application in gastroretentive drug delivery system, it should have sufficient mechanical strength so that it can withstand contractile movements in stomach. This criteria

is met by third generation superporous hydogels which have high swelling and have elastic properties which imparts mechanical strength which is sufficient to withstand pressure by gastric contraction (Bardonnet et al., 2006; Omdian at al., 2005).

1.4.8 Mucoadhesive or bioadhesive systems

A mucoadhesive used in oral drug delivery should have sufficient adhesiveness with the mucus layer so that it can prolong its residence time at desired site. It should be compatible with active entity and allow drug release. It should not create cytotoxicity or any irreversible alterations of the mucosal surface and should be biodegradability (Dodou et al., 2005).

Mucoadhesion mechanism is described by electronic, adsorption, wetting and diffusion theories. Electronic theory describes mucoadhesion due to electron transfer between mucus and mucoadhesive. As per adsorption theory attraction between mucus and mucoadhesive is achieved via molecular bonding caused by secondary forces such as hydrogen and van der Waals bonds. The wetting theory correlates the surface tension of mucus and mucoadhesive. As per this theory, interfacial energy plays an important role in mucoadhesion. Physical entanglement of the protein and polymer chains of the mucus and the mucoadhesive and their interpenetration to sufficient depth is important for proper mucoadhesion. Overall mucoadhesion phenomenon is a combined result of all these theories. First, the polymer gets wet and swells (wetting theory). Then, noncovalent (physical) bonds are created at the mucus– polymer interface (electronic and adsorption theory). Then, the polymer and protein chains interpenetrate (diffusion theory) and entangle together, to form further non-covalent (physical) and covalent (chemical) bonds (electronic and adsorption theory). Mucoadhesive efficiency depends upon ability of the mucoadhesive to swell, ability to form molecular bonds (covalent and non-covalent) with the mucus layer and their spatial conformation due to the entanglement of chains. (Dodou et al., 2005).

1.4.9 Magnetic systems

In this system the dosage form contains a small internal magnet. The formulation is specifically kept in stomach by placing an external magnet is placed on the abdomen over the position of the stomach (Bardonnet et al., 2006).

1.4.10 Drug delivery systems with specific interaction with *H.Pylori*

Adherence of pathogenic bacteria to target cells is an important step in the pathogenesis of many bacterial diseases. Adherence is also important for entry of organisms into epithelial cells. Phosphatidyl ethanolamine (PE) is a predominant lipid in the antrum of the human stomach and functions as a receptor for H. pylori adhesion. Correlation of the ability of H. pylori to adhere to eukaryotic cells with the detected presence of the PE receptor, however, underscores the importance of this lipid as a major receptor in promoting H. pylori adhesion to intact cells. PE bacterial adhesin exists as a cell surface associated ligand. On the basis of the above facts, antiadhesion drug delivery system based on PE has been developed as a receptor-mediated drug delivery system for use in blocking adhesion of Helicobacter and thereby preventing the sequelae of chronic gastric infections (Umamaheshwari and Jain, 2004).

1.5 FACTORS AFFECTING EFFICACY OF A GASTRORETENTIVE SYSTEM:

Gastric residence time of a dosage form is affected by various physiological and pharmaceutical factors (Streubel et al., 2006; Garg and Sharma, 2003).

1.5.1 Physiological Factors

i. Fed or unfed state: GI motility is characterised by periods of strong motor activity or the migrating myoelectric complex (MMC) in fasted state. The MMC sweeps undigested material from the stomach. If the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

ii. Nature of meal and its caloric content: feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

iii. Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states (e.g. diabetes, Crohn's disease).

iv. Gender: Mean ambulatory GRT in males is less compared to females regardless of the weight, height and body surface.

v. Age: elderly people, especially those over 70, have a significantly longer GRT;

vi. Disease state: Diabetes and Crohn's disease, etc may alter GI motility.

1.5.2 Pharmaceutical factors

i. Density, size and shape of the dosage form

ii. Single or multiple unit formulation: Unexpected evacuation of single unit system from stomach may lead to complete failure of therapy. Such all or none principle can be avoided in multiple unit formulations. Also these systems allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

iii. Simultaneous administration of drugs such as anticholinergic agents (e.g. atropine, propantheline), opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride) which affect GI motility.

1.6 LITERATURE REVIEW

High-density systems

Rouge et al studied pharmacokinetic parameters of atenolol when it was administered through a high-density multiple-unit capsule, floating multiple-unit capsule and an immediate-release tablet. Atenolol was chosen as a model drug because of its poor absorption in the lower gastrointestinal tract. The two multiple-unit dosage forms were composed of compressed minitablets and had sustained release properties. The bioavailability of the two gastroretentive preparations with sustained release characteristics was significantly decreased when compared to the immediate-release tablet. The study showed that it was not possible to increase the bioavailability of a poorly absorbed drug such as atenolol using gastroretentive formulations. (Rouge et al, 1998)

Floating systems

Calcium is absorbed primarily in duodenum due to presence of active absorption sites i.e. calcium-binding protein. Due to this unique absorption characteristic, the gastric residence time of a calcium-containing formulation should be prolonged to permit calcium to reach the site of active absorption in a controlled manner. Floating formulation has been developed and optimized for controlled release of calcium (Li et al., 2001). Optimisation exercise has been done by central composite Box-Wilson design with HPMC loading, citric acid loading and magnesium stearate loading as formulation variables. Data has been analysed by response surface methodology. Dissolution study and floating kinetics were performed on the formulations. The dissolution data was fitted to the Power Law. All 3 formulation significantly affected release properties while only HPMC loading was found to be significant for floating properties. Optimized formulation delivered calcium at the release rate of 40 mg/hr.

Formulation components play crucial role in imparting floating properties to a designed formulation. A continuous floating monitoring system consisting of an electric balance interfacing with a PC was designed to perform the continuous monitoring of floating kinetics of drug delivery system and studying role of formulation variables (Li et al., 2002). Floating formulations were designed for stomach specific delivery of calcium. Formulation variables, such as different grades of HPMC, different ratio HPMC / Carbopol and presence or absence of

magnesium stearate were evaluated using Taguchi design and the effects of these variables were subjected to statistical analysis. Results of this study demonstrated that the hydrophobic agent, magnesium stearate, significantly improved the floating capacity of the delivery system. A high-viscosity polymer had a beneficial effect on the floating properties of the GFDDS. Different types of polymers with the same viscosity, i.e., K4M and E4M, on the other hand, did not demonstrate any significant impact on the floating properties of the GFDDS. Carbopol, although it could introduce another gastroretentive mechanism into the delivery system, was found to have a negative impact on its floating behavior.

US Patent (Talwar et al., 2005) describes a formulation providing a combination of temporal and spatial control of drug delivery for effective therapeutic results. The pharmaceutical composition comprised of a drug, a gas generating component, a swelling agent, a viscolyzing agent and optionally a gel forming polymer. The swelling agent involved was superdisintegrant (e.g., cross-linked polyvinylpyrrolidone or sodium carboxymethylcellulose). After coming in contact with gastric fluid, initially a viscolyzing agent and thereafter gel forming polymer form a hydrated gel matrix which entraps the gas bubbles, imparts floating feature in the formulation.(tablet or capsule) and keeps it in upper part of small intestine (spatial control). Hydrated gel matrix simultaneously creates a tortuous diffusion path for the drug, resulting in sustained release phenomenon (temporal control).

Deshpande et al have reported development of controlled release matrix tablet with gastroretentive feature which expand in contact with gastric fluid and remains expanded for eighteen to twenty hours. Chlorpheniramine maleate and riboflavin were used as water soluble and poorly soluble model drugs. Tablets were coated with Eudragit. Carbopol provided firm structure to the swollen tablet. Carbonates present in the formulation provided initial alkaline microenvironment for carbopol to gel. Eudragit coating provided support for the matrix to remain intact (Deshpande et al., 1997).

Calcium pectinate gel beads capable of floating in the gastric condition have been designed and tested by Sriamornsa et al (Sriamornsa et al., 2004). The gel beads containing edible oil were prepared by either being gently mixed or

homogenized an oil phase and a water phase containing pectin, and then extruded into calcium chloride solution with gentle agitation at room temperature. The gel beads formed were then separated, washed with distilled water, and dried at 37°C for 12 hours. Effect of oil type, percentage of oil, and type of pectin on morphology and floating properties was investigated. Results suggested that oil-entrapped calcium pectinate gel beads were promising as a carrier for intragastric floating drug delivery.

Orlistat, a lipase inhibitor for obesity management, acts by inhibiting the absorption of dietary fats. It has short half-life of 2 h and requires administration thrice a day. Its main sites of action of are stomach and pancreas. Due to short half-life, dosing frequency and gastric side effects at high concentration, it was considered as a potential candidate for floating controlled release formulation. Jain et al (Jain et al., 2006) have prepared floating microspheres of orlistat by using calcium silicate as a porous carrier and Eudragit S as polymer. Ethanolic solution of orlistat was prepared and calcium silicate was dispersed in it. The slurry was ultrasonicated to entrap the drug inside pores of porous carrier. Modified emulsion solvent diffusion technique was used for preparation of microspheres. Eudragit was dissolved in 2:1 solution of ethanol : dichloromethane. Orlistat absorbed porous carrier was added into it and sonicated using probe sonicator. Resulting suspension was poured into a 200-mL aqueous PVA solution at 40^0C. The emulsion/suspension was stirred at high speed for 3 hours and the microspheres were separated by filtration. Effect of various formulation and process variables on the particle morphology, micromeritic properties, in vitro floating behavior, percentage drug entrapment, and in vitro drug release was studied. Transit of floating microspheres in GIT was evaluated in albino rabbits by gamma scintigraphy.

Bisphosphonates are best absorbed from duodenum and jejunum and these also cause gastric irritation. Incorporation of bisphosphonates in the lipid reduces gastric irritation. Only gastric retention with sustained release allows the drug to reach the duodenum and jejunum and improves the availability of bisphosphonates. Risedronate sodium and Gelucire floating matrices were prepared using melt solidification by Chauhan at al (Chauhan et al., 2004). The matrix systems were prepared by melting Gelucire® and Caprol PGE 860 at 10

°C above the melting point of Gelucire®. Risedronate sodium (30 mg) was added to the molten mass under stirring. The homogeneous molten mixture was filled into Licap capsules using a preheated glass Pasteur pipette and allowed to solidify at 4 °C. The capsules were equilibrated to room temperature for 6 h before evaluation. The matrices were evaluated for in vitro and in vivo floating ability and in vitro drug release. In vivo floating ability was studied by gamma scintigraphy in healthy male human volunteers. Ageing of the matrices was studied by differential scanning calorimetry, hot stage polarizing microscopy, scanning electron microscopy and in vitro drug release.

Murata et al (Murata et al., 2003) have prepared alginate gel beads containing ethylcellulose and evaluated for buoyancy, in vitro and in vivo drug release profile and drug targeting specificity in the gastric mucosa. In vivo studies have shown that metronidazole concentration in gastric mucosa after administration of ALECs was greater than that observed with administration of metronidazole solution. The results suggest that alginate beads may become an effective strategy for delivering drug to the gastric mucosa.

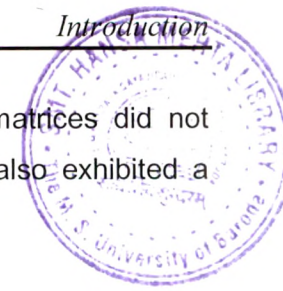
Furosemide is reported to have specific absorption site in stomach. Ozdemir et al, have developed controlled release floating dosage form of furosemide for enhancing its bioavailability. This drug moiety is less soluble in acidic atmosphere of stomach. Hence its solubility was enhanced by preparing an inclusion complex with beta-cyclodextrin. Floating tablets were prepared in the form of bilayer floating tablets. Dissolution studies were performed using continuous flow-through cell method. In vivo studies were carried out in human volunteers by x ray technique using $BaSO_4$ as radiocontrast medium. The formulations stayed in stomach for 6 h. Area under plasma concentration-time curve values obtained with floating dosage form were about 1.8 times those of the conventional
tablet (Ozdemir et al., 2000).

Captopril, an angiotensin-converting enzyme inhibitor, is stable at pH 1.2 and a becomes unstable and undergoes degradation at high pH. Captopril floating tablets have been prepared, by non aqueous granulation using ethanol, for stomach specific drug delivery (Nur and Zhang, 2000). Two viscosity grades of

HPMC (K4M CR and K15M CR) and Carbopol 934P were used. Drug release best fit both the Higuchi model and the Korsmeyer and Peppas equation, followed by first order kinetics. Tablet hardness had no or little effect on release kinetics but significantly affected buoyancy of tablets.

Wei et al (Wei et al., 2001) have developed bilayer floating tablets of Cisapride, which has better solubility in acidic medium, by granulation technique using ethanol as solvent. First layer consisted of sodium bicarbonate, starch 1500 and HPMC K100M CR while second layer contained cisapride, HPMC K15M CR, MCC and starch. Tablets having 12 mm diameter and 4.5 mm thickness were prepared. Drug release studies were carried out in SGF and SIF. Results indicated that increase in HPMC level decrease drug release.

Floating matrix tablets of atenolol have been developed to prolong gastric residence time (Srivastava et al., 2005). Atenolol is poorly absorbed from the lower GIT. Hence an increase in GRT may increase its bioavailability. Tablets were prepared by direct compression technique, using HPMC (K15M, K4M), guargum and sodium carboxymethylcellulose, alone or in combination, and other standard excipients. Tablets were evaluated for hardness, thickness, weight variation, swelling index, floating capacity and in vitro drug release. Guar gum and Sodium carboxy methyl cellulose based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. MCC reduces floating lag time in HPMC K4M based tablets. MCC has a porous structure and may have more entrapment of air, which helps the tablets to float. Effervescent moieties significantly reduce floating lag time. However larger amounts of effervescent may cause quicker depletion of tablet matrices with an expected decrease in floating duration. HPMC takes more time in swelling and is also able to impart tablet integrity. Incorporation of HPMC K4M to formulations containing Sodium CMC and guar gum increased the floating duration. Guar gum and sodium CMC significantly increased swelling indices. HPMC grade also affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC K15M. Effervescents have no significant effect on swelling index. Formulations based on guar gum and sodium CMC have higher rate of drug release as compared to HPMC based formulations. Incorporation of



water insoluble dibasic calcium phosphate into HPMC K4M matrices did not affect drug release significantly. Varying the amount of MCC also exhibited a non-significant effect on drug release (Srivastava et al., 2005).

Floating properties of coated sustained release Levodopa minitablets have been enhanced (Goole et al., 2008). Drug containing gas-generating cores were prepared by melt granulation, compressed and then coated with a flexible polymeric membrane. Eudragit RL30D was used as a film former and acetyl triethylcitrate was used as a plasticizer. The coating level was 20%w/w. The optimally coated minitablets had lag time of 10 min and remained buoyant for more than 13 h, regardless of the pH of the test medium. Release of levodopa was sustained for more than 12 h regardless of the pH. The studies shown that drug release increased with increase in stirring rate in accordance with the decrease in the
thickness of the stagnant layer as described in the Noyes–Whitney equation. Floating properties of the minitablets were significantly affected due to pH. Floating lag time significantly changed with test medium pH (1.2 and 3.0). At higher pH more quantity of tartaric acid was required to obtain less floating lag time. Release rate of the levodopa increased with an increase in amount of tartaric acid incorporated into the formulation. It may be due to pH-dependent solubility of levodopa.

Dave et al. (Dave et al., 2004) developed floating drug delivery system of ranitidine hydrochloride. Effect of citric acid and stearic acid on drug release and floating properties has been systematically investigated by 32 full factorial design. Guar gum, xanthan gum, and HPMC were evaluated for gel-forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. Results of full factorial design indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of ranitidine hydrochloride. Similarity factor f2 was applied between the factorial design batches and the theoretical dissolution profile and the formulation with highest similarity was selected as optimum formulation.

Sawicki developed floating pellets verapamil and norverapamil and determined its pharmacokinetics in human volunteers. Solubility of verapamil in the stomach is several times higher than in the small intestine. This feature make it suitable candidate for stomach specific delivery. Floating pellets filled in capsule were assumed to reside in stomach for several hours by floating mechanism and gradually release the drug in a controlled way. Verapamil hydrochloride floating pellets were prepared by using sodium hydrocarbonate, microcrystalline cellulose, lactose and povidone K-30. the pellets were coated with mixture of Eudragit NE 30D, Eudragit L-30D, triethyl citrate, talcum and distilled water. Area under plasma concentration time curve was higher for floating pellets as compared to conventional formulation (Sawicki, 2002).

A drug delivery system for Sotalol hydrochloride having floating and gastric adhesiveness properties has been developed (Jimenez-Castellanos et al., 1994). The tablets were prepared by using sodium carboxymethyl cellulose, hydroxypropyl cellulose and bicarbonate. Sodium stearyl fumarate was used as a lubricant. Prepared tablets were evaluated for floating feature, drug release parameters and bioadhesion.

El-Gibaly has prepared floating microcapsules for melatonin by ionic interaction of chitosan and a negatively charged surfactant, sodium dioctyl sulfosuccinate. The DOS/chitosan complex formation was confirmed by IR, DSC and XRD studies. The characteristics of the floating microcapsules were compared with the conventional non-floating microspheres prepared by cross linking of chitosan and sodium tripolyphosphate. Effect of crosslinking time, DOS and chitosan concentrations and drug/polymer ratio on microcapsule properties was evaluated. Microcapsules prepared using DOS solution were having round hollow core with 31.2 to/59.74% incorporation efficiency. Chitosan concentration and drug/polymer ratio had a remarkable effect on drug entrapment in DOS/chitosan microcapsules. Melatonin released form the microspheres by by zero order kinetics in SGF. Drug release from TPP/ chitosan non floating microcapsules was instantaneous while from DOS/chitosan microcapsules was retarded 8h. DOS/chitosan microcapsules showed less swelling and no dissolution in S.G.F. for more than 3 days, whereas, TPP/chitosan microspheres were were swollen and lost their integrity within 5 h (El-Gibaly, 2002).

Sustained release formulation with floating and swelling features has been prepared for stomach specific delivery of ofloxacin (Chavanpatil et al., 2005). Different polymers, such as psyllium husk, HPMC K100M, crospovidone and its combinations have been tried in order to get the desired sustained release profile over a period of 24 h. Sodium bicarbonate has been used as gas generating agent to achieve buoyancy. Prepared formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and in vitro drug release profile. Dimensional stability of the formulation was found to increase with increasing psyllium husk concentration. In vitro drug release rate increased with increasing amount of crospovidone and betacyclodextrin while it decreased with increasing HPMC concentration. Pharmacokinetic parameters of the optimum formulation were compared with marketed product.

Gastroretentive sustained release delivery system having floating, swellable and bioadhesive feature has been reported by Chvanpatil et al. Various release retarding polymers like psyllium husk, HPMC K100M and a swelling agent, crosspovidone in combinations were tried and optimized in order to sustain drug release for 24 h. HPMC K100M and psyllium husk together significantly increased bioadhesive property of the developed formulation as well as their increasing concentration decreased drug release. In vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type. Profiles of optimum and marketed formulations were compared and *f2* factor was 91.12 indicating similarity of the dissolution profiles.

Sustained release ketoprofen floating microparticles have been prepared by emulsion-solvent diffusion technique. Four different ratios of Eudragit S100 with Eudragit RL were used for preparing microparticles. The drug retained in the floating microparticles decreased with increase in Eudragit RL content. Drug release rates were generally low in 0.1 N HCl especially in presence of high content of Eudragit S100 while in phosphate buffer pH 6.8, high amounts of Eudragit S100 tended to give a higher release rate. The formulation containing Eudragit S100 and Eudragit RL in 1:1 ratio exhibited high percentage of floating particles (El-Kamel et al., 2001).

Alfuzosin is preferentially absorbed in the proximal part of the gastrointestinal tract and, in particular, jejunum appear to be the main region for absorption. Hence to enhance bioavailability of this moiety, gastro-retentive matrix formulation having for zero-order delivery has been designed (Liu and Fassihi, 2008). Two systems containing PEO, HPMC, sodium bicarbonate, citric acid and PVP were dry blended and compressed into triple layer and bi-layer composite matrices. Textural characteristics of each layer, the composite matrix as a whole and floatation potential were determined under conditions similar to dissolution. Dissolution profile of prepared and marketed formulation were compared. Similarity factor of 68 and 71 was observed for PEO and HPMC based matrices respectively.

Multiparticulate floating-pulsatile drug delivery system has been developed, using porous calcium silicate and sodium alginate, for time and site specific drug release of meloxicam (Sharma and Pawar, 2006). Floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in the upper GI tract after a definite time period of no drug release. Meloxicam was dissolved in chloroform and calcium silicate was dispersed in it with shaking. Solvent was evaporated under vacuum and dried dispersion was obtained. Drug adsorbed calcium silicate powder was used to prepare calcium alginate beads by ionotropic gelation method using 3^2 factorial design. Entrapment efficiency of different formulations varied from 70% to 94%. Formulations show a lag period ranging from 1.9 to 7.8 h in acidic medium followed by rapid release of meloxicam within 1h in simulated intestinal fluid.

Hollow polycarbonate microspheres of piroxicam capable of floating on simulated gastric and intestinal fluids have been prepared by solvent evaporation technique (Joseph et al., 2002). About 95% drug incorporation efficiency was achieved. Drug release in SGF increased with time upto 8h and very little was found to be released up to 24 h. There was no burst release. Release was faster in intestinal fluid. Results of this study shown that the prepared microspheres were capable of sustained delivery of the drug for longer periods with increased bioavailability.

The feasibility of preparing floating pellets by melt pelletization has been investigated (Hamdani et al., 2006). The pellets were prepared in a high shear mixer. Formulations
were based on a mixture of Compritol and Precirol as lipidic binders and sodium bicarbonate as a gas-generating agent. The floating ability of the pellets was evaluated in vitro. Good floating capabilities were obtained for formulations containing the gas-generating agent in both the inner matrix and the outer coating layer of the pellets.

Floating pellets of riboflavin were prepared using the melt pelletization process. Formulations were prepared by using mixture of Compritol and Precirol as meltable binders and sodium bicarbonate and tartaric acid as gas-generating agents. Good floating abilities were obtained by using the gas-generating agents in both the inner matrix and the outer coating layer of the pellets. Floating capability was evaluated by using the resultant weight apparatus and by counting floating pellets at the surface of beakers containing 0.1N HCl solution. In vivo evaluation was carried out in healthy human volunteers. An increase of urinary excretion of riboflavin was observed when the volunteers were dosed with the floating pellets, especially after feeding. As riboflavin has a narrow window of absorption in the upper part of small intestine, this phenomenon could be attributable to the gastric retention of floating pellets (Hamdani et al., 2006)

Chitosan and carboxymethylcellulose sodium interpolymer complexes have been prepared using the novel method "tablets-in-capsule" for stomach specific drug delivery of clarithromycin. Influence of molecular weight of chitosan and the proportion of chitosan and carboxymethylcellulose sodium on physical properties and clarithromycin release was investigated. Swelling was dependent on chitosan molecular weight, medium pH and on polymer proportion. Swelling kinetics at pH 1.2 were close to Fickian diffusion whereas at pH 4.2 were non-Fickian. Clarithromycin release were dependent on pH and on polymer proportion (Gomez-Burgaz et al., 2008).

Intra-gastric floating in situ gelling system has been prepared for controlled delivery of amoxicillin for the treatment of H.Pylori associated peptic ulcer. The gelling systems were prepared by dissolving varying concentrations of gellan

gum in deionized water which contained sodium citrate. To this, different concentrations of amoxicillin and calcium carbonate was added and dissolved. Gellan gum and calcium carbonate concentration significantly affected in vitro drug release. The in vivo *H. pylori* clearance efficacy of prepared formulation and amoxicillin suspension was tested in infected Mongolian gerbils following repeated oral administration. Polymerase chain reaction technique and microbial culture method was used in this evaluation. Developed in situ gelling formulation showed a significant anti-*H. pylori* effect in vivo. For eradication of *H. pylori*, ten times less amoxicillin was required when administered in the form of gelling system as compared to amoxicillin suspension (Rajinikanth et al., 2007).

Eudragit coated chitosan alginate floating microspheres were prepared by ionotropic gelation method using calcium carbonate as gas generating agent. Chitosan incorporation into gelation medium to enhance drug encapsulation efficiency and eudragit coating was done to sustain drug release. The GI transit of optimized formulation, along with non floating system prepared by identical material, was evaluated in healthy human volunteers by gamma-scintigraphy. Drug encapsulation efficiency of chitosan incorporated alginate microspheres was much higher than that of the calcium alginate microspheres and eudragit coating coating significantly extended drug release. Prolonged gastric retention time of over 5 h was achieved in the volunteer for the optimized coating floating microspheres (Maa et al., 2008).

For stomach specific sustained delivery of Captopril, floating tablets have been prepared using Metolose SH 4000 SR and sodium bicarbonate and effect of their varying proportions has been studied (Jiménez-Martínez et al., 2008). Effect of two different compaction pressures was also tested. Other variables such as kinetics of hydration volume, floating time and matrix density was were also studied. Matrices compacted at high pressure required sodium bicarbonate for its floating. Increase of matrix polymer proportion increased the maximal hydration volume as well as the time to attain this maximum. Hydration volume of matrices increased with the inclusion of sodium bicarbonate in the formulation. Inclusion of sodium bicarbonate in the formulation decreased drug release which was supposed be due to obstruction of the diffusion path due to carbon dioxide bubbles.

Multi-unit floating calcium alginate gel beads were synthesized with calcium alginate, sunflower oil and a hydrophilic or hydrophobic drug through an emulsification/gelation process. Incorporation of oil imparted floating feature in the alginate beads. Ibuprofen, niacinamide and metoclopramide hydrochloride were tested in the study. Ibuprofen, a hydrophobic drug, was released in a sustained manner for 24 h, due to the oil partitioning. Other two hydrophilic drugs required suitable modification in the beads for sustaining drug release (Tang et al., 2008).

Yang et al. (Yang et al., 2004) developed multiple-unit floating microspheres with microballoons inside by using xanthan gum and gelatin by a water in oil emulsification method. Theophylline was used as a model drug. Four formulations with different ratios of the two polymers were prepared. Ratio of the two polymers influenced the size distribution, encapsulation efficiency and drug release appreciably. Increasing amounts of gelatin decreased drug-encapsulation efficiency and drug-release rate.

Floating nifedipine hollow microspheres have been reported by Soppimath et al. (Soppimath et al., 2006). The microspheres were prepared by solvent diffusion–evaporation technique in the presence of coexcipients like polyethylene glycol, dibutyl phthalate, and poly(ε-caprolactone) using ethyl acetate as a dispersing solvent. These coexcipients have shown their effect on floating, physicochemical properties as well as drug release characteristics of the hollow microspheres.

Multiple unit systems avoid the all-or-none gastric emptying nature of single-unit systems. A controlled release floating microspheres of repaglinide have been prepared by emulsion solvent diffusion technique using calcium silicate as carrier and Eudragit S as polymer. Incorporation of calcium silicate in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. The designed system could possibly be advantageous in terms of increased bioavailability (Jain et al., 2005).

A freeze-dried calcium alginate multiple-unit floating dosage form has been developed which demonstrated favourable in vitro floating characteristics. In vivo transit of this system was monitored by gamma-scintigraphy. This study was carried out in healthy human volunteers. The results of this study suggest that, in

the fed state, this formulation has potential for sustained drug delivery for either local or systemic purposes (Whitehead et al., 1998).

Floating acrylic resin microspheres with an internal hollow structure have been reported Lee et al. (Lee et al., 1999). The microspheres were prepared by a solvent diffusion and evaporation method. The yield of microspheres depended on the diffusion rate of ethanol and/or isopropanol in the organic phase. They were successfully produced when amixture of ethanol and isopropanol was used instead of ethanol alone. Several different drugs with various physico-chemical properties were used as model drugs for encapsulation and release tests (Lee et al., 1999).

Triple layer matrix technology to control drug release for oral administration is presented by Yang and Fassihi (Yang and Fassihi, 1996). Directly compressed ripple layer asymmetric floatable system was prepared by using polyethylene oxide polymers of various molecular weight. Theophylline was a model drug. The core layer contains the active drug while external layers with different thickness, composition, and erosion rates are designed to delay the hydration of the middle layer, restrict the early drug diffusion only through cylindrical side surfaces of the tablet, and provide controlled drug release.

Expandable systems

Levodopa is having narrow absorption window in upper parts of intestine. Hence it is desirable to deliver it continuously to upper parts of the intestine in order to maintain sustained therapeutic levels. To achieve this goal controlled release gastroretentive dosage based on unfolding polymeric membranes have been prepared by Klausner et al. (Klausner et al., 2003). Formulations comprised of an inner layer composed of a ethylcellulose : levodopa matrix (1:1) framed with rigid polymeric strips (L-polylactic acid - ethylcellulose, 9:1) covered on both sides by two outer (shielding) layers (composed of enzymatically hydrolyzed gelatin, methacrylic acid copolymer type B, glycerine, and glutaraldehyde (48:30:20:2)). The exterior side of the shielding layers was covered with a thin anti-adhering layer of microcrystalline cellulose powder. All membranes used to construct these multilayer formulation were prepared by dissolving the polymers in suitable solvents with subsequent casting and solvent evaporation. The layers were

attached to each other using minute amounts of methylene chloride and ethyl alcohol. In vivo studies were carried out in beagle dogs to determine location of dosage form and pharmacokinetic parameters. Prepared formulations were administered to beagle dogs pretreated with carbidopa. Location of the formulation in GIT was determined by X- ray technique and blood samples were collected for studying pharmacokinetic parameters. Formulation optimization was carried out based on the in-vitro in-vivo correlation following modifications of the release rates which adjusted by various membrane thicknesses and drug loads.

Controlled release gastroretentive unfolding dosage, Accordion Pill, has been prepared to increase the bioavailability of riboflavin in humans. It is composed of three layers. Two envelope membranes that sandwich between them the third layer composed from the frame that affords the physical properties to the device and the drug reservoir in the center. Gastric residence time of pill was assessed by magnetic resonance imaging and found prolonged up to 10.5 h with significant elevation in bioavailability (Kagan et al., 2006).

U.S.Patent 5,443,843 describes gastric retention system for controlled release of drugs to the gastrointestinal tract. The system consists of one or more non-continuous compressible elements called retention arms and an attached controlled release device. In the expanded form it resists gastrointestinal transit (Curatolo and Lo, 1995).

Wong et al have patent for the invention of dosage form for the prolonged drug delivery in stomach. The delivery system is made up of active agent and a polymer matrix formed of a mixture of a swellable, water soluble polymer that expands when in contact with fluids in the gastric environment and a water insoluble hydroattractant. Swelling of the hydrogel is constrained to provide a rigid or semi-rigid section in the dosage form that facilitates the dosage form remaining in the stomach of a subject over a prolonged period of time (Wong et al., 2000)

US Patent 6,290,989 describes a device capable of controlling release of active compounds in GIT with delayed pyloric passage due to a component which get expanded on contact with gastric juice. Device core was surrounded by a

polymer covering which is permeable to gastric juice and active compounds (Asmussen et al., 2001).

US Patent 6,476,006 also describes expandable formulation comprising a non-hydrated hydrogel, a superdisintegrant and tannic acid suitable for delivering a therapeutic bis-phosphonate such as alendronate to the stomach of a patient over extended period. (Flashner et al., 2002).

Superporous hydrogels

Superporous hydrogels with improved swelling and mechanical properties were improved by adding crosscarmellose sodium during hydrogel synthesis. The gastric retention property of the prepared hydrogel composites was tested in dogs. The composites were placed in a hard gelatin capsule for oral administration. Under the fasted condition, the superporous hydrogel composites remained in the stomach for 2–3 h while in fed state these remained in the stomach for more than 24 h (Chen et al., 2000).

A pH-sensitive chitosan / polyvinyl pyrrolidone based controlled drug release system for amoxicillin delivery has been prepared (Risbud et al., 2000). Semi-interpenetrating polymer hydrogel network was synthesized by crosslinking chitosan and PVP blend with glutaraldehyde. Air- and freeze-dried systems were studied for antibiotic release. Results of the study shown that freeze-dried membranes could serve as potent candidates for antibiotic delivery in an acidic environment.

Mucoadhesive or bioadhesive systems

Ranitidine is absorbed from upper parts of GIT. Directly compressed ranitidine tablets with gastric bioadhesive feature have been prepared by direct compression method (Adhikary and Vavia, 2008). Dextrose was used as a channeling agent as it is highly water-soluble excipient which gets solubilized and released from the matrix when it gets hydrated. This phenomenon creates necessary pores and channels for the initial drug release. Ranitidine is unstable at lower pH. Alkaline microenvironmental pH was maintained by incorporating magnesium oxide as one of the formulation component. It reacts with water to produce magnesium hydroxide which is highly alkaline in nature and maintains microenvironmental pH about 6.5 till 12h. Throughout the release process, the

relaxation mechanism predominates over diffusion mechanism probably because carbopol and HPMC are water-soluble polymers capable of high hydration capacities.

US Patent by Inagi et al reports invention of a coated gastric and/or duodenal adhesive pharmaceutical composition. It contains a medicament acting at the stomach and/or duodenum and inactive ingredients selected from water insoluble polymers, polyglycerin fatty acid esters, lipids and waxes, with a polymer having adhesive capacity onto the surface of the mucosa of a digestive tract under acid conditions and separates from the mucosa of the digestive tract in neutral or alkaline conditions. This composition adheres only to the mucosa of the stomach and/or duodenum and releases the medicament over long hours so that sufficient effects are available by a small amount of the medicament (Inagi net al., 2003).

Magnetic systems

The magnetic dosage forms contain a small internal magnet. An extracorporal magnet controls the GI transit of the dosage form. Peroral depot tablets, containing 200 mg of acyclovir, with internal magnets have been developed (Groninga et al., 1998). An extracorporal magnet was used to prolong the gastric residence times of the dosage forms and to influence the duration of absorption of acyclovir. Plasma concentration-time profiles were estimated in healthy human volunteers. Though there was inter-subject variability, acyclovir plasma concentrations following peroral administration of magnetic depot tablets in the presence of extracorporal magnet were significantly higher. It clearly indicates that gastroretention of the dosage enhance acyclovir bioavailability.

Gastroretentive dosage forms against H. pylori

For effective eradication of *H.pylori infection* amoxicillin containing mucoadhesive gliadin nanoparticles have been prepared by Umamaheshwari et al by using desolvation method. The effect of process variables such as gliadin concentration and initial drug loading on particle size, shape, percent payload, percent entrapment efficiency, in vitro release profile, and mucoadhesive properties of the developed formulation were studied. In vitro antimicrobial activity of the developed nanoparticles was evaluated by growth inhibition studies on an isolated *H pylori* strain. They have studied in vivo gastric mucoadhesive property

in albino rats by rhodamine isothiocyanate–entrapped formulation. *H pylori* clearance study was carried out in infected Mongolian gerbils. This study shown that the amoxicillin nanoparticles eradicated *H pylori* more effectively than amoxicillin because of the prolonged gastrointestinal residence time attributed to mucoadhesion. In vivo mucoadhesion study revealed that more than 80% of the gliadin nanoparticles remained in the stomach after 2.5 hours. So it was expected that amoxicillin released from the nanoparticles would penetrate the mucus and effectively eradicate and kill the *H pylori* in stomach mucosa (Umamaheshwari et al., 2004).

Mucoadhesive microspheres of amoxicillin have been prepared by using ethylcellulose as matrix and carbopol 934P as mucoadhesive polymer (Liu et al., 2005). Microspheres were prepared by emulsification/evaporation method. Ethylcellulose was dissolved in acetone. Amoxicillin and Carbopol 934P were added to the ethyl cellulose solution under magnetic stirring and the mixture was blended for 24 h. This suspension was slowly dispersed in light liquid paraffin containing Span 80 and emulsified for 30 min. Acetone was evaporated by using vacuum pump until the microspheres were formed which were washed with petroleum ether and vacuum dried at room temperature. In vitro release test showed that amoxicillin released faster in pH 1.0 (HCl) than in pH 7.8 phosphate buffer. It was found that amoxicillin entrapped within the microspheres could keep stable. In vitro and in vivo mucoadhesive tests showed that the prepared microspheres adhered strongly to gastric mucous layer. Prepared microspheres and amoxicillin powder were orally administered to rats for determining amoxicillin concentration in gastric tissue. In vivo H. pylori clearance tests were carried out in H. pylori infectious BALB/c mice. Results shown that the prepared microspheres had a better clearance effect than amoxicillin powder.

Triple layer matrix formulation has been reported for stomach specific drug delivery of tetracycline, metronidazole and bismuth salt for treatment of *Helicobacter pylori* associated peptic ulcers. HPMC and PEO were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer while bismuth salt was incorporated in one of the outer layers for instant release. Results demonstrated that sustained delivery of

tetracycline and metronidazole over 6–8 h can be easily achieved while the tablet remained afloat (Yang, et al., 1999).

Ali et al (Ali et al., 2006) prepared hydrodynamically balanced capsules and microspheres of ofloxacin for intragastric ofloxacin delivery for treatment of H.pylori infection. The hydrodynamically balanced capsules were prepared by physical mixing of various grades of HPMC and PEO alone and in combinations. Cellulose acetate pthalate, liquid paraffin, and ethyl cellulose were used as release modifiers. The capsules prepared with PEO WSR 60K and drug coated with 2.5% ethyl cellulose gave the best in vitro release. Various grades of Eudragit and PEO were used in combination for formulating floating microspheres by solvent diffusion technique for preparation of multiple unit system.

Chitosan-based mucoadhesive microspheres of clarithromycin for prolonged clarithromycin delivery have been reported (Majithiya and Murthy, 2005). Microspheres were prepared by emulsification technique using glutaraldehyde as a crosslinking agent. Drug to polymer ratio, concentration of crosslinking agent and crosslinking time was varied to optimize with respect to drug entrapment and mucoadhesion. Prepared microspheres were evaluated for particle size, drug entrapment, swelling kinetics, in vitro mucoadhesion using rat stomach membrane and in vitro drug release studies. In vitro permeation studies across rat stomach membrane were carried out to determine diffusion parameters and drug retention in the stomach membrane of the formulation and the plain drug. Finally in vivo performance of microsphere formulation in comparison to plain drug was evaluated by pharmacokinetic studies in albino rats. Results of the study demonstrated good mucoadhesion of the microspheres with the stomach mucosa as well as higher accumulation of drug in the stomach membrane. Microspheres also exhibited sustained release of drug. Thus chitosan microspheres appear, technically, promising mucoadhesive drug delivery systems for delivering clarithromycin to treat stomach ulcers

Umamaheshwari et al have prepared cellulose acetate butyrate coated cholestyramine microcapsules as a intragastric floating drug delivery system having floating and mucoadhesive property. Ion-exchange resin particles can be loaded with bicarbonate followed by acetohydroxamic acid and coated with

cellulose acetatebutyrate by emulsion solvent evaporation method. Effect of cellulose acetatebutyrate : drug-resin ratio (2:1, 4:1, 6:1 w/w) was studied on the particle size, floating time and drug release. Cholestyramine microcapsules were characterized for shape, surface characteristics, and size distribution; cholestyramine/acetohydroxamic acid interactions inside microcapsules were investigated by X-ray diffractometry. Longer floating time was observed with a higher polymer:drug resin complex ratio (6:1). Drug release rate was higher in SGF than in SIF. The in vivo mucoadhesion studies were performed with rhodamineisothiocyanate by fluorescent probe method. Prepared microcapsules exhibited prolonged gastric residence via mucoadhesion. These results suggest that cellulose acetatebutyrate coated microcapsules could be a floating as well as a mucoadhesive drug delivery system (Umamaheshwari et al., 2003a).

In an effort to augment the anti-*H. pylori* effect of acetohydroxamic acid , floating polycarbonate microspheres were prepared by o/w emulsion solvent evaporation technique. The effect of polycarbonate concentration on the morphology, particle size, entrapment efficiency and drug release rate was studied In-vitro and in-vivo growth inhibition studies were performed on isolated cultures of *H. pylori* and *H. pylori*-infected Mongolian gerbils, respectively. Required dose of acetohydroxamic acid was effectively reduced by a factor of 10 in case of polycarbonate microspheres (Umamaheshwari et al., 2003b).

Chitosan microspheres have been prepared, by ionic cross linking for stomach-specific drug delivery of tetracycline for effective treatment of H.Pylori infection (Hejazi and Amiji, 2002). Chitosan microspheres were prepared by ionic cross-linking and precipitation with sodium sulfate. Tetracycline was loaded by two different methods. In first method tetracycline was mixed with chitosan solution before the cross-linking and precipitation and in second method it was incubated with pre-formed microspheres for 48 h. tetracycline release and its stability was examined in different pH medium at 37 °C. prepared microspheres were spherical shape with an average diameter of 2.0–3.0 micrometer . only 8% drug got incorporated by first method while a maximum of 69% was loaded be second method. About 30% of the released drug was found to degrade at pH 1.2 in 12 h.

In the present context, phosphatidyl ethanolamine liposomes anchored polyvinyl alcohol xerogel beads (lipobeads) bearing acetohydroxamic acid have been

developed as a receptor-mediated drug delivery system for use in blocking adhesion of H.pylori and thereby preventing the sequelae of chronic gastric infections. PVA beads containing AHA were prepared by emulsification followed by low temperature crystallization method. Surface acylation with fatty acid chain was accomplished by treating PVA bare beads with palmitoyl chloride. The completion of this reaction was characterized by attenuated total reflection Fourier transform infrared spectroscopy (ATR-FTIR) which confirmed the formation of an ester bond. Final formation of lipobeads was accomplished by combining acylated PVA beads with a PE liposome suspension. To confirm the specific binding propensity of lipobeads towards the PE specific surface receptors of H. pylori, in situ adherence assay and radiolabelling assay with human stomach cells and KATO-III cells was performed. In both of these studies, pretreatment of H. pylori with lipobeads completely inhibited the adhesion of H. pylori to human stomach cells and KATO-III cells. These assays could serve as suitable in-vitro models for the study of binding efficacy of lipobeads with H. pylori surface receptors. In addition, the antimicrobial activity of the formulations was evaluated by growth inhibition (GI) studies with isolated H. pylori strain. The inhibitory efficacy of lipobeads was significantly higher compared to that of PVA bare beads. These results suggest that lipobeads could be a potential targeted drug delivery system in the treatment of H. pylori (Umamaheshwari and Jain, 2004).