CHAPTER 1

INTRODUCTION

1.1. Introduction

Oral route of delivery, though not always the most optimal route of delivery, remains the route of choice for majority of clinical applications due to ease of administration, patient compliance, flexibility in dosage form design and ease and low cost of manufacturing [Lordi, 1987]. Majority of the marketed oral formulations are immediate release (IR) dosage forms (DFs) and have many drawbacks associated with them. Drugs, with short half-life, require frequent administration to achieve the desired therapeutic results. Multiple daily dosing often is inconvenient for the patient and can result in missed doses, made-up doses and patient noncompliance with the therapeutic regimen [Chien, 1981]. In case of multiple dosing regimens, sequential blood plasma level peaks and troughs of the therapeutic entity make it difficult to attain steady state condition. This reflects less than optimal drug therapy as it may lead to under/ over medication and precipitation of adverse or toxic effects especially of a drug with narrow therapeutic index [Lordi, 1987].

An ideal dosage regimen for the management of any disease condition is the one that immediately attains desired therapeutic concentration of drug in plasma or target tissues/ organs, and maintains it constant for the entire course of treatment [Chien, 1981]. Controlled release (CR) products are designed to provide an immediate release of drug to produce quickly the desired therapeutic effect, followed with gradual and continual release of additional amounts of drug in a controlled fashion, at a predetermined rate, duration and location to achieve and maintain optimum therapeutic blood levels of drug [Lordi, 1987; Jantzen and Robinson, 1996]. This leads to many advantages like, improved patient compliance and convenience due to reduced dosing frequency; reduction in fluctuation in steady-state levels leading to better therapeutic efficacy and reduction in local or systemic side effects; maximum utilization of drug therapy enabling reduction in total amount of dose administered; uniform absorption from gastrointestinal tract (GIT); and good margin of safety especially in the treatment/ management of chronic disease conditions. In addition to the therapeutic and patient benefits, controlled release dosage forms (CRDFs) offer commercial opportunity to the formulator through intellectual property, brand differentiation, and recognition [Brahmankar and Jaiswal, 1995; Hoffman, 1998].

The Biopharmaceutical Classification System (BCS), introduced by the United States, Food and Drug Administration (US FDA) in 1995, has categorized drugs in terms of their solubility, intestinal permeability and anticipated bioavailability [Davis, 2005]. Under BCS, simple CRDFs for Class-I compounds (high solubility and high permeability) with short half-life, improves the overall bioavailability and therapeutic efficacy. However, for other compounds belonging to classes II, III & IV, which suffer from either low solubility or low permeability issue or both, a simple CRDF may not result in acceptable oral bioavailability. In such cases, suboptimal (very short and highly variable) absorption kinetics have been reported due to the dependence on the transit time of the dosage form [Hwang et al., 1998; Garg and Sharma, 2003]. A large number of therapeutic agents belonging to classes II, III & IV of BCS display variable absorption in different regions of the human GIT or site-specific absorption, especially in the upper portion of GIT [Wilding and Prior, 2003]. To obtain optimal therapeutic benefits for these compounds, CRDFs with a prolonged residence time at/ above the desired absorption window becomes a prerequisite [Wilding and Prior, 2003; Davis, 2005].

Dosage forms with a prolonged gastric residence time (GRT), referred to as gastroretentive dosage forms (GRDFs), provide better therapeutic option with improved oral bioavailability for drugs with variable or site-specific absorption from different regions of the human GIT [Garg and Sharma, 2003]. Recent scientific and patent literature show increased interest towards gastroretention of drug formulations for drugs with issues pertaining to solubility, region-specific absorption or variable absorption, local action in the stomach, and for delivery through specialized vesicular or nanoparticulate systems [Klausner et al., 2003a].

This introductory chapter is aimed at discussing various aspects of gastroretentive controlled release dosage forms (GR-CRDFs) like, (i) Significance of GR-CRDFs; (ii) Biological aspects of GR-CRDFs; (iii) Various approaches for design of GR-CRDFs; and (iv) Evaluation techniques of gastroretentive dosage forms. It also elaborates on the main objectives of the present endeavour involving designing of oral GR-CRDFs for better therapeutic efficacy of two candidate drugs namely celecoxib and acyclovir.

1.2. Gastroretentive controlled release dosage forms

An increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups because they can provide optimal therapy in the following cases where conventional CRDFs may fail:

(a) Gastroretentive controlled release dosage forms (GR-CRDFs) have been found to be effective in the delivery of drugs that have slow rate of dissolution, or are sparingly soluble or insoluble. For drugs with low solubility, the time available for drug dissolution in the upper portion of the GIT (major absorption site) becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently, often several times per day [Klausner et al., 2003a]. After only a short period of less than 6 h, the CRDF leaves the upper GIT and the drug is released in non-absorbing distal segments of the GIT [Klausner et al., 2003a; Davis, 2005]. GR-CRDFs by virtue of being able to retain the formulation in the upper portion of the GIT for long duration can provide continuous, controlled delivery of these drugs at the absorption site, thus significantly extending the bioavailability of the drug. Thus, they not only prolong dosing intervals, but also increase therapeutic efficacy and patient compliance better than the existing CRDFs [Gutierrez-Rocca et al., 2003].

(b) Another potential application of GRDFs is in the treatment of local ailments of the stomach. GRDFs can significantly improve the pharmacotherapy of the diseases of stomach and upper GIT through local site specific drug release. Such systems can result in high drug concentrations at the gastric mucosa, making it possible to effectively treat peptic/ duodenal ulcers, gastritis and oesophagitis, eradication of *Helicobacter pylori* from the submucosal tissue of the stomach, reduce the risk of gastric carcinoma and also aid in the administration of non-systemic, controlled release antacids [Spickett et al., 1993; Fabregas et al., 1994; Katayama et al., 1999; Garg and Sharma, 2003; Dave et al., 2004]. GRDFs with mucoadhesive properties can provide increased penetration of drug into the mucus layer, and therefore increased drug concentration and prolonged activity at mucus-epithelial interface [Yang et al., 1999; Conway, 2005].

(c) Many drugs exhibit region specific absorption, which can be related to differential drug solubility and stability in different regions of the intestine as a result of changes in environmental pH (e.g. idarubucin), degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile [Macheras et al., 1995; Hwang et al., 1998; Siegmund et al., 2003; Tamura et al., 2003; Kakar et al., 2004]. For drugs absorbed by active transport mechanisms involving carriers (e.g. ACE inhibitors, certain antibiotics and some polar compounds) and pump systems (e.g. acyclovir, vitamin B, ions, sugars, and amino acids) lead to their uptake from very specific sites [Bardelmeijer et al., 2000]. This limited absorptive site can affect the overall oral

bioavailability of such drugs due to the relatively short transit time of the conventional CRDF in these anatomical segments of GIT. GR-CRDFs can be very effective for drugs with narrow absorption windows (i.e. stomach or upper GIT), enabling continuous supply of drug to its absorption sites in the upper GIT and extending the absorption phase [Hoffman and Stepensky, 1999; Garg and Sharma, 2003].

(d) GR-CRDFs are useful in case of drugs that are poorly soluble in the alkaline intestinal pH but have high solubility in the acidic environment of the stomach (e.g. acyclovir) or that have non-concentration dependent pharmacodynamics (e.g. ß-lactam antibiotics) [Chien, 1981].

(e) GRDFs can also be exploited in case of drugs that have undesirable/ adverse activities in the colon (e.g. penicillin derivatives, cephalosporins and ß-lactamase inhibitors) or are degraded in the colon (e.g. idarubucin) and thus, should not reach the colon [Klausner et al., 2003a].

(f) In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteinoid microspheres and pharmacosomes, etc. In this case the frequency of dosing may be the same, but the GRDFs alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability. For example, a significant increase in the bioavailability of furosemide multiparticulate floating dosage form has been reported, compared with commercially available and enteric products [Garg and Sharma, 2003; Klausner et al., 2003b].

Representative examples of certain class of drugs that show suboptimal efficacy when formulated as IR/ CRDFs but show improved efficacy when formulated as gastroretentive devices are given in Table 1.1 [Chien, 1981; Babu and Khar, 1990; Cook et al., 1990; Hilton and Deasy; 1992; Menon et al., 1994; Kohri et al., 1995; Wu et al., 1997; Rouge et al., 1998a; Rouge et al., 1998b; Roth et al., 2000; Li et al., 2003; Klausner et al., 2003a; Gutierrez-Rocca et al., 2003; Garg and Sharma, 2003; Davis, 2005].

Not all drugs are suitable for being formulated as GR-CRDFs. Examples include drugs that irritate the stomach lining or cause gastric lesions (e.g. conventional non-steroidal anti-inflammatory drugs like, aspirin); drugs that are unstable in acidic environment (e.g. benzyl penicillin, chloramphenicol palmitate and azithtromycin); drugs that conjugate in the gut wall (e.g. isoproterenol); drugs that are predominantly metabolized by metabolic enzymes present in intestinal wall and/ or liver (e.g. isoproterenol, norepinephrine and testosterone); drugs that are absorbed equally well throughout the GIT (e.g. isosorbide

dinitrate); and drugs that are too polar to cross phospholipid bilayer (e.g. aminoglycosides) [Gutierrez-Rocca et al., 2003].

Table 1.1: List of drug candidates that show improved efficacy when formulated as GR-CRDFs

Drug/ therapeutic regimen related issue	Specific indication/ property	Class of drug	Representative examples
Sparingly soluble or insoluble	-	Antiviral	Acyclovir
	-	Antifungal	Griseofulvin
	-	NSAIDs	Nimesulide and Celecoxib
Absorbed primarily in the stomach	Weakly acidic drugs	NSAIDs	Nimesulide and Celecoxib
Higher solubility in the stomach in comparison to intestine	-	Antiviral	Acyclovir
Required for local action in upper GIT	*Helicobacter pylori* infection in the stomach	Antibiotics	Amoxicillin, Clarithromycin, Metronidazole and Tetracycline
	Treating stomach and duodenal ulcers, gastritis and oesophagitis	H_2-blockers	Cimetidine, Famotidine, Nizatidine and Ranitidine
		Proton pump inhibitors (PPIs)	Esomeprazole, Lansoprazole, Omeprazole, Patoprazole and Rabeprazole
		Cytoprotective agents	Bismuth subsalicylate, Sucralfate and Rebamipide
		Non-systemic antacid	Calcium carbonate
		Combination drug regimens	e.g. Bismuth + Metronidazole + Tetracycline + H2 Blocker; or Bismuth + Metronidazole + Clarithromycin + PPI
	Reducing the risk of gastric carcinoma		Docetaxel and Cisplatin
Narrow absorption window in upper part of GIT/ absorbed by active transport	-	Immunosuppressant	Cyclosporin
	-	Antiviral	Acyclovir and Ganciclovir
	-	Antifungal	Griseofulvin
	-	Antibiotics	Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines
	-	Antidiabetic	Metformin
		Antiparkinson's	Levodopa
	-	Peptide and protein drugs	Calcitonin, Erythropoietin, Vasopressin, Insulin, Low-molecular-weight heparin, Protease inhibitors and Luteinising hormone-releasing hormone analogues
	Highly polar substances (lower membrane permeability; absorbed by facilitated transport process)	-	Vitamin B (e.g. riboflavin), Ions, Sugars, Amino acids and Many antibiotics
Degraded in the colon	-	Anticancer	Idarubucin
	-	ß$_1$-blocker	Metoprolol
Drugs that have non-concentration dependent pharmacodynamics	-	ß-lactam antibiotics	Penicillin derivatives, Cephalosporins, Monobactams, Carbapenems and ß-lactamase inhibitors
Toxic to the microbial flora of the colon	-	ß-lactam antibiotics	Penicillin derivatives, Cephalosporins, Monobactams, Carbapenems and ß-lactamase inhibitors
Incorporated into vesicles	-	Peptide and protein drugs	Calcitonin, Erythropoietin, Vasopressin, Insulin, Low-molecular-weight heparin, Protease inhibitors and Luteinising hormone-releasing hormone analogues

	-	Diuretic	Furosemide

1.3. Biological aspects of GR-CRDFs

To comprehend the considerations taken in the design of GRDFs and to evaluate their performance, the relevant anatomy and physiology of the GIT; gastric motility and emptying rate of food and dosage form from the stomach; and factors affecting GRT must be fully understood [Klausner et al., 2003a]. Following sections briefly discuss the above aspects.

1.3.1. Anatomy and physiology of the stomach/ GIT

The GIT is essentially a muscular tube about nine meters long that runs through the middle of the body from the mouth to the anus. It includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the GIT has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations in each region. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GIT [Gutierrez-Rocca et al., 2003].

Stomach: Anatomically, the stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm [Wilson and Washington, 1989]. Its size varies according to the amount of distention with a resting empty volume of only 25-50 ml [Rubinstein et al., 1988] to a fully distended volume of up to 1500 ml following a meal [Bannister, 1995]. It is composed of the following parts: fundus (just below the opening of the esophagus into the stomach), body (the central part), and the antrum. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum. The pyloric sphincter has a diameter of 12.8±7 mm in humans [Salessiotis, 1972] and acts as a sieve or mechanical stricture to the passage of large particles into duodenum [Hasler, 1995]. The fundus and the body store food temporarily, secrete digestive juices and propulse chime (a milky mixture of food with gastric juices) to the antrum. The antrum grinds and triturates food particles and regulates the secretion of hydrochloric acid as well as ensures emptying of food into the intestine [Hasler, 1995].

The gastric pH under fasting condition is approximately 2.0 (with a range of 1.0-3.0), but there are short periods (approx. 7±6 min) characterized by higher pH values. Food buffers neutralize gastric acid, thus increasing the pH up to about 6.5 during food ingestion [Klausner et al., 2003a]. After food ingestion is completed, the pH rapidly falls back below 5.0 and then gradually declines to fasting state values within a few hours [Dressman et al., 1990]. It is reported that about 20 % of the elderly population, are hypochlorhydric, i.e. with

reduced gastric secretion [Russell et al., 1993]. Gastric emptying time is usually 1 to 2 h in fasted state, but can be extended to over 14 h if fed state conditions are maintained.

Duodenum: It is the first part of the small intestine, located between the stomach and the jejunum (the middle part of the small intestine). After the food combine with stomach acid, they move down into the duodenum where they mix with bile from the gall bladder, and digestive juices from the pancreas. The duodenal pH is about 6.1 [Dressman et al., 1990] and its epithelial surface contains transporters for peptides [Ogihara et al., 1999] and metals [Cousins and McMahon, 2000; Barley et al., 2001]. The transit time in the duodenum is relatively very short (less than 1 min). Absorption of vitamins, minerals, and other nutrients begins in the duodenum [Hwang et al., 1998].

Small intestine: The small intestine has a large surface area of 463 m^2, comparable to the area of a basketball court [Read and Sugden, 1987]. Due to its large surface area, it acts as the primary absorption site of water, ions, vitamins and nutrients such as amino acids, fats and sugars. In addition, the digestion of fats, peptides and sugars occurs in this segment of the GIT. The pH of the small intestine is 6.0-7.0 [Kararli, 1995]. In humans, the small intestine transit time of 3±1 h, needed for drug formulation or meal to pass from the stomach to the ileo-caecal junction is relatively constant and is unaffected by food [Davis et al., 1986; Davis et al., 1993; Kararli, 1995].

Colon: The colon lacks villi and thus has limited surface area and absorption properties. Despite of lesser surface area, certain drugs, especially peptide molecules, water and ions are well absorbed from colon [Rubinstein et al., 1988; Rubinstein, 1995; Rubinstein et al., 1997]. In fasted subjects, a dosage form can reach the colon in 4-5 h, but the transit through the colon is much longer and can be 20 h or more [Wilson and Washington, 1989; Davis, 2005].

1.3.2. Gastric motility and emptying of food from the stomach

The motility of the stomach is mostly contractile, which causes food grinding into smaller particles, mixing with gastric juices, forward and backward movements of gastric contents and emptying, with all of the actions occurring together [Wilson and Washington, 1989]. There is a marked difference between motility in the fasting state and the fed state. The motoric activity in the fasting state, termed interdigestive myoelectric motor complex (IMMC), is approximately a 2 hour cycle of peristaltic activity that is generated in the stomach and progresses aborally to the ileo-caecal junction [Klausner et al., 2003a]. Its aim is to clear the stomach and the small intestine of indigested debris, swallowed saliva and sloughed epithelial cells [Hasler, 1995].

It is composed of four phases:

(a) Phase I lasts 45-60 min, which is quiescent, with rare low amplitude contractions;

(b) Phase II with a length of 30-45 min, has intermediate amplitude contractions [Minami and McCallum, 1984], and involves bile secretion [Gruber et al., 1987];

(c) Phase III, also termed as 'housekeeper wave' (since it serves to sweep undigested materials out of the stomach and down the small intestine), extends for 5-15 min. It is initiated in the stomach in most cases (71 %), or in the duodenum [Hasler, 1995]. This phase is characterized by very high amplitude contractions, with a frequency of 4-5 per min [Rubinstein et al., 1988], and maximal pyloric opening [Ehrlein, 1988]. This enables efficient evacuation of the stomach contents (fasting contents and indigestible debris);

(d) Phase IV lasts for less than 5 min and connects between the maximal amplitude contractions to the basal phase [Minami and McCallum, 1984].

The ingestion of food particles rapidly interrupts the IMMC cycle and initiates the digestive phase. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions [Gutierrez-Rocca et al., 2003]. The motor activity in the fed state is induced 5-10 min after ingestion of the meal. Its phasic contractions are similar to those seen during Phase II of the IMMC, and persist as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with a usual time span of 2-6 h, and more typically, 3-4 h [Klausner et al., 2003a]. The duration of the contractions is dependent on the physicochemical characteristics of the ingested meal. Generally, a meal of 450 kcal will interrupt the fasted state motility for about 3-4 h. It is reported that the antral contractions reduce the size of food particles to = 1 mm [Hasler, 1995] and propel suspended fine particles through the pylorus every 20 sec to the duodenum. This controlled rate enables proper digestion and absorption of the food in the small intestine [Wilding, 2000]. The food particles in the size range of 1-2.4 mm are passed with the calorie content of the solid meal. Food particles larger than this size are generally retained in the stomach by the retropulsion reflex of the distal antrum [Kelly et al., 1973; Ehrlein, 1990; Shalaby et al., 1992a]. However, it has been shown that ingestible solids = 7mm can spontaneously empty from the fed stomach in humans [Gutierrez-Rocca et al., 2003].

In the fed state, the gastric emptying rate is slowed since the onset of IMMC is delayed, i.e. feeding results in a lag time prior to the onset of gastric emptying [Wilson and Washington, 1989]. Larger object are retained by the stomach during the fed pattern but are allowed to

pass into duodenum during Phase III of the IMMC. It is thought that the ability of the stomach to grind the food into smaller size is enhanced by the fed pattern and/ or by the presence of food. The fasted state emptying pattern is independent of the presence of any indigestible solids in the stomach.

1.3.3. Emptying of DFs from the stomach

The emptying of food and dosage forms from the stomach follows different mechanisms. Non-disintegrating DFs (resembling indigestible solids) when administered in the fasting state, are not retained in the stomach for more than 2 h due to the IMMC [Klausner et al., 2003a]. On the other hand, in the fed state stomach retention time of non-disintegrating DFs depends mostly on the DF size and also on the composition and the caloric value of food [Dressman et al., 1998]. Indigestible spheres smaller than 1 mm in diameter freely pass into the intestine, often at rates faster than solid nutritive food. Therefore, while designing a GR-CRDF using microencapsulation technique, where the normal particle size is in micron range, it should be ensured that it floats in the gastric contents immediately upon ingestion. Spheres with diameters of 1-2.4 mm pass with the calorie containing components of a solid meal [Hasler, 1995].

It has been postulated that very small particles can also get trapped in the folds of the stomach and between the villae of the small intestine. In a reported study the GI transit of very small particles (in the range of 70-80 µm, 1-10 µm and 500 nm) were investigated in the human gut using gamma scintigraphy. The results showed that the particles in all the three size ranges had similar transit behaviours [Davis, 2005].

In general, the gastroretention of DFs and in particular large DFs, is longer in the fed state in comparison to the fasting state [Klausner et al., 2003a]. Large DFs are retropelled from the pyloric-antrum for further digestion and evacuation at the end of the fed state, or are retained until the arrival of the subsequent ‘housekeeper wave’. In such cases, the GRT becomes a function of the length of the digestive process. Thus theoretically, continuous feeding can prolong GRT of the DF for more than 24 h [Read and Sugden, 1987].

Studies have been reported that were aimed at identifying the cut-off size above which the DF will be automatically retained in the stomach for prolonged periods of times. Large DFs, such as 13 mm diameter non-disintegrating tablets, were retained in the stomach for 171±29 min, almost an hour more than 7 mm tablets, after a light breakfast of 360 kcal [Khosla and Davis, 1990]. It was suggested that 7 mm tablets empty during the fed state while 13 mm tablets are retained until arrival of the subsequent sweeping ‘housekeeper wave’. This emphasizes the need for substantial size enlargement of the DF at the stomach

in order to prolong GRT [Klausner et al., 2003a]. In cases of expandable drug delivery systems, the formulation in the stomach expands such that the elimination of the system from the stomach is physically impossible, as the dimensions achieved are greater than the size of the pyloric sphincter [Asmussen et al., 2001; Gutierrez-Rocca et al., 2003].

The 'housekeeper wave' does not always completely clear the stomach from non-disintegrating DFs [Wilding, 2000]. For instance, a radiotelemetric capsule for pH measurements (Heidelberg capsule) with a dimension of 25 mm in length and 8 mm diameter was randomly retained in the stomach of one healthy subject from a group of eight for over 12 h. During that time three 'housekeeper waves' were recorded [Coupe et al., 1991]. Other studies suggested that a radiotelemetric capsule is unable to induce fed state motility [Mojaverian et al., 1991].

The dimensions which are desirable in order to prevent rapid evacuation of DFs from the human stomach can also be determined from reports on foreign bodies retained in the stomach where medical intervention was required to draw them out using gastroscopy [Klausner et al., 2003a]. It has been suggested that a size of > 5 cm in length or 3 cm in diameter prolongs gastroretention [Hamilton and Polter, 1993]. As opposed to foreign bodies, DFs should be tailored to degrade, disintegrate, and be minimized in size or 'collapse' in the stomach at a plausible time interval, i.e. before the subsequent dosing time [Klausner et al., 2003a].

1.3.4. Factors affecting GRT and efficacy of GRDFs

Various factors that affect GRT and thus, efficacy of GRDFs are summarized below [Mojaverian et al., 1988; Clarke at al. 1993; Timmermans and Moes, 1994; Singh and Kim, 2000; Garg and Sharma, 2003].

(a) Density- Floating capacity of DFs and thus GRT is a function of its buoyancy. Studies suggest that GRDFs having low and very high densities have longer GRT. Low density systems are more buoyant and thus float easily, whereas high density systems settle down or get trapped in rugae or folds of the stomach body near the pyloric region [Bechgaard and Ladefoged, 1978; Phuapradit and Bolton, 1991].

(b) Size- Objects less than 10 mm in size can empty from the fed stomach and large objects (> 20 mm in size) will be retained in the fed stomach [Bechgaard and Ladefoged, 1978; Davis, 2005].

(c) Shape of dosage form- Tetrahedral and ring shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch respectively are reported to have better GRT

with approximately 90 to 100 % retention for 24 h compared with other shapes [Garg and Sharma, 2003].

(d) Single or multiple unit formulation- Multiple unit systems avoid the 'all-or-nothing' gastric emptying nature of single unit systems and show a more predictable release profile and insignificant impairing of performance due to failure of units [Garg and Sharma, 2003].

(e) Fed or unfed state- Gastric emptying is controlled by feeding status. Under fasting conditions, the IMMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the IMMC, the GRT of the unit can be expected to be very short. However, in the fed state, IMMC is delayed and GRT is considerably longer [Garg and Sharma, 2003].

(f) Frequency of feed- When the stomach is continuously maintained in the fed state, for instance, by repeated administration of small meals, a single unit could have extended retention for up to 14 h [Davis, 2005].

(g) Nature of meal and 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. Generally, the residence time of the food in the stomach depends upon its nutritive and physical properties: emptying of liquid nutrients has a rate of 200 kcal h^{-1}, regardless of whether those calories are in the form of fats, proteins or carbohydrates [Mojaverian et al., 1985; Klausner et al., 2003a]. Non-nutrient liquids empty rapidly, with a time to 50 % emptying of 8-18 min. Solids empty much more slowly than liquids. Digestible non fat solids are first ground for up to 1 h, and then emptied in zero order kinetics. Solid or semisolid fats, after being consumed and warmed to body temperature in the stomach, are converted into a liquid. Due to a nervous mechanism inhibiting gastric peristalsis and floating over gastric liquids, liquid fats empty much more slowly than aqueous liquids [Hasler, 1995]. GRT can be increased by 4 to 10 h with a meal that is high in protein and fat content. Gastric emptying also depends upon osmolarity and pH of food [Rubinstein et al., 1988].

(h) Gender- The mean ambulatory GRT in males (3.4±0.6 h) is less compared to their female counterparts (4.6±1.2 h) with matched age and race regardless of the weight, height and body surface area [Garg and Sharma, 2003].

(i) Age- Elderly people, especially those over 70, have a significantly longer GRT [Mojaverian et al., 1988].

(j) Posture- GRT can vary between supine and upright ambulatory states of the patient [Backon and Hoffman, 1991]. Floating systems could also have their limitations even in the fed state because a change in body position to supine state will have a direct effect on the floating system and its proximity to the pyloric sphincter [Davis, 2005].

(k) Biological factors- Mental stress and disease state like, diabetes and Crohn's disease also decrease the GRT of DFs [Read and Sugden, 1987; Garg and Sharma, 2003].

An optimally designed GRDF should satisfy certain requirements to achieve satisfactory gastric retention as mentioned below [Wilson and Washington, 1989; Liu et al., 1995; Gutierrez-Rocca et al., 2003].

(i) GRDFs should be retained in the stomach according to the clinical condition and the demand characteristics and should be safe and effective.

(ii) The size should be convenient to administer, at the same time should be large enough to hold substantial amounts of the active and inactive ingredient(s) for entire period of prolonged release.

(iii) The dosage form should have high mechanical strength to withstand the high-amplitude waves of stomach and should be capable of resisting premature gastric emptying.

(iv) The formulation should not have any stability problems in the acidic pH. The size and the ingredients of the DF should not have any adverse effects on normal digestive processes, gastric motility and emptying pattern of the stomach.

(v) In case of floating drug delivery systems (both single and multiple unit systems), density less than that of the gastric contents (1.004 to 1.010 gm/L) should be attained to aid the system to float.

(vi) In case of expandable systems, once the purpose has been served, the dosage form should shrink or collapse or disintegrate and be washed off from the stomach/ system with ease, without causing disturbance to the normal physiology of the GIT.

(vii) All the formulation additives used should be of FDA approved grades, easily available, and economically viable, and should not cause inter and intra batch variations. The excipients employed should have adequate stability and should not affect the final characteristics of the formulation (drug release, floatation, expandability, etc.).

1.4. Approaches to design gastroretentive systems

Various approaches have been investigated to enhance retention of the dosage form in stomach, at the same time control the release of the active ingredient. These systems can be single unit or multiple unit systems. Based on the gastroretention approach employed, these systems can be classified into following types as given in Table 1.2 [Rubinstein and Friend, 1994; Deshpande et al., 1996; Hwang et al., 1998; Garg and Sharma, 2003].

Table 1.2: Classification of approaches to gastric retention and their sub-types

Approaches to gastric retention	Sub-types
Floating systems	Hydrodynamically balanced system Floatation chamber based system Effervescent/ gas generating/ raft system Low density system
Bioadhesive or mucoadhesive systems	Bioadhesive single or multiple unit system
High-density systems	
Systems based on modified shape and size	*System with any of the following attribute:* Extendable arms Unfolding shapes Swellable/ expandable structures (e.g. superporous superabsorbent hydrogels)
Co-administration of gastric-emptying delaying drugs or pharmaceutical excipients	
Co-administration of naturally occurring products	
Combination approach	

1.4.1. Floating systems

Floating systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [Bolton and Desai, 1992; Desai and Bolton, 1993; Whitehead et al., 1996; Iannuccelli et al., 1998]. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [Garg and Sharma, 2003]. Such systems are shown to prematurely sink under conditions when the stomach is completely emptied of gastric fluid.

Formulations of various drugs reported in literature as floating systems include floating microspheres (aspirin, griseofulvin, p-nitroaniline, ibuprofen, terfinadine and tranilast), floating granules (diclofenac sodium, indomethacin and prednisolone), floating films (cinnarizine), floating capsules (chlordiazepoxide hydrogen chloride, diazepam, furosemide, isardipine, misoprostol, L-Dopa, benserazide, ursodeoxycholic acid, pepstatin and nicardipine hydrochloride) and floating tablets/ pills (acetaminophen, acetylsalicylic acid,

ampicillin, amoxycillin trihydrate, atenolol, diltiazem, fluorouracil, isosorbide mononitrate, para-aminobenzoic acid, piretamide, theophylline and verapimil hydrochloride) [Hou et al., 1991; Mazer et al., 1988; Gu et al., 1992; Moursy et al, 2003]. Various polymers and excipients commonly employed in these systems include hydroxy propyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonate (PC) [Thanoo et al., 1993]. Some of the marketed formulations in this category include Valrelease®- floating capsule of diazepam; Madopar®- benserazide and L-Dopa combination formulation; Liquid Gaviscon®- floating liquid alginate preparations; Topalkan®-aluminium and magnesium antacid preparation; and Almagate Flot-Coat®- antacid preparation [Singh and Kim, 2000; Klausner et al., 2003c; Garg and Sharma, 2003].

Floating systems can be classified into different types based on the mechanism employed [Talwar et al., 2001; Gutierrez-Rocca et al., 2003; Arora et al., 2005]. Various types of floating systems are discussed below.

Hydrodynamically balanced system (HBS): This system forms a cohesive gel barrier, and at the same time, maintains the specific gravity lower than that of the gastric contents. HBS system was first introduced by Sheth and Tossounian and contained high levels (20-75 % w/w) of one or more gel forming hydrocolloids like, hydroxy ethyl cellulose (HEC), hydroxy propyl cellulose (HPC), HPMC, and sodium carboxy methyl cellulose (SCMC) in the formulation [Sheth and Tossouniam, 1978]. They can be either compressed to a tablet or filled in capsules [Sheth and Tossouniam, 1984].

Madopar® is a floating HBS containing 200mg levodopa and 50mg benserazide. The formulation consists of a capsule designed to float on the stomach contents. Following dissolution of the gelatin shell, a matrix body is formed consisting of the active drug and other substances. The drug diffuses as successively hydrated boundary layers of the matrix dissolute. Valrelease® is a HBS system based floating capsule containing diazepam with prolonged GRT and is used as a once-a-day dosage form with therapeutic efficacy comparable to the previous three-times-a-day non-floating dosage form [Gutierrez-Rocca et al., 2003].

HBS based tablets, as gastroretentive sustained release dosage forms, have been designed for propranolol hydrochloride [Khattar et al., 1990] and nicardipine hydrochloride [Moursy et al., 2003]. A bilayered floating capsule of misoprostal, as stomach directed drug delivery system, was developed [Oth et al., 1992]. Optimization technique (factorial design) was employed to study the effects of HPMC and carbopol on the release and floating properties

of hydrodynamically balanced floating tablets [Li et al., 2003]. Sustained release floating matrices of Gelucire® 39/01, containing risedronate sodium were prepared using melt solidification and evaluated for in vitro and in vivo floating ability and in vitro drug release [Chauhan et al., 2004]. The effects of polymer to drug ratio, polymer one to polymer two ratio, and different viscosity grades of HPMC on bilayer floating tablet containing metoprolol tartrate as a model drug were studied using optimization technique [Narendra et al., 2006]. Similarly, factorial design was employed to evaluate contribution of HPMC K4M/ HPMC K100 low viscosity (LV) ratio (polymer blend) and sodium lauryl sulfate on drug release from HPMC matrices [Patel and Patel, 2006].

Floatation chamber system: These systems make use of floatation chamber principle, which may be vacuum or filled with air or an inert gas. The first floatation chamber based system containing an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule was developed way back in 1974. When the drug delivery device reached the stomach, the capsule quickly disintegrated to release the intra-gastric osmotically controlled drug delivery device [Michaelis, 1974]. The same group of researchers incorporated an inflatable chamber containing ether that gasifies at body temperature, into their device. The inflatable chamber was loaded with drug reservoir (drug-impregnated polymeric matrix) and encapsulated in gelatin capsule. After oral ingestion, the capsule dissolved in gastric fluid to release the drug reservoir compartment together with the attached inflatable chamber. The inflatable chamber automatically gets inflated and retains the drug reservoir compartment in the stomach [Michaelis et al., 1975]. This approach was also used to encapsulate the drug reservoir inside a microporous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment were completely sealed to prevent any direct contact of the stomach mucosal surface with the undissolved drug [Harringan, 1977]. In another study, inflatable chamber containing a biodegradable polymer filament that gradually dissolve in the gastric fluid and finally deflate and collapse the chamber after predetermined time period to permit the spontaneous ejection of the device from the stomach was reported [Chien, 1981]. Bilayered compressed capsules, multi-layered floatable sheets, single and multiple unit devices with floatation chambers have also been reported [Ozdemir et al., 2000].

Alza Corporation developed a gastroretentive platform for the OROS® system, which showed prolonged GRT in a dog model as the product remained in the canine stomach for 12 h post dosing. In humans, in the fasted state, the average GRT for the same system was 33 min [Wilding and Newman, 2001].

Effervescent/ gas generating/ raft system: These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides (chitosan and alginate gels) and effervescent components like sodium bicarbonate, citric acid and tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 [Baumgartner et al., 2000]. Upon reaction with gastric acid, bubbles form in the gel, enabling floating. These systems are called 'rafts' as the gas trapped viscous hydrogel layer can 'ride' the stomach waves [Gutierrez-Rocca et al., 2003]. Capsules filled with mixtures of verapamil, HPC and effervescent components were reported to provide floating and sustained release over a period of 10 h [Chen and Hao, 1998]. Other approaches and materials that have been reported for designing effervescent system are highly swellable hydrocolloids and light mineral oils; a mixture of sodium alginate and sodium bicarbonate; multiple unit floating pills that generate carbon dioxide when ingested; floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with HPMC; and floating systems based on ion exchange resin technology, etc [Atyabi et al., 1996; Garg and Sharma, 2003].

Another approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose (EC) [Garg and Sharma, 2003]. The coating, which is insoluble but permeable, allows permeation of gastric juice. Bicarbonate reacts with gastric acid and produces carbon dioxide, causing the beads to float in the stomach [Gutierrez-Rocca et al., 2003]. Gaviscon® is an effervescent gastroretentive system designed for the suppression of gastro-oesophageal reflux. It consists of alginate that gels in the gastric environment due to the carbonate or bicarbonate content [Gutierrez-Rocca et al., 2003]. Gastroretentive drug delivery system of ranitidine hydrochloride employing guar gum, xanthan gum, and HPMC as gel-forming agents and sodium bicarbonate with organic acid as a gas generating agent were prepared. A full factorial design was applied to systemically optimize the drug release profile [Dave et al., 2004]. In another study intragastric buoyant sustained release tablets of amoxicillin comprising of hydroxy propyl cellulose, citric acid and sodium hydrogen carbonate were prepared and evaluated. A sustained release pattern of amoxicillin for 24 h with appropriate floating characteristics in water and buffer solutions of pH 1.2 and 6.8 was achieved using granulated amoxicillin with a particle size of 300-500 μm and coating the surface of the tablet [Tokumura and Machida, 2006]. Rahman and colleagues have designed and evaluated bilayered floating tablets of captopril, in which the release layer (containing drug and various polymers alone and in combination) is distinct from the floating layer (composed of polymer, acid and

base). Best formulation of this study floated in 10 min and remained afloat throughout in vitro study and its corresponding placebo tablet (with barium sulphate) stayed in the stomach of human volunteers for 6.4±0.8 h [Rahman et al., 2006]. In vitro and in vivo evaluation were carried out for floating HPMC K4M and carbopol 971P NF based matrix dosage form for phenoporlamine hydrochloride based on gas forming agent, in healthy volunteers. Data obtained in these studies demonstrated that the floating matrix tablet containing higher proportion of carbopol was capable of sustained delivery of the drug for longer periods with better floating characteristics and increased bioavailability [Xu et al., 2006].

Low-density system: This system is designed to have density lower than that of the gastric fluid so as to make them buoyant. Most of the low-density systems developed are multiple unit systems. Multiple unit systems are relatively advantageous as they can overcome the 'all or nothing' gastric emptying nature of single unit systems. The concept of floating microparticles can also be utilized to minimize the irritant effect of weakly acidic drugs on the stomach mucosa by avoiding direct contact and also provide sustained release for prolonged period [Jayanthi et al., 1995; Iannuccelli et al., 1998; El-Kamel et al., 2001; Streubel et al., 2002].

An example of patent employing this concept includes a core of the drug coated with a gas generating layer followed by an envelope of an expandable film. The film is permeable to gastric juice but impermeable to CO_2 gas and so expands like a balloon so that the granules float on gastric juice and remain buoyant thereon for a period of time [Ichikawa et al., 1989]. A multiple unit type of oral floating dosage system composed of both an effervescent layer and a swellable membrane layer coated on sustained release pills was shown to have excellent floating ability and sustained release characteristics in vitro, irrespective of the pH and viscosity of the medium [Ichikawa et al., 1991a]. Under fed state in beagle dogs and humans most of these pills containing barium sulfate were floating in the stomach at 10 min, and they kept floating for at least 3 h after administration (observed by periodic X-ray photographs), whereas control pills without the effervescent layers were evacuated into the small intestine by 3 h. Para amino benzoic acid and isosorbide dinitrate were employed as model drugs for these studies [Ichikawa et al., 1991b].

Kawashima et al prepared multiple unit hollow microspheres by emulsion solvent diffusion technique employing acrylic polymer. The rate of drug release in microballoons (MBs) was controlled by changing the polymer-to-drug ratio. MBs were floatable in vitro for 12 h when immersed in aqueous media. Radiographical studies proved that MBs orally administered to

humans were dispersed in the upper part of stomach and retained there for 3 h against peristaltic movements [Kawashima et al., 1991]. Floating freeze-dried calcium alginate multiple unit dosage form was designed and its in vivo transit was monitored by gamma scintigraphy in human subjects in a fed state. Prolonged GRTs of over 5.5 h were achieved in all subjects for the floating formulations. In contrast, the non-floating beads displayed short GRTs, with a mean emptying time of 1 h [Whitehead et al., 1998]. Floating alginate beads were prepared from alginate solutions containing either dissolved or suspended amoxicillin. Preparation of the beads from alginate solutions containing the drug in suspension allowed higher drug loadings, at the expense of faster release and lower buoyancy [Whitehead et al., 2000]. Casein gelatin beads were prepared by emulsification extraction method and cross-linked with glyceraldehyde. Increase in proportion of casein in the formulation lead to increased porosity, higher drug release rate and enhanced floatability [Bulgarelli et al., 2000].

Sustained release floating microparticles of ketoprofen employing different ratios of Eudragit S100 with Eudragit RL were prepared by emulsion solvent diffusion technique. 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 the two polymers in the ratio 1:1 exhibited high percentage of floating particles in all examined media [El-Kamel et al., 2001]. Hollow microspheres of cellulose acetate loaded with four different cardiovascular drugs (nifedipine, nicardapine hydrochloride, verapamil hydrochloride and dipyridamole) were prepared. The microspheres floated over the gastric media for more than 12 h and the release of the drugs was controlled for more than 8 h with different transport mechanisms depending on the nature of the drug molecules [Soppimath et al., 2001a; Soppimath et al., 2001b]. Hollow PC microspheres of piroxicam capable of floating on simulated gastric and intestinal fluids was prepared and evaluated. Pharmacokinetic analysis showed that the bioavailability from PC microspheres alone was about 1.4 times that of the free drug and it was about 4.8 times for the dosage form consisting of the microspheres plus the loading dose [Joseph et al., 2002].

Floating microparticles consisting of polypropylene foam powder; verapamil hydrochloride as model drug; and Eudragit RS, EC or polymethyl methacrylate as polymers were prepared with an o/w solvent evaporation method. The effect of various formulation and processing parameters on the internal and external particle morphology, drug loading, in vitro floating behavior, in vitro drug release kinetics, particle size distribution and physical state of the

incorporated drug was studied [Streubel et al., 2002]. In another study, a novel preparation of low-density polypropylene foam powder based floating microparticles was studied. This technique with short processing time, low-temperature handing of the drug and excipients, non-toxic chemical utilization and high encapsulation efficiency (close to 100 %) was an improvement over earlier reported methods. A significant increase in the bioavailability of furosemide from this floating dosage form (42.9 %) was reported in comparison to commercially available tablets Lasix® (33.4 %) and enteric coated product (29.5 %) [Streubel et al., 2003a]. Floating matrix tablets based on this low density foam powder was also tried by this group with very good gastroretention [Streubel et al., 2003b].

Floating beads, containing riboflavin as model drug, were prepared from a sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas-forming agents. The effects of gas-forming agents on bead size and floating properties were investigated. $CaCO_3$ containing beads showed enhanced buoyancy and sustained release properties than $NaHCO_3$ containing beads in this study [Choi et al., 2002]. Riboflavin containing MBs floatable in acidic solution (pH 1.2) were prepared by the emulsion solvent diffusion method using enteric acrylic polymers. MBs prepared by mixing enteric acrylic polymers with HPMC in different ratio, resulted in improved riboflavin release properties. The intragastric behavior of ^{99m}Tc labeled MBs and nonfloating microspheres (control) following oral administration in fasted and fed humans were investigated by gamma scintigraphy. Simultaneously, pharmacokinetic examination of riboflavin released from MBs and nonfloating microspheres was conducted in fasted and fed human subjects. Pharmacokinetic parameters, e.g., excretion half-life time and total urinary excretion, were well correlated with the GRT determined by the gamma scintigraphy analysis [Sato et al., 2003; Sato et al., 2004a; Sato et al., 2004b].

Cost effective systems of calcium alginate-pectinate and methoxylated pectin hollow microspheres floated on the simulated gastric fluid for 12 h. It was claimed that the hollowness of the alginate beads, due to the sublimation of the water entrapped during the bead formation, assisted in floating [Talukder and Fassihi, 2004]. An emulsion gelation method to prepare oil entrapped calcium pectinate gel (CaPG) beads capable of floating in the gastric condition was designed and tested. The oil-entrapped CaPG beads showed excellent buoyancy in the acidic environment of the gastric fluid as well as in distilled water or normal saline solution when sufficient amount of oil, depending on the relative density of the oil was used [Sriamornsak et al., 2004]. Metronidazole loaded emulsion gel (EMG) beads of CaPG capable of floating in the gastric condition were developed using the above method. Increasing the drug to pectin ratio in the beads, using 2% glutaraldehyde as a

hardening agent and coating the beads with Eudragit RL significantly sustained the drug release [Sriamornsak et al, 2005].

A sustained release system for lansoprazole, designed to increase its residence time in the stomach without contact with the mucosa, was achieved through the preparation of floating micropellets by emulsion solvent diffusion technique using HPMC, methyl cellulose (MC) and chitosan. The drug loaded micropellets were found to float on simulated gastric fluid and simulated intestinal fluid for more than 12 h [Muthusamy et al., 2005]. Floating microspheres of repaglinide consisting of calcium silicate as porous carrier and Eudragit S100 as polymer were prepared by emulsion solvent diffusion technique. Incorporation of porous calcium silicate in the microspheres ensured very high drug encapsulation efficiency and favorable in vitro floating and release characteristics [Jain et al., 2005]. Formulation, characterization and in vitro evaluation of floating HPMC and EC based microspheres of cimetidine were carried out. The prepared microspheres exhibited prolonged drug release (~ 8 h) and remained buoyant for > 10 h [Srivastava et al., 2005]. A multiparticulate floating pulsatile drug delivery system was developed using porous calcium silicate (Florite RE®) and sodium alginate, for time and site specific drug release of meloxicam. Formulations showed a lag period for drug release ranging from 1.9 to 7.8 h in acidic medium followed by rapid release of meloxicam in simulated intestinal fluid (SIF) USP, without enzymes. Complete drug release in SIF occurred in less than 1 h from the formulations. A pulsatile release of meloxicam was demonstrated, which could be useful in chronopharmacotherapy of rheumatoid arthritis [Sharma and Pawar, 2006]. Frances and co-workers developed floating freeze-dried calcium alginate beads of riboflavin and studied their gastroretentive property. The bioavailability of riboflavin improved when calcium alginate beads were administered in the fasted state with citric acid solution, compared to the bioavailability obtained when the calcium alginate beads were administered in the absence of citric acid [Frances et. al., 2006].

1.4.2. Bioadhesive or mucoadhesive systems

Oral bioadhesive drug delivery systems (BDDS) are used to localise a delivery device within the lumen to enhance the drug absorption in a site-specific manner [Moes, 1993; Mathiowitz et al., 1999]. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach walls, thus resisting gastric emptying [Jimenez-Castellanos et al., 1993; Cheuh et al., 1995]. A limitation with this type of system is that gastric mucoadhesion does not tend to be strong enough to impart dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production

of mucus by the gastric mucosa to replace the mucus that is lost through peristaltic contractions results in unpredictable adherence properties [Gutierrez-Rocca et al., 2003] and the dilution of the stomach content also limits the potential of mucoadhesion as a gastroretentive force [Garg and Sharma, 2003].

Some of the most promising bioadhesive excipients that have been used commonly in these systems include polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose (CMC) and gliadin, etc [Chitnis et al., 1991]. A novel adhesive material, adhesin, derived from the *fimbriae* of bacteria or synthetic analogues or fragments has been found to be useful [Illum et al., 1998; Garg and Sharma, 2003]. Inagi and co-workers studied the bioadhesive property of formulations coated with a water insoluble polymer (like, polyglycerin fatty acid esters, lipids and waxes) onto the surface of the gastric mucosa. These polymers were found to have better bioadhesive property in digestive tract under acid conditions in comparison to neutral or alkaline conditions. Such delivery systems provided adherence only to the mucosa of the stomach and/ or duodenum, and ensured that the release of the medicament over long hours occurred only at the required site and sufficient therapeutic effect was generated by relatively smaller amount of the medicament [Inagi et al., 2003].

Bioadhesive systems may be divided into single unit or multiple unit systems.

Bioadhesive single unit system: Mucoadhesive thiolated polycarbophil based low molecular weight heparin mini-discs, coated with triglyceride, have been found useful in enhancing the uptake of heparin from GIT [Schmitz et al., 2005]. Trilayered gastroretentive, bioadhesive tablets of acyclovir (BioVir^{TM} CR) were shown to be gastroretentive for at least 6-8 h in a fed beagle dog model. This study demonstrated extended release of the drug to target absorptive sites in duodenum and jejunum and resulted in 72 % increase in area under the plasma concentration-time curves (AUC) when compared to Zovirax, an IR formulation of acyclovir [GlaxoSmithKline, 2003; Jacob et al., 2006].

Bioadhesive multiple unit system: Two kinds of sustained release microspheres, adhesive and non-adhesive, containing furosemide and riboflavin, were prepared and administered to fasted volunteers in hard gelatin capsules. AUCs were 1.8 times larger for furosemide and the urinary recovery was 2.4 times higher for riboflavin when adhesive microspheres were used as compared with the non-adhesive system [Akiyama et al., 1998]. Chitosan, a popular choice as a coating material because of its regulatory status and its positive charge, is known to bind well to mucus. Several reports also suggest that microparticles coated with chitosan adhere well in the intestine of animals [He et al., 1999; Takishima et al., 2002; Hejazi, 2003; Guddi et al., 2003; Bernkop-Schnürch et al., 2003; Bernkop-Schnürch et al.,

2004]. In designing controlled release chitosan based bioadhesive microsphere formulations, it is important to retain the positive nature of the material [Inouye et al., 1988; Inouye et al., 1989; He et al., 1999]. Sustained release, intragastric floating granules of indomethacin using chitosan were evaluated in rabbits. The granules were shown to be retained in stomach longer and delivered the drug for an extended period [Miyazaki et al., 1988]. However, good adhesion and delayed transit do not always translate into improved bioavailability of certain administered drugs. Shimoda et al. reported that insulin loaded chitosan microsphere system showed good adhesion to the intestinal mucosa, but did not facilitate absorption of insulin through GIT mucosa [Shimoda et al., 2001]. Säkkinen et al. have described a gamma scintigraphic evaluation of the fate of microcrystalline chitosan granules in the fasted human stomach [Säkkinen et al., 2004]. Chitosan based systems for local delivery of antibiotics in the stomach have been described by Torrado and group. The swelling chitosan-poly (acrylic) acid based controlled drug release system in humans were shown to have gastric half-emptying time of the polyionic complex was significantly delayed when compared with that of a reference formulation [Torrado et al., 2004].

Flamel Technologies have described the design of a proprietary drug delivery system, Micropump® microparticles, that is claimed to be bioadhesive and which allows an extended transit time in the small intestine with mean residence time in the plasma extended up to 24 h. This system is reported to be particularly suitable for drugs with short half-life that are absorbed only in the small intestine [Davis, 2005]. Chitosan microspheres of glipizide were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. The in vitro and in vivo performances of these mucoadhesive microspheres showed increased gastric residence and prolonged drug release [Patel et al., 2005]. Amoxicillin mucoadhesive microspheres were prepared using EC as matrix and carbopol 934P as mucoadhesive polymer for the potential use of treating gastric and duodenal ulcers, which were associated with *Helicobacter pylori*. A remarkable improvement in therapeutic outcome in case of designed microspheres was reported [Liu et al., 2005].

1.4.3. High-density systems

Sedimentation has been employed as retention mechanism for pellets that are much denser than GI fluid and small enough to be retained in the rugae or folds of the stomach body near the pyloric region. Dense pellets (approximately 3 g/cm^3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended in the range 5.8-25 h, depending more on density than on diameter of the

pellets. In preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, zinc oxide, titanium dioxide and iron powder. These materials increase density by up to 1.5-2.4 g/cm^3. The weighed pellet can then be covered with a diffusion controlled membrane. However, no successful high density system has been commercialized till date [Chien, 1981; Rouge et al., 1998a; Klausner et al., 2003a].

1.4.4. Systems based on modified shape and size

The most promising approach to achieving gastroretention is that of creating an in situ swelling or expanding system. Such systems will require to be expanded to a size larger than the pyrolic sphincter and at the same time must not swell or expand in the oesophagus or in the intestines. If emptied prematurely from the stomach, physiological problems could arise from the formation of an insoluble mass in the intestine known as a bezoar [Chien, 1981; Davis, 2005]. The system should have sufficient rigidity to remain intact in the stomach and to withstand the mechanical forces therein. After releasing the drug in the stomach, it should decrease in size or disintegrate and then empty through the intestine [Davis, 2005]. Various systems described in the literature, including numerous patents, achieve this increase in size through the processes of expansion or swelling, or through unfolding. There are some drawbacks associated with this approach. Permanent retention of rigid large sized single unit dosage forms can cause bowel obstruction, intestinal adhesion and gastroplasty [Garg and Sharma, 2003; Gutierrez-Rocca et al., 2003]. Some of the designs investigated are summarized below.

Extendable arms: Curatolo and Lo reported an unfolding spiral or coil configuration GRDF. This contained a receptacle that can hold the drug in a reservoir in the form of tablet or capsule and possessed retention arms in the form of ribbons or fiber which possess the ability to stay in the stomach on their own [Curatolo and Lo, 1995]. Other systems, based on novel geometries, such as long worm-like structures, have been designed [Reddy and Murthy, 2002; Hou et al., 2003]. Pfizer Pharmaceuticals has patents for gastric retention technology that uses extendable arms, but has no product of this type in the market [Gutierrez-Rocca et al., 2003].

Unfolding shapes: The design of GRDFs based on unfolding to a large configuration, was pioneered by Laby for veterinary applications [Laby, 1974]. These DFs were constructed for ruminants and particularly for releasing in a controlled manner bloat preventing surfactants in bovines. The DF unfolds inside the rumen and simply resists the passage into the lumen by physical means.

A study on unfolding devices characterized by different erodibility, mechanical properties, sizes and geometries was conducted by Caldwell and co-workers. Various geometric configurations like stick, ring, tetrahedron, planar disc, planar multi-lobe and string were developed. The designs were reported to have sufficient resistance to the forces applied in the stomach [Caldwell et al., 1988a; Caldwell et al., 1988b; Caldwell et al., 1988c]. Sonobe and co-workers developed unfolding DFs, which have the dimensions and shape and durability necessary for prolonged gastroretentivity [Sonobe et al, 1991].

The problem with all the above designs was the lack of mechanical memory of these devices. This problem was addressed by Pogany and Zentner. They designed bioerodible thermoset, covalently cross-linked, elastomeric poly ortho-esters with a prolonged shape memory. The three dimensional network structures induced dimensional stability and resiliency after compression for extended periods of time [Pogany and Zentner, 1993]. Klausner and co-workers designed rectangular shaped unfolding GRDFs, which use a combination of rigid components with large dimensions to enhance gastroretentivity [Klausner et al., 2002; Klausner et al., 2003c]. An unfolding expandable compressed-dosage form, comprising of an inner polymeric and/ or drug matrix layer, with two shielding outer layers containing a coating of microcrystalline cellulose to prevent adhesion has been reported [Klausner et al., 2003d]. Enhanced bioavailability was reported for marker compounds in dogs from this system. Two clinical studies have been reported where the GRDF containing furosemide were given to human subjects. Furosemide conatining GRDF provided better pharmacokinetics and pharmacodynamics, which correlated well with the longer residence of the DF in the stomach [Klausner et al., 2003b]. In a second study, the unfolding and physical integrity of the dosage systems were evaluated in vitro and in vivo by gastroscopy and radiology [Klausner et al., 2003d]. A combination of rigidity and large dimension of the dosage forms was considered to be a decisive parameter to ensure prolonged gastroretention of 5 h or longer. A significant extension of the absorption phase was demonstrated for levodopa, a drug with a narrow absorption window, upon dosing in an unfolding system after light breakfast [Klausner et al., 2003c].

Drugs like acyclovir, adendronate, atenolol, captopril, cinnarizine, ciprofloxacin, cisapride, furosemide, ganciclovir, glipizide, ketoprofen, levodopa, melatonin, metformin, minocyclin, misoprostol, micardipine, riboflavin, sotalol, tetracycline, verapamil, and vitamin E have been investigated in different studies using unfolding dosage form design [Wilding et al., 2001; Martin et al., 2003; Gutierrez-Rocca et al., 2003].

Swellable/ expandable structures: Expansion and swelling based system either involves the generation of gas, in the form of carbon dioxide, or exploit the properties of compressed porous materials such as hydrogels. This type of system, after swallowing, swells in an unrestrained fashion by imbibing gastric fluid to an extent that it prevents its exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. The fasted stomach presents a severe challenge in terms of the limited time available for increase in retainable size post administration. In contrast, the lightly fed stomach can provide sufficient residence time for optimal increase in size. Therefore, majority of studies conducted on putative GRDFs in human have employed the fed state condition [Davis, 2005].

An expandable GRDF in tablet form comprising of thiolated gelatin, a cross-linking agent and a drug has been reported. Once this DF reaches the stomach, the thiolated gelatin becomes hydrated, swells and gets cross-linked to form a matrix, too large to pass through the pylorus [Johnson and Rowe, 1971]. Michaelis described swellable DFs by constructing tubular GRDFs from a swelling retention arm bonded to a chamber containing the drug reservoir, a pressure generating compartment (containing a low boiling liquid or a solid with high osmotic pressure) and a pressure responsive flexible bladder in between [Michaelis, 1974; Michaelis et al, 1975]. Mamajek and Moyer designed a GRDF comprising of an envelope from an elastic nonhydratable polymeric membrane, which was permeable to drug and body fluid. The envelope contained the drug and the reservoir and an expanding agent [Mamajek and Moyer, 1980]. Urquhart and Theeuwes developed a DF with a very high swelling ratio exhibiting a 2 to 50 folds volume increase. The proposed mechanism of retention was not only due to the large dimensions, but also by maintaining the stomach in the fed mode, i.e. delaying the house keeper waves, by mechanical sensation. Controlled release of the drug was achieved by incorporating the system in a wax matrix base [Urquhart and Theeuwes, 1984].

Shalaby and co-workers developed albumin-crosslinked polyvinyl pyrrolidone (PVP) gel with swelling and degradation properties. The swelling and degradation property was controlled by adjusting the degree of vinylic functionality of the albumin cross linker [Shalaby and Park, 1990; Shalaby et al., 1992b]. The planar projection of the shape is one that has two orthogonal axes of different lengths. The longer axis is short enough to permit easy swallowing prior to swelling, while the shorter axis is long enough that within 1.5 h of swelling it can prevent passage of DF through the pylorus [Berner and Louie-Helm, 2002]. DepoMed, Inc. developed a technology that consisted of a swellable tablet. These systems

were based on polyethylene oxide (PEO) in combination with HPMC to produce a sustained release matrix tablet that can swell in the stomach after oral ingestion. According to the company, candidate molecules investigated using the design included metformin, gabapentin, ciprofloxacin and furosemide [Gutierrez-Rocca et al., 2003].

Chen and co-workers have designed unique superporous hydrogel (SPH) composites, which combine a high swelling rate and swelling ratio of more than 100 times the original weight of the dried matrix with substantial mechanical strength [Chen and Park, 2000; Chen et al., 2000; Polnok et al., 2004]. Conventional hydrogels have relatively small pore sizes, take several hours to swell, and cannot withstand the high amplitude waves generated in the stomach because of the low mechanical strength. In contrast, in case of SPHs, rapid swelling occurs within few min due to presence of the super disintegrants (Ac-Di-Sol®), which increases effective cross linking density by physical entanglement and yields SPH composite. By modification of the hydrogel synthesis in terms of monomers, cross-linkers and other additives/ components, the physical and/ or mechanical properties of the SPH can be controlled. In vivo evaluation of this system in pig model showed that the hydrogel enhanced the intestinal absorption of insulin [Dorkoosh et al., 2002]. This system was also evaluated in dogs, under both fasted and fed conditions. Under fasted conditions, the composites remained in the stomach of the dog for 2-3 h before breaking into two pieces and then were emptied into the lumen. Under fed state, the composites remained in the stomach for more than 24 h, although the fed condition was maintained only for the first few hours [Davis, 2005].

1.4.5. Co-administration of gastric-emptying delaying drugs or pharmaceutical excipients

This concept of simultaneous administration of an agent drug to delay gastric emptying together with a therapeutic drug containing formulation has not received the favour of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices [Garg and Sharma, 2003]. It is well established that certain drugs and/ or pharmaceutical excipients can alter GI transit. For example, scintigraphic data have indicated that pre-treatment with propantheline increased gastric emptying time and decreased GI motility, whereas pre-treatment with metoclopramide had the opposite effect [Marathe et al., 2000]. The extent of metformin absorption, a drug primarily absorbed from the small intestine, was improved when the GI motility was slowed [Rubinstein and Friend, 1994]. The bioavailability of cimetidine, a polar drug that is almost exclusively absorbed from the small intestine, was reduced when a formulation excipient capable of increasing

the rate of transit in the small intestine through osmotic effect was included in the formula [Adkin et al., 1995].

1.4.6. Co-administration of products derived from natural source

Dietary components such as fats, certain amino acids and peptides can slow gastric emptying and intestinal transit [Singh, 1999; Lin et al., 2003]. A lesser-known phenomenon is the ileal brake [Van-Citters and Lin, 1999]. Certain dietary components like, fats and fatty acids when infused into the terminal ileum can cause slowing of intestinal transit. This 'braking' mechanism appears to be a feedback process for the improved digestion of dietary components. Studies have been performed in humans to identify optimal ileal brake activators [Davis, 2005]. In one of the investigations, atenolol, oleic acid and a monoglyceride were formulated into modified release capsules that were targeted to the small intestine. The results showed that, in some volunteers, an increase in small intestine transit time led to an increase in the amount of drug absorbed. However, drug absorption was related not only to the total time spent by the drug in the small intestine, but also on proportion of such time spent at the ileo-caecal junction. This study highlighted the complexities of exploiting natural GI processes to enhance the oral bioavailability of drugs [Dobson et al., 2002].

Kroening and colleagues reported that tapeworms can slow the transit of intestinal contents [Kroening et al., 2003]. Out of the tapeworm secreted compounds tested, only luminal infusion of guanosine 3', 5'-cyclic monophosphate (cGMP) induced contractile patterns that mimicked those observed during tapeworm infection. As a consequence, it was suggested that cGMP might be used in proprietary pharmaceutical formulations to improve drug absorption [Davis, 2005]. Few researchers have investigated the use of purified fimbriae from *Escherichia coli* as a natural bioadhesive. Fimbriae are long filamentous protein projections on the surface of certain organisms that allow them to adhere to the receptors on the brush borders of villous enterocytes [Cleary et al., 2004], were attached to small microspheres. Encouraging data were reported in rat model in terms of increase in small intestine transit time [Caston et al., 1990].

Similarly, various groups have studied the use of plant lectins for their affinity of the luminal surface of the small intestine with promising results based on animal studies. For example, two plant lectins selected by Montisci and his group, *Lycopersicon esculentum* and *Lotus tetragonolobus* lectins, were reported to be specific for oligomers of N-acetyl-D-glucosamine and L-fucose, respectively. These lectins were later on conjugated to small radiolabeled poly (lactide) microspheres and studied for the transport and

distribution of the particles along the intestine, as well as their interactions with the intestinal mucosa after oral administration in rat. The overall transit of the particles was delayed when the microspheres were conjugated to the lectins, mainly because of gastric retention. A significant fraction of the conjugates adhered to the gastric and intestinal mucosae, but the interaction process was reported to be largely a result of non-specific interactions [Montisci et al., 2001]. It was found that premature adsorption of soluble mucin to glycoprotein limited the specific lectin mediated adhesion. Mucoadhesive properties of small 'bioadhesive' tablets, which carry a net positive charge, were examined using the technique of gastroscopy. In vitro studies showed that such a charge provided a good interaction with the negatively charged sialic acid groups on gastric mucus [Jordon, 1990].

1.4.7. Combination approach

Combination approach implies concoction of two or more systems/ approaches. Some investigators have tried out a synergistic approach between floating and bioadhesive systems [Davis, 2005]. Oral dosage forms containing finely divided ion-exchange resins of low density with a positive charge were shown to provide prolonged gastric residence and uniform distribution within the stomach. Floatability on gastric fluid/ content and adherence to the mucus lining as the stomach empties helped in further prolonging the gastric GRT [Burton et al., 1995]. Floating microcapsules containing melatonin prepared by the ionic interaction of chitosan and a negatively charged surfactant, sodium dioctyl sulfosuccinate, were shown to float for more than 12 h on simulated biofluids [El-Gibaly, 2002a; El-Gibaly, 2002b]. For the treatment and eradication of *Helicobacter pylori* infection, Umamaheshwari and co-workers incorporated gas generating agent and mucoadhesive agent in the formulation and prepared cellulose-acetate-butyrate coated cholestyramine microcapsules by emulsion-solvent-evaporation technique [Umamaheshwari et al., 2003].

Another combination approach is to confer swelling/ expansion and buoyancy to the system. One of the formulation methods of such dosage forms involves mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms [Garg and Sharma, 2003]. Kos gastroretentive platform technology, which is a SPH system, with very fast swelling rate, high swelling capacity, platform flexibility in a dry state (facilitates handling), platform elasticity in the swollen state (provides resilience against contractions), ability of the platform to float, controllable platform erodability, and ease of drug and/ or

drug delivery system loading in a broad range of solid dosages is another example of this type of combination approach [Gutierrez-Rocca et al., 2003].

1.5. Evaluation of gastroretentive dosage forms

There exists sufficient literature on development of animal models for the evaluation of gastroretentive formulations in vivo [Hossain et al., 1990; Kararli, 1995; Chiou and Barve, 1998]. The dog model is most commonly used to evaluate the GRDF preclinically, either for the gastroretentivity or enhancement in bioavailability or both. The similarities between the human and dog digestive tracts make this model a useful tool. A comparison between the two species has shown that the fasting gastric motility, (IMMC periodicity, including the housekeeper wave) of dogs and humans are very similar. But, the evidence of gastric 'destructive forces', applied by the stomach walls on its contents, was much pronounced in dogs than in humans [Kamba et al., 2000]. Thus, a DF that fails in dog model study for its gastroretentive ability may be misleading. Pigs are better model than dogs with respect to forces applied by stomach wall, but pigs have a longer gastric retention of pellets and tablets than that in humans [Davis et al., 2001].

Models to demonstrate the effect of GRDDS on the motility of the GIT have also been studied, like magnetic-field goniometry/ magnetic marker monitoring, which uses an electronic compass to measure angular changes in the direction of the magnetic field generated by a previously swallowed magnet. Imaging techniques like γ-scintigraphy, radiology/ X-ray, gastroscopy, and ultrasonography monitoring are also used for the in vivo characterization and evaluation of performance of these formulations [Timmermans et al., 1989; Whitehead et al., 1998; Kedzierewicz et al., 1999; Wilding et al., 2001; Klausner et al., 2003a; Sato et al., 2003; Säkkinen et al., 2004; Sato et al., 2004a; Sato et al., 2004b; Patel et al., 2005; Frances et al., 2006; Rahman et al., 2006; Xu et al., 2006].

1.6. Objective of the present research work

Gastroretentive controlled release dosage forms (GR-CRDFs) have been found to enhance the therapeutic benefits of such drug molecules which otherwise show low and/ or variable bioavailability when compounded into conventional IR/ CR dosage forms. Thus, objective of this research work was to apply the principles and concepts of novel oral drug delivery systems and design GR-CRDFs of two candidate drugs, namely celecoxib, having very poor solubility throughout the GIT, and acyclovir, having narrow absorption window and poor solubility in neutral/ alkaline pH. The two drugs when administered in the form of

conventional IR/ CR formulations have shown low and/ or variable bioavailability and short duration of action.

Single unit (SU) and multiple unit (MU) GR-CRDFs for celecoxib and acyclovir, possessing buoyancy due to gas generation/ low density and mucoadhesive properties were designed employing various methodologies. Systems developed and evaluated were:

(a) Buoyant gas generating SU-GR-CRDFs prepared by employing matrix embedding technique, in which effects of type and proportion of gas generating agent, effect of polymer type and proportion and combination of polymers were studied on floating behaviour and release kinetics of the formulations.

(b) Floating gas generating MU-GR-CRDFs prepared by microencapsulation, in which effects of core composition, core to coat ratio, coat composition and hydrophobic to hydrophilic polymer ratio in the coat were investigated for floating characteristics and drug release kinetics. Porous low density MU-GR-CRDFs were also prepared by ionic cross-linking technique, in which effects of processing variables, inclusion/ exclusion of a floating agent and drug to polymer ratio were studied on floating behaviour and release kinetics of the formulations.

Designed formulations were characterized with respect to their physical properties, floating characteristics, swelling behaviour, mucoadhesive property and drug release kinetics. Ultrasonography was employed for in vivo evaluation of SU-GR-CRDFs in healthy human subject. In vivo evaluation of MU-GR-CRDFs was carried out in Wistar rats for studying their gastroretention. For studies involving human subject, approval of Institutional Human Ethics Committee of B.I.T.S., Pilani was taken. All the animal experiments were carried out with the approval of Institutional Animal Ethics Committee of B.I.T.S., Pilani.

Reproducibility of the manufacturing processes employed was also established. Real time stability studies were carried out to establish the reproducibility in release profile and floating characteristics on storage of the formulations under ambient storage condition.

As part of the broader approach for formulation development, preformulation studies like optimization of dissolution media, saturation solubility studies of the drugs in various media, stability studies of the drugs in their respective dissolution media, effect of excipients on the UV absorbency, and drug-excipient compatibility/ interaction studies under accelerated conditions were carried out. To estimate the drugs in pure form, in its pharmaceutical dosage forms, stability samples and in vitro release studies samples, simple,

sensitive, accurate and reproducible UV-visible analytical method was developed and validated for estimation of each drug.

1.7. References

Adkin DA, Davis SS, Sparrow RA, Huckle PD, Wilding IR. The effect of mannitol on the oral bioavailability of cimetidine. *J. Pharm. Sci.,* 1995, 84(12): 1405-1409.

Akiyama Y, Nagahara N, Nara E, Kitano M, Iwasa S, Yamamoto I, Azuma J, Ogawa Y. Evaluation of oral mucoadhesive microspheres in man on the basis of the pharmacokinetics of furosemide and riboflavin, compounds with limited gastrointestinal absorption sites. *J. Pharm. Pharmacol*., 1998, 50(2): 159-66.

Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. *AAPS Pharm. Sci. Tech*., 2005, 6(3): E372-E390.

Asmussen B, Cremer K, Hoffmann HR, Ludwig K, Roreger M, inventors. Expandable gastroretentive therapeutic system with controlled active substance release in gastrointestinal tract. US Patent 6290989, 2001.

Atyabi F, Sharma HL, Mohammed HAH, Fell JT. In vivo evaluation of a novel gastro retentive formulation based on ion exchange resins. *J. Control. Release,* 1996, 42(2): 105-113.

Babu VBM, Khar RK. In vitro and in vivo studies of sustained release floating dosage forms containing salbutamol sulphate. *Pharmazie,* 1990, 45(4): 268-270.

Backon J, Hoffman A. The lateral decubitus position may affect gastric emptying through an autonomic mechanism: the skin pressure-vegetative reflex. *Br. J. Clin. Pharmacol.*, 1991, 32(1): 138-139.

Bannister LH. Alimentary system. In: *Gray's Anatomy. XXXVIII*. Williams PL. Ed., Churchill Livingstone, New York, USA, 1995, p. 1683-1812.

Bardelmeijer HA, van Tellingen O, Schellens JH, Beijnen JH. The oral route for the administration of cytotoxic drugs: strategies to increase the efficiency and consistency of drug delivery. *Invest. New Drugs,* 2000, 18(3): 231-241.

Barley NF, Howard A, Callaghan DO, Legon S, Walters JRF. Epithelial calcium transporter expression in human duodenum. *Am. J. Physiol. Gastrointest. Liver Physiol.,* 2001, 280(2): G285-G290.

Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int. J. Pharm.,* 2000, 195(1): 125-135.

Bechgaard H, Ladefoged K. Distribution of pellets in gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. *J. Pharm. Pharmacol.*, 1978, 30(11): 690-692.

Berner B, Louie-Helm J. Tablet shapes to enhance gastric retention of swellable controlled release oral dosage forms. US Patent 6488962, 2002.

Bernkop-Schnürch A, Hornof M, Guddi D. Thiolated chitosans. *Eur. J. Pharm. Biopharm.*, 2004, 57(1): 9-17.

Bernkop-Schnürch A, Kast CE, Guddi D. Permeation enhancing polymers in oral delivery of hydrophilic macromolecules: thiomer/ GSH systems. *J. Control. Release*, 2003, 93(2): 95-103.

Bolton S, Desai S. Floating non-compressed sustained release tablets. US Patent 4814179, 1992.

Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics: A treatise. 1st Edn., Vallabh Prakashan, Delhi, India, 1995, p. 335-371.

Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein gelatin beads floating properties. *Int. J. Pharm.*, 2000, 198(2): 157-165.

Burton S, Washington N, Steele RJ, Musson R, Feely L. Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa. *J. Pharm. Pharmacol*., 1995, 47(11): 901-906.

Caldwell LJ, Gardner CR, Cargill RC, Higuchi T. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 4758436, 1988a.

Caldwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 4736904, 1988b.

Caldwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 4767627, 1988c.

Caston AJ, Davis SS, Williams P. The potential of fimbrial proteins for delaying intestinal transit of oral drug delivery systems. *Proc. Intern. Symp. Control. Release Bioact. Mater.*, 1990, 17: 313-314.

Chauhan B, Shimpi S, Mahadik KR, Paradkar A. Preparation and evaluation of floating risedronate sodium Gelucire® 39/01 matrices. *Acta Pharm.*, 2004, 54(3): 205-214.

Chen J, Belvins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. *J. Control. Release*, 2000, 64(1): 39-51.

Chen J, Park K. Synthesis and characterization of superporous hydrogel composites. *J. Control. Release*, 2000, 65(1): 73-82.

Chen GL, Hao WH. In vitro performance of floating sustained release capsules of verapamil. *Drug Dev. Ind. Pharm.*, 1998, 24(11): 1067-1072.

Cheuh HR, Zia H, Rhodes CT. Optimization of sotalol floating and bioadhesive extended release tablet formulation. *Drug Dev. Ind. Pharm.*, 1995, 21(15): 1725-1747.

Chien YW. Novel drug delivery systems. 2nd Edn,, Marcel Dekker, New York, USA, 1981, p. 2-35.

Chiou WL, Barve A. Linear correlation of the fraction of oral dose absorbed of 64 drugs between humans and rats. *Pharm. Res.*, 1998, 15(11): 1792-1795.

Chitnis V, Malshe VS, Lalla JK. Bioadhesive polymers synthesis, evaluation and application in controlled release tablets. *Drug Dev. Ind. Pharm.,* 1991, 17(6): 879-892.

Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate beads for floating drug delivery: effects of CO_2 gas forming agents. *Int. J. Pharm.*, 2002, 239(1-2): 81-91.

Clarke GM, Newton JM, Short MD. Gastro intestinal transit of pellets of differing size and density. *Int. J. Pharm.*, 1993, 100(1-3): 81-92.

Cleary J, Lai LC, Shaw RK, Straatman-Iwanowska A, Donnenberg MS, Frankel G, Knutton S. Enteropathogenic Escherichia coli (EPEC) adhesion to intestinal epithelial cells: Role of bundle-forming pili (BFP), EspA filaments and intimin. *Microbiology*, 2004, 150(3): 527-538.

Conway BR. Drug delivery strategies for the treatment of *Helicobacter pylori* infections. *Curr. Pharm. Des.*, 2005, 11(6): 775-790.

Cook JD, Carriaga M, Kahn SG, Schalch W, Skikne BS. Gastric delivery system for iron supplementation. *Lancet*, 1990, 335(8698): 1136-1139.

Coupe AJ, Davis SS, Evans DF, Wilding IR. Correlation of the gastric emptying of non-disintegrating tablets with gastrointestinal motility. *Pharm. Res.*, 1991, 8(10): 1281-1285.

Cousins RJ, McMahon RJ. Integrative aspects of zinc transporters. *J. Nutrition*, 2000, 130(5): 1384S-1387S.

Curatolo WJ, Lo J. Gastric retention system for controlled drug release. US Patent 5443843, 1995.

Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system ranitidine hydrochloride: Formulation and in vitro evaluation. *AAPS Pharm. Sci. Tech.,* 2004, 5(2): Article 34.

Davis SS, Hardy JG, Fara JW. Transit of pharmaceutical dosage forms through the small intestine. *Gut*, 1986, 27(8): 886-892.

Davis SS, Wilding EA, Wilding IR. Gastrointestinal transit of a matrix tablet formulation: comparison of canine and human data. *Int. J. Pharm.*, 1993, 94(1-3): 235-238.

Davis SS, Illum L, Hinchcliffe M. Gastrointestinal transit of dosage forms in the pig. *J. Pharm. Pharmacol.*, 2001, 53(1): 33-39.

Davis SS. Formulation strategies for absorption windows. *Drug Discov. Today*, 2005, 10(4): 249-257.

Desai S, Bolton S. A floating controlled release drug delivery system: In vitro - in vivo evaluation. *Pharm. Res.*, 1993, 10(9): 1321-1325.

Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled release drug delivery systems for prolonged gastric residence: An overview. *Drug Dev. Ind. Pharm.*, 1996, 22(6): 531-539.

Dobson CL, Davis SS, Chauhan S, Sparrow RA, Wilding IR. The effect of ileal brake activators on the oral bioavailability of atenolol in man. *Int. J. Pharm.*, 2002, 248(1): 61-70.

Dorkoosh FA, Verhoef JC, Borchard G, Rafiee-Tehrani M, Verheijden JH, Junginger HE. Intestinal absorption of human insulin in pigs using delivery systems based on superporous hydrogel polymers. *Int. J. Pharm.*, 2002, 247(1-2): 47-55.

Dressman JB, Berardi RR, Dermentzoglou LC, Russel TL, Schmaltz SP, Barnett JL, Jarvenpaa KM. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm. Res.*, 1990, 7(7): 756-761.

Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm. Res.*, 1998, 15(1): 11-22.

Ehrlein H-J. Motility of the pyloric sphincter studied by the inductograph method in conscious dogs. *Am. J. Physiol.*, 1988, 17(5): G650-G657.

Ehrlein H-J. A new technique for simultaneous radiography and recording of gastrointestinal motility in unanesthetized dogs. *Lab. Anim. Sci.*, 1990, 30(5): 879-884.

El-Gibaly I. Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres. *Int. J. Pharm.*, 2002a, 249(1-2): 7-21.

El-Gibaly I. Development and evaluation of novel floating chitosan microcapsules: comparision with non floating chitosan microspheres. *Int. J. Pharm.*, 2002b, 249(1-2): 39-47.

El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral drug delivery system. *Int. J. Pharm.*, 2001, 220(1-2): 13-21.

Fabregas JL, Claramunt J, Cucala J, Pous R, Siles A. In vitro testing of an antacid formulation with prolonged gastric residence time. *Drug Dev. Ind. Pharm.*, 1994, 20: 1199-1212.

Frances S, Fella JT, Colletta JH, Martini LG, Sharma HL, Smith AM. Citric acid prolongs the gastro-retention of a floating dosage form and increases bioavailability of riboflavin in the fasted state. *Int. J. Pharm.*, 2006, 308(1-2): 14-24

Garg S, Sharma S. Gastroretentive drug delivery systems. In: *Business Briefing: Pharmatech*. 5th Edn., 2003, p. 160-166.

GlaxoSmithKline- Zovirax Prescribing Information. 2003, p. 1-9. Available at: http://us.gsk.com/products/assets/us_zovirax.pdf.

Gruber P, Rubinstein A, Li VHK, Bass P, Robinson JR. Gastric emptying of nondigestible solids in the fasted dog. *J. Pharm. Sci.*, 1987, 76(2): 117-122.

Gu TH, Chen SX, Zhu JB, Song DJ, Guo JZ, Hou JM. Pharmacokinetics and pharmaco-dynamics of diltiazem floating tablets [in Chinese]. *Chung Kao Yao Li Hsuesh Pao.*, 1992, 13(6): 527-531.

Guddi D, Krauland AH, Bernkop-Schnürch A. Systemic peptide delivery via the stomach: In vivo evaluation of an oral dosage form for salmon calcitonin. *J. Control. Release*, 2003, 92(1-2): 125-135.

Gutierrez-Rocca DJ, Omidian H, Shah K. A report on progress in gastroretentive drug delivery systems. *Pharmatech.*, 2003, p. 152-156.

Hamilton JK, Polter DE. Gastrointestinal Disease-V. Sleisenger MH, Fordtran JS. Eds., W.B. Saunders, Philadelphia, USA, 1993, p. 286-292.

Harringan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 4055178, 1977.

Hasler WL. Textbook of Gastroenterology II. Vol. 1**.** Yamada T. Ed., J.B. Lippincott, Philadelphia, USA, 1995, p. 181-206.

He P, Davis SS, Illum L. Chitosan microspheres prepared by spray drying. *Int. J. Pharm*., 1999, 187(1): 53-65.

Hejazi R. Chitosan based gastrointestinal delivery systems. *J. Control. Release*, 2003, 89(2): 151-165.

Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxycillin trihydrate. *Int. J. Pharm.*, 1992, 86(1): 79-88.

Hoffman A, Stepensky D. Pharmacodynamic aspects of modes of drug administration for optimization of drug therapy. *Crit. Rev. Ther. Drug Carrier Sys.*, 1999, 16(6): 571-639.

Hoffman A. Pharmacodynamic aspects of sustained release preparations. *Adv. Drug Deliv. Rev.* 1998, 33(3): 185-199.

Hossain M, Abramowitz W, Watrous BJ, Szpunar GJ, Ayres JW. Gastrointestinal transit of nondisintegrating, noneroadible oral dosage forms in pigs. *Pharm. Res.*, 1990, 7: 1163-1166.

Hou H, Zhu JB, Xiong Q. Sustained release intragastric tablets containing diltiazem HCl. *Zhogguo Yiyao Gongye Zazhi*, 1991, 22: 156-169.

Hou SY, Cowles VE, Berner B. Gastric retentive dosage forms: A review. *Crit. Rev. Ther. Drug Carrier Sys.*, 2003, 20(6): 459-497.

Hwang S-J, Park H, Park K. Gastric retentive drug delivery systems. *Crit. Rev. Ther. Drug Carrier Sys.*, 1998, 15(3): 243-284.

Iannuccelli V, Coppi G, Sansone R, Ferolla G. Air compartment multiple unit system for prolonged gastric residence. Part II. In vivo evaluation. *Int. J. Pharm.*, 1998, 174(1-2): 55-62.

Ichikawa M, Watanabe S, Miyake Y. Granule remaining in stomach. US Patent 4844905, 1989.

Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. I: Prepration and in vitro evaluation of floating and sustained release kinetics. *J. Pharm. Sci.*, 1991a, 80(11): 1062-1066.

Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. II: In vivo evaluation of floating and sustained release characteristics with para amino benzoic acid and isosorbide dinitrate as model drugs. *J. Pharm. Sci.*, 1991b, 80(12):1153-1156.

Illum L, Williams P, Caston, AJ. Adhesive drug delivery composition. US Patent 6387408, 1998.

Inagi T, Shirai H, Yamaguchi N, Nishino T. Medicinal compositions adhering to stomach/duodenum. US Patent 6582720, 2003.

Inouye K, Machida Y, Sannan T, Nagai T. Buoyant sustained release tablets based on chitosan. *Drug Des. Deliv.*, 1988, 2(3): 165-175.

Inouye K, Machida Y, Sannan T, Nagai T. Buoyant sustained release granules based on chitosan. *Drug Des. Deliv.*, 1989, 4(1): 55-67.

Jacob J, Carter B, Doane R, Magiera D, Mathiowitz E, Medeiros S, Nangia A, Santos C, Shohat-Ezer D, Shaked Z. Gastroretentive, bioadhesive drug delivery system for controlled release of acyclovir: pharmacokinetics of BioVir^{TM} CR in a fed beagle dog model. Spherics Inc., Rhode Island, USA, 2006.

Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and in vitro characterization. *J. Control. Release*, 2005, 107(2): 300-309.

Jantzen GM, Robinson JR. Modern Pharmaceutics. Gilbert S, Rhodes CT. Eds., 3rd Edn. Marcel Dekker, New York, USA, 1996, p. 575-610.

Jayanthi G, Jayaswal SB, Srivastava AK. Formulation and evaluation of terfenadine microballoons for oral controlled release. *Pharmazie*, 1995, 50(11): 769-770.

Jimenez-Castellanos NR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. *Drug Dev. Ind. Pharm.*, 1993, 19: 143.

Johnson RH, Rowe EL. Medicinal dosage forms of unpolymerized thiolated gelatin with a crosslinking accelerating agent providing slowly released medication from a swollen matrix. US Patent 3574820, 1971.

Jordon DE. Gastroretention in controlled drug delivery. In: *Bioadhesion - Possibilities and Future Trends*. Gurney R, Junginger HE. Eds., Wissenschaftliche Verlag, 1990, p. 165-176.

Joseph NJ, Laxmi S, Jayakrishnan A. A floating type oral dosage from for piroxicam based on hollow microspheres: In vitro and in vivo evaluation in rabbits. *J. Control. Release*, 2002, 79(1-3): 71-79.

Kakar SM, Paine MF, Stewart PW, Watkins PB. 6'7'-Dihydroxybergamottin contributes to the grapefruit juice effect. *Clin. Pharmacol. Ther.*, 2004, 75: 569-579.

Kamba M, Seta Y, Kusai A, Ikeda M, Nishimura K. A unique dosage from to evaluate the mechanical destructive force in the gastrointestinal tract. *Int. J. Pharm.*, 2000, 208(1-2): 61-70.

Kararli TT. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. *Biopharm. Drug Dispos.*, 1995, 16(5): 351-380.

Katayama H, Nishimura T, Ochi S, Tsuruta Y, Yamazaki Y. Sustained release liquid preparation using sodium alginate for eradication of Helicobacter pylori. *Biol. Pharm. Bull.*, 1999, 22(1): 55-60.

Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drug release characteristics (in vivo). *J. Control. Release*, 1991, 16(3): 279-290.

Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma scintigraphy. *J. Control. Release*, 1999, 58(2): 195-205.

Kelly KA, Morley KD, Wilbur BG. Effect of corporal and antral gastrojejunostomy on canine gastric emptying of solid spheres and liquids. *Br. J. Surg.*, 1973, 60(11): 880-884.

Khattar D, Ahuja A, Khar RK. Hydrodynamically balanced systems as sustained release dosage form for propranolol hydrochloride. *Pharmazie*, 1990, 45(5): 356-358.

Khosla R, Davis SS. The effect of tablet size on the gastric emptying of non-disintegrating tablets. *Int J. Pharm.*, 1990, 62: R9-R11.

Klausner EA, Lavy E, Stepensky D, Friedman M, Hoffman A. Novel gastroretentive dosage forms: Evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. *Pharm. Res.*, 2002, 19(10): 1516-1523.

Klausner EA, Lavy E, Friedman M, Hoffman A. Review: Expandable gastroretentive dosage forms. *J. Control. Release*, 2003a, 90(2): 143-162.

Klausner EA, Lavy E, Stepensky D, Cserepes E, Barta M, Friedman M, Hoffman A. Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration to healthy volunteers. *J. Clin. Pharmacol*., 2003b, 43(7): 711-720.

Klausner EA, Lavy E, Barta M, Cserepes E, Friedman M, Hoffman A. Novel gastroretentive dosage forms: Evaluation of gastroretentivity and its effect on levodopa absorption in humans. *Pharm. Res.*, 2003c, 20(9): 1466-1473.

Klausner EA, Eyal S, Lavy E, Friedman M, Hoffman A. Novel levodopa gastroretentive dosage form: In vivo evaluation in dogs. *J. Control. Release*, 2003d, 88(1): 117-126.

Kohri N, Naasani I, Iseki K. Improving the oral bioavailability of sulphiride by a gastric retained form in rabbits. *J. Pharm. Pharmacol.*, 1995, 48: 371-374.

Kroening KD, Zimmerman NP, Bass P, Oaks JA. Guanosine 3', 5'-cyclic monophosphate: A tapeworm-secreted signal molecule communicating with the rat host's small intestine. *J. Parasitol*., 2003, 89(6): 1136-1141.

Laby RH. Device for administration to ruminants. US Patent 3844285, 1974.

Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. *Int. J. Pharm.*, 2003, 253(1-2): 13-22.

Lin HC, Neevel C, Chen PS, Suh G, Chen JH. Slowing of intestinal transit by fat or peptide YY depends on beta-adrenergic pathway. *Am. J. Physiol. Gastrointest. Liver Physiol*., 2003, 285(6): G1310-G1316.

Liu CH, Kao YH, Chen SC, Sokoloski TD, Sheu MT. In vitro and in vivo studies of the diclofenac sodium controlled release matrix tablets. *J. Pharm. Pharmacol*., 1995, 47(5): 360-364.

Liu Z, Lu W, Qianb L, Zhang X, Zeng P, Pan J. In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin. *J. Control. Release*, 2005, 102(1): 135-144.

Lordi NG. Sustained release dosage forms. In: *The Theory and Practice of Industrial Pharmacy*. Lachman L, Lieberman HA, Kanig JL. Eds., 4th Edn., Varghese Publishing House, Bombay, India, 1987, p. 430-456.

Macheras P, Reppas C, Dressman JB. Biopharmaceutics of Orally Administered Drugs. Ellis Horwood, London, 1995, p. 72-75.

Mamajek RC, Moyer ES. Drug-dispensing device and method. US Patent 4207890, 1980.

Marathe PH, Wen Y, Norton J, Greene DS, Barbhaiya RH, Wilding IR. Effect of altered gastric emptying and gastrointestinal motility on metformin absorption. *Br. J. Clin. Pharmacol*., 2000, 50(4): 325-332.

Martin NE, Collison KR, Martin LL, Tardif S, Wilding I, Wray H, Barrett JS. Pharmacoscintigraphic assessment of the regional drug absorption of the dual angiotensin-converting enzyme/neutral endopeptidase inhibitor, M100240, in healthy volunteers. *J. Clin. Pharmacol*., 2003, 43(5): 529-538.

Mathiowitz E, Chickering D, Jacob J, Santos C. Bioadhesive drug delivery systems. In: *Encyclopedia of Controlled Drug Delivery*. John Wiley & Sons, Singapore, 1999, p. 9-45.

Mazer N, Abisch E, Gfeller JC, Laplanche R, Bauerfeind P, Cucala M, Lukachich M, Blum A. Intragastric behaviour and absorption kinetics of a normal and floating modified release capsules of isardipine under fasted and fed conditions. *J. Pharm. Sci.*, 1988, 77(8): 647-657.

Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J. Pharm. Sci.*, 1994, 83(2): 239-245.

Michaelis AS. Drug delivery device with self activated mechanism for retaining device in selected area. US Patent 3786813, 1974.

Michaelis AS, Bashwa JD, Zaffaroni A. Integrated device for administering beneficial drug at programmed rate. US Patent 3901232, 1975.

Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology*, 1984, 86(6): 1592-1610.

Miyazaki S, Yamaguchi H, Yokouchi C, Takada M, Huo WM. Sustained release and intra gastric floating granules of indomethacin using chitosan in rabbits. *Chem. Pharm. Bull.*, 1988, 36(10): 4033-4038.

Moes AJ. Gastroretentive dosage forms. *Crit. Rev. Ther. Drug Carrier Sys.*, 1993, 10(2): 143-195.

Mojaverian P, Ferguson RK, Vlasses PH, Rocci ML Jr, Oren A, Fix JA, Caldwell LJ, Gardner C. Estimation of gastric residence time of the Heidelberg capsules in humans: Effect of varying food composition. *Gastroenterology*, 1985, 89(2): 392-397.

Mojaverian P, Vlasses PH, Kellner PE, Rocci ML Jr. Effects of gender, posture, and age on gastric residence time of an indigestible solid: Pharmaceutical considerations. *Pharm. Res.*, 1988, 5(10): 639-644.

Mojaverian P, Reynolds JC, Ouyang A, Wirth F, Kellner PE, Vlasses PH. Mechanism of gastric emptying of a non-disintegrating radiotelemetry capsule in man. *Pharm. Res.*, 1991, 8(1): 97-100.

Montisci MJ, Dembri A, Giovannuci G, Chacun H, Duchene D, Ponchel G. Gastrointestinal transit and mucoadhesion of colloidal suspensions of Lycopersicon esculentum L. and Lotus tetragonolobus lectin-PLA microsphere conjugates in rats. *Pharm. Res.*, 2001, 18(6): 829-837.

Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. *Pharmazie*, 2003, 58(1): 38-43.

Muthusamy KG, Indarazan G, Ravi TK. Preparation and evaluation of lansoprazole floating micropellets. *Indian J. Pharm. Sci.*, 2005, 67(1): 75-79.

Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. *AAPS Pharm. Sci. Tech.*, 2006, 7(2): Article 34.

Ogihara H, Suzuki T, Nagamachi Y, Inui K, Takata K. Peptide transporter in the rat small intestine: ultrastructural localization and the effect of starvation and administration of amino acids. *Histochem. J.*, 1999, 31(3): 169-174.

Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsule: a stomach directed drug delivery system for misoprostal. *Pharm. Res.*, 1992, 9(3): 298-302.

Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: In vitro and in vivo evaluations of bilayer tablet formulations. *Drug Dev. Ind. Pharm.*, 2000, 26(8): 857-866.

Patel JK, Patel RP, Amin AF, Patel AM. Formulation and evaluation of mucoadhesive glipizide microspheres. *AAPS Pharm. Sci. Tech.*, 2005, 6(1): E49-E55.

Patel VF, Patel NM. Intragastric Floating drug delivery system of cefuroxime axetil: In vitro evaluation. *AAPS Pharm. Sci. Tech.*, 2006, 7(1): Article 17.

Phuapradit W, Bolton S. Influence of tablet density on oral absorption of sustained release acetaminophen matrix tablets. *Drug Dev. Ind. Pharm.*, 1991, 17(8): 1097-1107.

Pogany SA, Zentner GM. Bioerodible thermoset elastomers. US Patent 5217712, 1993.

Polnok A, Verhoef JC, Borchard G, Sarisuta N, Junginger HE. In vitro evaluation of intestinal absorption of desmopressin using drug delivery systems based on superporous hydrogels. *Int. J. Pharm.*, 2004, 269(2): 303-310.

Rahman Z, Ali M, Khar RK. Design and evaluation of bilayer floating tablets of captopril. *Acta Pharm.*, 2006, 56(1): 49-57.

Read NW, Sugden K. Gastrointestinal dynamics and pharmacology for the optimum design of controlled release oral dosage forms. *Crit. Rev. Ther. Drug Carrier Sys.*, 1987, 4(3): 221-263.

Reddy LH, Murthy RSR. Floating dosage systems in drug delivery. *Crit. Rev. Ther. Drug Carrier Sys.*, 2002, 19(6): 553-585.

Roth AD, Maibach R, Martinelli G, Fazio N, Aapro MS, Pagani O, Morant R, Borner MM, Herrmann R, Honegger H, Cavalli F, Alberto P, Castiglione M, Goldhirsch A. Docetaxel (Taxotere®)-cisplatin (TC): An effective drug combination in gastric carcinoma. *Annals. Oncology*, 2000, 11(3): 301-306.

Rouge N, Allemann E, Gex-Fabry M, Balant L, Cole ET, Buri P, Doelker E. Comparative pharmacokinetic study of a floating multiple unit capsules, a high density multiple unit capsule and an immediate release tablet containing 25 mg atenolol. *Pharm. Acta Helv.*, 1998a, 73(2): 81-87.

Rouge N, Cole ET, Doelker E, Buri P. Buoyancy and drug release patterns of floating minutesitablets containing piretanide and atenolol as model drugs. *Pharm. Dev. Technol.*, 1998b, 3(1): 73-84.

Rubinstein A, Friend DR. Polymeric site-specific pharmacotherapy. Domb AJ Ed., Wiley, Chichester, UK, 1994, p. 267-313.

Rubinstein A, Li VHK, Gruber P, Robinson JR. Oral sustained release formulations: design and evaluation. Yacobi A, Halperin-Walega E. Eds., Pergamon Press, New York, USA, 1988, p. 125-156.

Rubinstein A. Approaches and opportunities in colon-specific drug delivery. *Crit. Rev. Ther. Drug Carrier Sys.*, 1995, 12(2-3): 101-149.

Rubinstein A, Tirosh B, Baluom M, Nassar T, David A, Radai R, Gliko-Kabir I, Friedman M. The rationale for peptide drug delivery to the colon and the potential of polymeric carries as effective tools. *J. Control. Release*, 1997, 46(1): 59-73.

Russell TL, Berardi RR, Barnett JL, Dermentzoglou LC, Jarvenpaa KM, Schmaltz SP, Dressman JB. Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women. *Pharm. Res.*, 1993, 10(2): 187-196.

Säkkinen M, Marvola J, Kanerva H, Lindevall K, Lipponen M, Kekki T, Ahonen A, Marvola M, Gamma scintigraphic evaluation of the fate of microcrystalline chitosan granules in human stomach. *Eur. J. Pharm. Biopharm*., 2004, 57(1): 133-143.

Salessiotis N. Measurement of the diameter of the pylorus in man. I. Experimental project for clinical application. *Am. J. Surg*., 1972, 124: 331-333.

Sato Y, Kawashima Y, Takeuchi H, Yamamoto H, Fujibayashi Y. In vivo evaluation of riboflavin containing microballoons for a floating controlled drug delivery system in healthy human volunteers. *J. Control. Release*, 2003, 93(1): 39-47.

Sato Y, Kawashima Y, Takeuchi H, Yamamoto H, Fujibayashi Y. Pharmacoscintigraphic evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. *J. Control. Release*, 2004a, 98(1): 75-85.

Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. In vitro and in vivo evaluation of riboflavin containing microballoons for a floating controlled drug delivery system in healthy humans. *Int. J. Pharm.*, 2004b, 275(1-2): 97-107.

Schmitz T, Leitner VM, Bernkop-Schnürch A. Oral heparin delivery: Design and in vivo evaluation of a stomach-targeted mucoadhesive delivery system. *J. Pharm. Sci.*, 2005, 94(5): 966-973.

Shalaby WSW, Park K. Biochemical and mechanical characterization of enzyme-digestible hydrogels. *Pharm. Res.*, 1990, 7(8): 816-823.

Shalaby WSW, Blevins WE, Park K. Use of ultrasound imaging and fluoroscopic imaging to study gastric retention of enzyme-digestible hydrogels. *Biomaterials*, 1992a, 13(5): 289-296.

Shalaby WSW, Blevins WE, Park K. In vitro and in vivo studies of enzyme-digestible hydrogels for oral drug delivery. *J. Control. Release*, 1992b, 19(1-3): 131-144.

Sharma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. *Int. J. Pharm.*, 2006, 313(1-2): 150-158.

Sheth PR, Tossouniam JL. Sustained release tablet formulations. US Patent 4126672, 1978.

Sheth PR, Tossouniam JL. The hydrodynamically balanced system: A novel drug delivery system for oral use. *Drug Dev. Ind. Pharm.*, 1984, 10(2): 313-339.

Shimoda J, Onishi H, Machida Y. Bioadhesive characteristics of chitosan microspheres to the mucosa of rat small intestine. *Drug Dev. Ind. Pharm.*, 2001, 27(6): 567-576.

Siegmund W, Ludwig K, Engel G, Zschiesche M, Franke G, Hoffmann A, Terhaag B, Weitschies W. Variability of intestinal expression of P-glycoprotein in healthy volunteers as described by absorption of talinolol from four bioequivalent tablets. *J. Pharm. Sci.*, 2003, 92(3): 604-610.

Singh BN. Effects of food on clinical pharmacokinetics. *Clin. Pharmacokinet*., 1999, 37(3): 213-255**.**

Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J. Control. Release*, 2000, 63(3): 235-59.

Sonobe T, Watanabe S, Katsuma M, Takamatsu N, Kouno Y, Takagi H. Gastric retention device. Eur. Patent 0415671, 1991.

Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled release systems for cardiovascular drugs: Preparation and release characteristics. *Drug Dev. Ind. Pharm.*, 2001a, 27(6): 507-515.

Soppimath KS, Kulkarni AR, Rudzinski WE, Aminabhavi TM. Microspheres as floating drug delivery system to increase the gastric residence of drugs. *Drug Metab. Rev*., 2001b, 33(2): 149-160.

Spickett RGW, Vidal JLF, Escoi JC. Antacid preparation having prolonged gastric residence. US Patent 5288506, 1993.

Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Morphology and buoyancy of oil-entrapped calcium pectinate gel beads. *AAPS J.,* 2004, 6(3): Article 24.

Sriamornsak P, Thirawong N, Puttipipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behaviour of metronidazole. *Eur. J. Pharm. Sci.*, 2005, 24(4): 363-373.

Srivastava AK, Ridhurkar DN, Wadha WS. Floating microspheres of cimetidine: Formulation, characterization and in vitro evaluation. *Acta Pharm.,* 2005, 55(3): 277-285.

Streubel A, Siepmann J, Bodmeier R. Floating microparticles based on low density foam powder. *Int. J. Pharm.*, 2002, 241(2): 279-292.

Streubel A, Siepmann J, Bodmeier R. Multiple unit gastroretentive drug delivery systems: A new preparation method for low density microparticles. *J. Microencapsul.*, 2003a, 20(3): 329-347.

Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: Effect of formulation and processing parameters on drug release. *Eur. J. Pharm. Sci*. 2003b, 18(1): 37-45.

Takishima J, Onishi H, Machida Y. Prolonged intestinal absorption of cephradine with chitosan-coated ethylcellulose microparticles in rats. *Biol. Pharm. Bull.*, 2002, 25(11): 1498-1502.

Talukder R, Fassihi R. Gastroretentive delivery systems: Hollow beads. *Drug Dev. Ind. Pharm.*, 2004, 30(4): 405-412.

Talwar N, Sen H, Staniforth JN. Orally administered controlled drug delivery system providing temporal and spatial control. US Patent 6261601, 2001.

Tamura S, Tokunaga Y, Ibuki R, Amidon GL, Sezaki H, Yamashita S. The site-specific transport and metabolism of tacrolimus in rat small intestine. *J. Pharmacol. Exp. Ther.*, 2003, 306(1): 310-316.

Thanoo BC, Sunny MC, Jayakrishnan A. Oral sustained release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluids. *J. Pharm. Pharmacol.*, 1993, 45(1): 21-24.

Timmermans J, Gansbeke VB, Moes AJ. Assessing by gamma scintigraphy the in vivo buoyancy of dosage forms having known size and floating force profiles as a function of time. Vol I. Proceedings of the 5th International Conference on Pharmacy Technology. APGI, Paris, France, 1989, p. 42-51.

Timmermans J, Moes AJ. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. *J. Pharm. Sci.*, 1994, 83(1): 18-24.

Tokumura T, Machida Y. Preparation of amoxicillin intragastric buoyant sustained release tablets and the dissolution characteristics. *J. Control. Release,* 2006, 110(3): 581-586.

Torrado S, Prada P, de la Torre PM, Torrado S. Chitosan-poly(acrylic) acid polyionic complex: In vivo study to demonstrate prolonged gastric retention. *Biomaterials*, 2004, 25(5): 917-923.

Umamaheshwari RB, Jain S, Jain NK. A new approach in gastroretentive drug delivery system using cholestyramine. *Drug Deliv.*, 2003, 10(3): 151-160.

Urquhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US Patent 4434153, 1984.

Van-Citters GW, Lin HC. The ileal brake: A fifteen-year progress report. *Curr. Gastroenterol. Rep.*, 1999, 1(5): 404-409.

Whitehead L, Fell JT, Collett JH. Development of a gastroretentive dosage form. *Eur. J. Pharm. Sci.*, 1996, 4(Suppl.1): 182.

Whitehead L, Fell JT, Collett JH, Sharma HL, Smith A. Floating dosage forms: An in vivo study demonstrating prolonged gastric retention. *J. Control. Release,* 1998, 55(1): 3-12.

Whitehead L, Collett JH, Fell JT. Amoxycillin release from a floating dosage form based on alginates. *Int. J. Pharm.*, 2000, 210(1): 45-49.

Wilding IR. Site-specific drug delivery in the gastrointestinal tract. *Crit. Rev. Ther. Drug Carrier Sys.*, 2000, 17(6): 557-620.

Wilding IR, Coupe AJ, Davis SS. The role of γ-scintigraphy in oral drug delivery. *Adv. Drug Deliv. Rev.*, 2001, 46(1-3): 103-124.

Wilding IR, Newman SP. Giving decisions more precisions in drug development: Use of radionuclide imaging. *Drug Deliv. Sys. Sci.*, 2001, 1: 5-10.

Wilding IR, Prior DV. Remote controlled release capsules in human drug absorption (HDA) studies. *Crit. Rev. Ther. Drug Carrier Sys.*, 2003, 20(6): 405-431.

Wilson CG, Washington N. The stomach: Its role in oral drug delivery. In: *Physiological pharmacetical: Biological barriers to drug absorption.* Rubinstein MH. Ed., Ellis Horwood, Chichester, UK, 1989, p. 47-70.

Wu W, Zhou Q, Zhang HB, Ma GD, Fu CD. Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. *Yao Xue Xue Bao.*, 1997, 32(10): 786-790.

Xu X, Sun M, Zhi F, Hu Y. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. *Int. J. Pharm.*, 2006, 310(1-2): 139-145.

Yang L, Esharghi J, Fassihi R. A new intra gastric delivery system for the treatment of helicobacter pylori associated gastric ulcers: In vitro evaluation. *J. Control. Release,* 1999, 57(3): 215-222.