3. Literature Review

Patel et al., 2006; investigated an intragastric drug delivery system for Cefuroxime axetil. The 3\(^2\) full factorial design was employed to evaluate contribution of HPMC K4M / HPMC K100 LV ratio (polymer blend) and SLS on drug release from HPMC matrices. Tablets were prepared using direct compression technique. Formulations were evaluated for in vitro buoyancy and drug release study using USP 24 paddle type dissolution apparatus using 0.1 N HCl as a dissolution medium. Multiple regression analysis was performed for factorial design batches to evaluate the response. All formulation had floating lag time below 2 minutes and constantly floated on dissolution medium for more than 8 hours. It was found that polymer blend and SLS significantly affect the time required for 50% of drug release, percentage drug release at 12 hours, release rate constant and diffusion exponent (p<0.05).

Chien et al., 2003; have studied effect of HPMC and Carbopol on release and floating properties of calcium carbonate drug delivery system using 2\(^3\) factorial design. The aim of this study is to investigate the effect of formulation variable on drug release and floating properties.

Klausner et al., 2003; designed expandable Gastro retentive dosage form and found improved in vivo absorption for narrow absorption window drugs, and evaluated their gastroretentive properties. Then to asses the pharmacokinetics of Levodopa compound in healthy volunteers.

Sonar et al., 2005; The aim of the present research was to develop a bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach using Rosiglitazone Maleate as a model drug. The *in vitro* drug release, buoyancy lag-time, detachment force and swelling index were evaluated. The *in vitro* drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The floating ability of the tablets was studied by gamma scintigraphy. The release of Rosiglitazone Maleate from the matrix tablet was followed the first-order release model. The concentration of HPMC significantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 h in the human stomach.
Dave et al., 2004; Prepared gastro retentive drug delivery system of Ranitidine hydrochloride by using low amount of citric acid and high amount of stearic acid favors sustained release and desired dissolution profile.

Baumgartner et al., 2000; developed floating matrix tablet based HPMC and gas generating agents. The investigation shows that tablet composition and mechanical strength have the greatest influence on the floating properties and drug release. With incorporation of a gas generating agent together with MCC, besides optimum floating (floating lag time 30 sec, duration of floating 8 h), the drug loading was also increased. Radiological evidence suggests that, the formulated tablets did not adhere to stomach mucus and that the mean GRT was prolonged by more than 4 hr.

Ichikawa et al., 1991; prepared multiple-unit type of oral floating dosage system in order to prolong the gastric emptying time of the preparation. The inner layer was an effervescent layer and outer layer was a swellable membrane layer and found that drug release from this system was zero order.

Gambhire et al., 2007; Developed effervescent based floating drug delivery is a promising approach to achieve in vitro buoyancy by using gel forming polymer Methocel K 100 M CR and gas generating agent sodium bicarbonate using Diltiazem hydrochloride .The optimized formulation gives the best result i.e. lag time 4.4 min. and floating duration 24 hrs.

Joseph et al. 2002; prepared floating type hollow polycarbonate microsphere of piroxicam using solvent evaporation technique which were capable of floating on simulated gastric fluid. Pharmacokinetic analysis showed that the bioavailability of piroxicam hollow microsphere was about 1.4 times that of free drug and was about 4.8 times for the dosage form consisting of microsphere plus the loading dose the elimination half life was increased by three times that of free drug.

Desai et al., 1993; formulated a novel floating controlled release drug delivery system to increase the gastric retention time and to control drug release. A floating controlled release Theophylline tablet 300 mg having a density of 0.67 was prepared and compared in vitro and in vivo. The in vitro release rate of the floating tablet was
slower. *In vivo* scintigraphy studies for a floating and heavy non floating tablet, under fasting and non fasting conditions, showed that the presence of food significantly increased the gastric retention time for both tablets; the tablet density did not appear to make a difference in the gastric retention time. The floating controlled release Theophylline levels of 2 mg/ml for 24 h. were obtained.

**Chavanpatil et al., 2005;** Sustained release (SR) gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. Different polymers, such as psyllium husk, HPMC K100 M, crospovidone and its combinations were tried in order to get the desired sustained release profile over a period of 24 h. All formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and *in vitro* drug release profile. It was found that dimensional stability of the formulation increases with the increasing psyllium husk. We conclude that psyllium husk and HPMC K100M increases the dimensional stability of the formulations, which is necessary in case of once daily formulations. Sodium bicarbonate acts as a gas-generating agent, which is necessary in case of gastroretentive dosage forms. Crospovidone improved the drug release profile and swelling factor of psyllium husk based formulations. We also conclude that channeling agents, such as betacyclodextrin were useful to increase the initial burst release from psyllium husk based formulations.

**Atyabi et al., 1996;** developed a floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semi permeable membrane to avoid sudden loss of CO$_2$. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO$_2$ generation thereby floating the beads. The *in vivo* behavior of the coated and uncoated beads was monitored in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 h) compared with uncoated beads (1 to 3 h).
Rouge et al., 1998; evaluated the possible advantages of floating and high density dosage forms and their influence on pharmacokinetic parameters. Three formulations of Atenolol, a floating multiple unit capsule, a high density multiple unit capsule, and an immediate release tablet were compared with respect to estimated pharmacokinetic parameters and they found the bioavailability of the two gastro retentive preparations with sustained release characteristics was significantly decreased when compared to the immediate release tablet and floating Minitab lets retained longer in the stomach then the density dosage form.

Iannuccelli et al., 1998; prepared air compartment multiple-unit system for prolonged gastric residence. The floating time (FT) and gastric residence time (GRT) of the floating bead formulation loaded with barium sulphate (Mixobar 60 % Ventricolo), which contained a core of calcium alginate separated by an air compartment from a membrane of calcium alginate / polyvinyl alcohol (molecular weight 100.000), were investigated in an open, controlled, 3-way cross-over conducted study in 6 healthy subjects who were randomized to receive 10 floating beads in a hard gelatin capsule on 3 separate occasions, including the fasted state and the fed state after a single meal or succession of meals. The results showed that barium sulphate floating beads remained buoyant in the gastric contents in both the fed and fasted states. In the fed state after a single meal, the FT and GRT of all the beads were prolonged. After a succession of meals, the FT and GRT of most of the barium sulphate beads were more prolonged than after a single meal.

Jaimini et al., 2006; Prepared effervescent based floating drug delivery system was promising approach to achieve in-vitro buoyancy. The addition of gel forming polymer Methocel (K100 M and K 15 M) and gas generating agent’s sodium bicarbonate along with citric acid was essential for to Sustained the Drug.

Machida et al., 2008; Design and prepared two drug formulations which floated in gastric juice. One a buoyant tablet considered of powdered soyabean protein, drug sodium bicarbonates. The other, a laminated film-type preparation considered of a drug film, an effervescing film containing sodium bicarbonate outer and other drug release regulating time. Cinnarizine, an acid soluble drug was the model drug and cellulose carboxy vinyl polymer was used in preparation of film. Both formulations
showed buoyancy in vitro for the almost five hrs. and the tablet floated for almost 3 hrs in vivo (Beagle dogs) with sustained release properties.

**Xiaoging et al., 2006;** Developed sustained release tablet for Phenoporlamine hydrochloride based on gas forming sodium bicarbonate and matrix forming HPMC K4 M and Carbopol 971 P resulted in tablet floating over simulated gastric fluid for more than 6 h and dissolution profile shows non-fickian diffusion in simulated gastric fluid. Studies demonstrate that floating matrix tablet containing more Carbopol was capable of sustained delivery of the drug for longer period with increased bioavailability.

**Patel et al., 2008;** Developed hydrodynamically balanced tablet of an antibacterial drug Clarithromycin increases gastric residence time and improve bioavailability. Polymer used HPMC K15 M; HPMC K4 M shows better improve in gastric residence time.

**El-Kamel et al., 2001;** Designed a sustained release system for Ketoprofen to increase its residence time in the stomach without contact with the mucosa and were achieved through the preparation of floating microparticles by the emulsion solvent diffusion technique. All the floating microparticle formulations were evaluated for flow properties, packability and release rate.

**Nur et al., 2000;** Developed Captopril floating tablet having bioadhesive property using HPMC (4000 cps and 15000 cps) and Carbopol 934 P as a matrix forming material. They reported that compared to conventional tablet, release of floating tablet was apparently prolonged and tablet hardness was found to be determining factor to the buoyancy of the tablets.

**Kakumanu et al., 2006;** Learning about the behavior of a drug in biological environment enables application of better formulation strategies to improve bioavailability of the same. Cefpodoxime Proxetil (CP) is a prodrug, which is orally administered cephalosporin with only 50 % absolute bioavailability. Despite previous studies, reasons responsible for low bioavailability of CP remain poorly understood. The present study tries to ascertain reasons for the low oral bioavailability of CP. The
in vitro, in situ and ex vivo studies showed interesting results, where metabolism of CP into Cefpodoxime acid (CA) inside the intestinal epithelial cell and preferential efflux of CA into lumen was identified as primary reason for low oral bioavailability of CP. Presence of specific carriers or transportation mechanism on the apical side membrane of enterocyte, than basal side of the same was observed.

Kakumanu et al., 2006; Cefpodoxime Proxetil (CP) is a prodrug with poor oral bioavailability because of its metabolism to Cefpodoxime acid (CA) in luminal contents and intestinal epithelial cells. In the present investigation, regional variability in different segments of the gastrointestinal tract vis-à-vis solubility and metabolism were investigated, and the results indicated potential for a gastro retentive (GR) dosage form. Suitability of a GR dosage from for CP and finally in vivo efficacy were investigated. Thereafter, an effervescent floating GR dosage form was developed for CP and evaluated in rats. The GR dosage form improved the oral bioavailability of CP significantly by about 75%, hence providing a proof-of-concept. The $T_{\text{max}}$ value increased to $1.43 \pm 0.24$ h from $0.91 \pm 0.23$ h of pure drug, while $C_{\text{max}}$ values of $4735 \pm 802$ ng / ml and $3094 \pm 567$ ng / ml were obtained for the GR dosage form and pure drug respectively.

Jaweria et al., 2006; developed once daily formulation and in vitro release evaluation of Cefpodoxime Proxetil using HPMC.

Arvind et al., 2007; investigation of factor responsible for low bioavailability of Cefpodoxime Proxetil. The result of this work showed that enzymatic hydrolysis of cefpodoxime proxetil into parent form in the specific region of GIT is contributing to low bioavailability of it. The higher stability of Cefpodoxime Proxetil in the enzymatic fraction collected from upper part of GIT (stomach and duodenum) indicates potential of gastroretentive dosage form to improve bioavailability of it.

Hill et al., 2010; US patent number US 2010/0216754 described the use of H2 receptor blockers including Lafutidine for the treatment of Gastroesophagal reflux disease (GERD) as well as for non Gastroesophagal reflux disease (NERD).
Satyam et al., 2011; US patent number US2011/0263526 A1 described the use of Nitric oxide releasing drugs including lafutidine for the treatment of GERD and other gastric disorders.

Plachetka et al., 2006; US patent number US 2006/0165797 describes the use of alkaline buffering agents to deliver the drugs H₂ blocker Lafutidine to the acidic environment of stomach. It also describes the use of enteric coating composition to deliver the acid labile drugs to the intestine.

Kajino et al., 2011; described the use of pyrrole compounds including Lafutidine for the treatment of diseases like gastroesophageal reflux disease (GERD), peptic ulcer; NSAIDs induced gastric acid secretion. The invention also describes superiority of these compounds for the treatment of above mentioned diseases as compared to currently available proton pump inhibitors (PPIs).

Carmelo et al., 2005; (Laboratory of Clinical Pharmacology, Department of Anatomy, Pharmacology and Forensic Sciences, School of Medicine and Dentistry, University of Parma, Italy) found that Lafutidine among other newly developed drugs is the most promising drug which can be used for the treatment of GERD and non ulcer dyspepsia. They found that; conversely from ranitidine and Famotidine, Lafutidine increases both daytime and night time intragastric pH in H. pylori-negative subjects and conversely from Omeprazole (and other PPIs) its efficacy is not influenced by the CYP2C19 genotype status. Study in healthy volunteers did show that a single dose (10 mg) of Lafutidine is able to increase intragastric pH more quickly than a single dose (20 mg) of Rabeprazole, the fastest amongst the available PPIs. Both in fasting conditions and in the postprandial state, the duration of the antisecretory action was longer than that of the PPI because the drug maintained the pH over a given threshold for a sustained period of time.

Hiroshi et al., 2003; studied the effect of Lafutidine on gastric mucosa. Based on the study carried out by them it was concluded that Lafutidine is a novel, potent antisecretory agent having lost lasting antisecretory effect. Their findings say that: Lafutidine is a novel histamine H₂-receptor antagonist with both antigastric secretory and gastroprotective actions. In experimental animal models, it has been shown to
have several unique characteristics; among them a potent protective effect against Indomethacin induced intestinal ulceration and necrotizing agent–induced gastro duodenal damage. The effect of the drug has been shown to be mediated at least partially by capsaicin-sensitive sensory neurons, independent of its antisecretory activity; the mucoprotective effect of Lafutidine was shown to be antagonized or attenuated by chemical differentiation with a high dose of capsaicin.

Taking into consideration the research work pursued in the subject and the observed in the review of literature, the following objectives were put up and mentioned in the next chapter.