

THE PHARMA INNOVATION

Gastroretentive Drug Delivery Systems: A Review of Formulation Approaches

Permender Rathee¹, Manish jain¹, Sushila Rathee¹, Arun Nanda², Aashima Hooda*¹

1. Department of Pharmaceutics, PDM College of Pharmacy, Bahadurgarh, India
2. Department of Pharmaceutical Sciences, MDU, Rohtak, India

Gastroretentive dosage forms (GRDF) has received significant interest in the past few decades as they can improve the limitation of most conventional and oral controlled release drug delivery system related to fast gastric-emptying time. An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner. This article gives an overview of the parameters affecting gastric emptying as well as on the main concepts used to design pharmaceutical dosage forms with prolonged gastric residence times. In particular, bioadhesive, size-increasing and floating drug delivery systems are presented and their major advantages and shortcomings are discussed. Both single and multiple unit dosage forms with dual working systems are reviewed. Dual working systems are more efficient than the traditional systems.

Keyword: Gastroretentive Dosage Forms, Gastrointestinal Tract, Bioadhesive Systems, Unfolding Systems, Density Controlled Systems

INTRODUCTION: Now days the oral route represents the predominant and most preferable route for drug delivery for the administration of therapeutic agents. Numerous oral extended release drug delivery systems have been developed to prolong drug release.

An important prerequisite for successful performance for an oral extended release drug delivery system is that the drug should have good absorption throughout the whole gastrointestinal tract (GIT) to ensure continuous absorption of released drug (Chawla et al.2003; Hwang et al., 1998). But for large number of drugs, transport across the intestinal epithelium in each segment of GIT is not uniform and often limited to a particular segment (window) only. So, the oral extended release drug delivery becomes more difficult due to the inability to restrain and localize the drug delivery system within the desired region of GIT.

Corresponding Author's Contact information:
Aashima Hooda *
Department of Pharmaceutics,
PDM College of Pharmacy, Bahadurgarh, India
E-mail: getin.ash@gmail.com

Under such conditions, one of the most feasible approach for achieving a prolonged and predictable drug delivery profile in GIT is to control the gastric residence time by designing a delivery system that is able to reside in stomach or preferably prior to absorption window that would increase the absorption of drugs. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance (Fell, 1996; Streubel et al., 2006; Dave et al., 2005). These considerations have led to development of unique oral controlled release dosage forms with gastroretentive properties.

1. GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Dosage forms that can be retained in the stomach are called gastroretentive drug delivery system (GRDDS). These are the systems which can remain in gastric region for several hours and significantly prolongs the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It will release the drug there in a controlled & prolonged manner, so that the drug could be supplied continuously to absorption site in GIT (Nayak et al., 2010).

1.1 DRUG CANDIDATES FOR GASTRIC RETENTION

The rationale for the selection of active pharmaceutical ingredients for fabrication as a GRDDS is described in **Table 1**.

Table 1: Rationale for gastro-retention of drugs

Rationale for gastro-retention	Name of drug
Narrow absorption window at upper part of GIT (Hoffman et al., 2004; Klausner et al., 2003)	Levodopa, Atenolol, Theophylline, Riboflavin, Repaglinide, Diltiazem, Risedronate
pH dependent absorption from stomach (acidic drugs) (Ozdemir et al., 2000; Parikh and Amin, 2008)	Furosemide
Degradation at higher pH (higher stability at lower pH) (Robles et al., 2008; Srivastava et al., 2005)	Captopril
Degradation in intestine or colon (Basit and Lacey, 2001)	Ranitidine hydrochloride
Higher solubility at lower pH or weakly basic drugs (Soppimath et al., 2001)	Cinnarizine, Diazepam, Verapamil, Cefpodoxime proxetil, Dipyridamole, Rosiglitazole maleate
Drugs for local action – antacids, anti-ulcer drugs, antibacterial for <i>H. pylori</i> infection (Bardonnet et al., 2006; Whitehead et al., 2006)	Misoprostol, Clarithromycin, Metronidazole, Amoxicillin

Gastroretentive DDS, on the other hand, are not suitable for drugs that:

- May cause gastric lesions, e.g. NSAIDS
- Are unstable in the strong acidic environment of the stomach.
- Have very limited acid solubility e.g. phenytoin etc.
- Intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids.

In addition, gastroretentive systems do not offer significant advantages over conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract (Talukder and Fassihi, 2004).

2.2 APPROACHES TO PROLONG GASTRIC RETENTION

Various approaches have been pursued over the last three decades, to increase the retention of oral dosage forms in the stomach. The approaches

used for GRDDS are mentioned in **Figure 1** and represented diagrammatically in **Figure 2** (Rocca et al., 2004; Singh et al., 2009; Garg and Sharma, 2003).

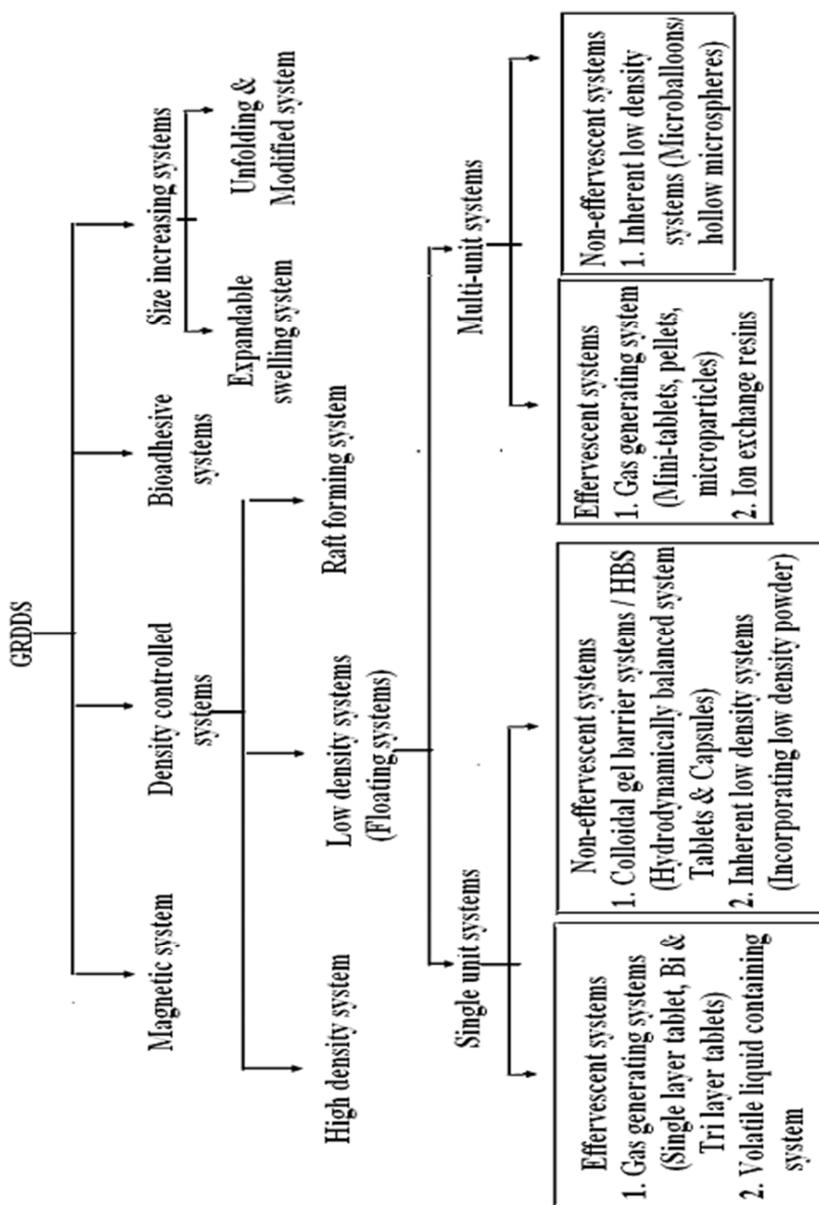


Figure 1: Various approaches used for GRDDS

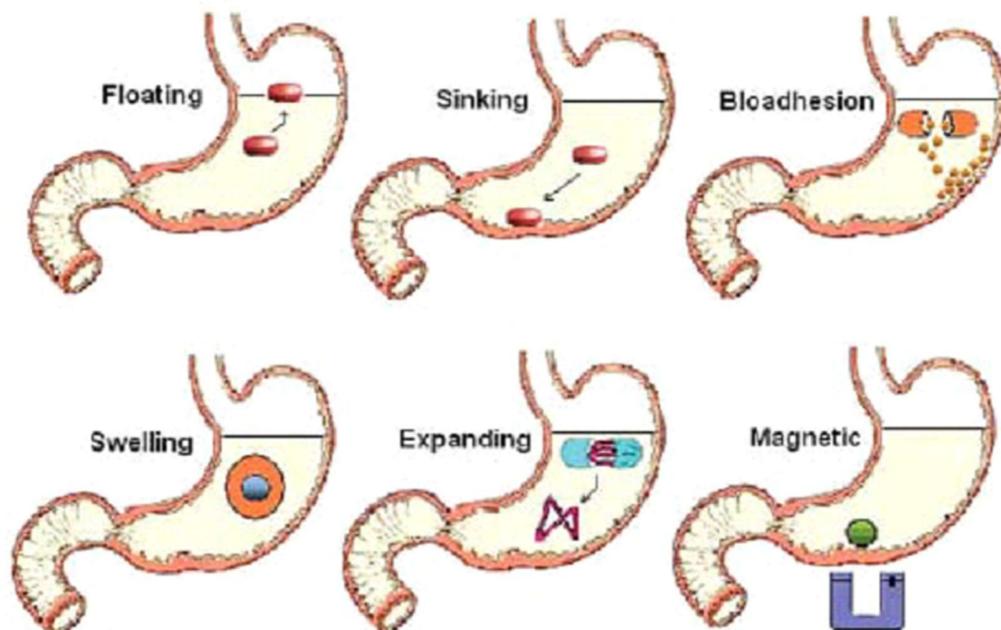


Figure 2: Working representation of various approaches of gastroretentive drug delivery system (Jain, 2011)

2.2.1 Size Increasing Systems

Retention of dosage form in the stomach can be achieved by increasing its size above the diameter of pylorus (13 mm), even during the housekeeper wave also. Initially, the dosage form should be of small size to facilitate swallowing but after coming in contact with the gastric fluid, it should increase in size quickly to avoid the premature gastric emptying. After a definite time interval, the system should be cleared from the stomach. The size increase can be achieved by several principles, including expansion and unfolding in stomach (Klausner et al., 2003).

2.2.2 Expandable Swelling Systems

The dosage form containing specific hydrogel polymers having fast swelling properties increase in dimension immediately after coming in contact with aqueous media. Superporous hydrogels (SPH) are an excellent example working on this approach. **Figure 3** shows the concept of gastric retention of such a system (Chen and Park, 2000). The dosage form swells significantly to several times of original volume upon contact with gastric fluids (A), the gastric contractions pushes

the dosage form to the pylorus but due to larger size of dosage form, the contractions slips over the surface of the system (B-E), due to which the dosage form pushes back into the stomach (F). Earlier first generation SPH was developed having fast swelling and weak mechanical properties. In order to improve the mechanical properties, second generation SPH composites were then developed (Omidian et al., 2007). Park et al. (Park et al., 2001) for the first time introduced SPH composites by modifying conventional SPHs through the addition of super disintegrants into the formulation. Crosslinked sodium carboxymethyl cellulose (Ac-Di-Sol), crosslinked sodium starch glycolate (Primojel) and crosslinked polyvinyl pyrrolidone (Crosspovidone) have been tried for these preparations. Later, Kim & Park (Kim and Park, 2004) prepared poly acrylamide-co-acrylic acid based SPH utilizing polyethylene amine. In another study, Yang et al. (Yang et al., 2004) used polyvinyl alcohol to improve the mechanical properties of sulfopropyl acrylate-co-acrylic acid SPHs.

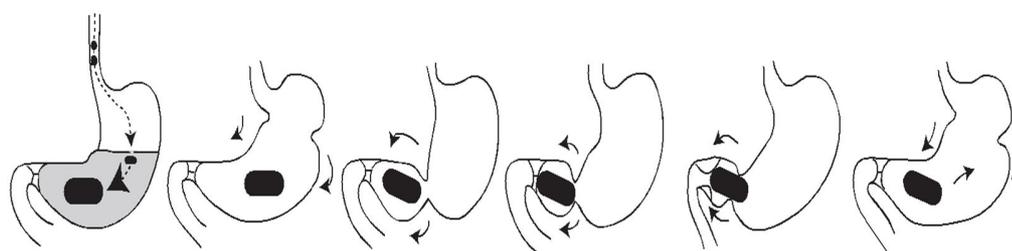


Figure 3: Concept of the gastric retention of a highly swellable, gastroretentive drug delivery system (Chen et al., 2000)

Recent advances in this field are the development of SPH hybrids, which are prepared by incorporating water soluble or water dispersible polymer and it can be crosslinked after the superporous hydrogel is formed (Omidian et al., 2000). Examples for hybrid agents are polysaccharides, including sodium alginate, pectin, chitosan or synthetic water soluble hydrophilic polymers, such as polyvinyl alcohol. Compared with first generation and second generation SPH, third generation SPH hybrids are not easily breakable when stretched because they possess highly elastic properties in the swollen state, which can be very useful for the development of gastrointestinal devices (Omidian et al., 2000). **Figure 4** represents the typical swelling and mechanical properties of these SPH. Park (Park et al., 2006) prepared the chitosan hydrogels and evaluated its ability for increasing the gastric retention. They concluded that glycol chitosan hydrogels offer better swelling properties over the chitosan alone. Moreover, the hydrogel swelling property was found significantly dependent on the foaming/ drying method, pH and crosslink density.

Omidian (Omidian et al., 2005) formulate superporous hydrogel hybrid (SPHH) using acrylamide and methylene-bis-acrylamide as their preferred monomer and chemical cross linker respectively. Water soluble hydrocolloids, including sodium alginate, sodium carboxymethyl cellulose and chitosan, have been used alone or in combination as the preferred

hybrid agents. To induce ionotropic gelation of these hydro-colloids, calcium, iron and phosphates have been used respectively.

	Structure	Swelling Property	Mechanical Property
First Generation	Polymer Chain Primary Crosslinker		
Second Generation	Composite Agent		
Third Generation	Hybrid Agent		

Figure 4: represents the typical swelling and mechanical properties of various SPH (Omidian et al., 2000)

Later, same group of workers prepared and evaluated a variety of SPH hybrids GRDDS (Omidian et al., 2006). The major requirements for a swellable gastroretentive platform were found to be swelling rate (within minutes), swelling capacity (preferably 8–15% v/v), shape, mechanical strength (resist pressures in the range 0.5–2.0 N cm⁻², preferably in the fed state),

flexibility, controlled disintegration, ease of drug loading, stability and pharmaceutical acceptability. All these concerns were addressed by a single SPH platform which requires careful selection of monomers and other activators, reaction conditions, type of additives, treatment method, purification and necessary steps during the entire preparation process. The SPH is prepared as a reservoir system (**Figure 5**) with the ability to house a drug delivery system (DDS). The DDS itself can be a controlled release tablet or semi-solid carrier for example. The whole platform is encapsulated in a regular capsule (e.g. 00 HPMC or gelatin) for oral administration (Rocca et al., 2005). Another class of SPHH based on cryogelation was prepared utilizing poly (vinyl alcohol) as a hybrid agent (Omidian et al., 2006). To optimize the swelling and mechanical properties, the SPHHs have been treated with mixed calcium, aluminium and iron cations.

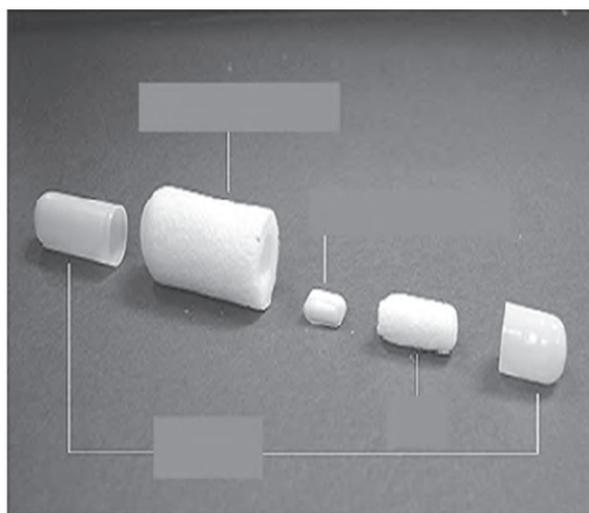


Figure 5: A reservoir type SPH based platform (Chavda et al., 2010).

Chavda & Patel (Chavda and Patel, 2006) synthesized superporous hydrogel composites (SPHCs) using carboxyl methyl cellulose sodium (Na CMC) as a composite material by solution polymerization. The SPHC was found to possess tremendous increase in equilibrium swelling capacity in double distilled water. But in SGF, SPHCs showed less equilibrium swelling capacity. SPHCs showed improved penetration pressure as the Na CMC concentration increased.

SEM images clearly indicate the formation of interconnected pore, capillary channels, and the adherence of Na CMC molecules around the periphery of pores.

The same group of workers then formulated a drug delivery system based on bioadhesive superporous hydrogel composite for sustained delivery of ranitidine hydrochloride (Chavda et al., 2010). SEM images clearly indicated the formation of interconnected pores, capillary channels, and the cross linked Carbopol 934P molecules were observed around the peripheries of pores. The prepared drug delivery system floated and delivered the drug for about 17 h. Recently they studied the effect of different concentrations of crosslinker (methylene-bis-acrylamide) on the characteristics of superporous hydrogel. They found that as the concentration of cross linker increased from 7.37% to 14.36% the porosities decreased. Characterization studies revealed that the increase in cross linker concentration is beneficial from the mechanical stability point of view, but at the same time the decrease in porosity may lead to decrease in drug release rate by diffusion through these capillary channels. Formulations B1 and B2 with low concentrations of crosslinker provide good porous structure, swelling characteristics, and mechanical strength appropriate for further applications of superporous hydrogel based drug delivery systems (Chavda and Patel., 2011).

2.2.3 Unfolding systems

The unfolding of devices to several geometric shapes increases the dimensions of dosage form ultimately prevents its passage through the pylorus. For convenient uptake, the dosage form should be filled into a gelatin capsule. In the stomach, the capsule dissolved and the device unfolds or opens out to achieve extended configuration (Klausner et al., 2003). Several geometric shapes have been patented (**Figure 6**) which can be packed tightly into a gelatin capsule and unfolds in the gastric fluids (39-42). These systems consist of at least one erodible polymer (e.g., hydroxypropyl cellulose, Eudragit® E; Röhm Pharma GmbH), one nonerodible polymer

(e.g., polyolefins, polyamides, polyurethanes), and a drug that is dispersed within the polymer matrix.

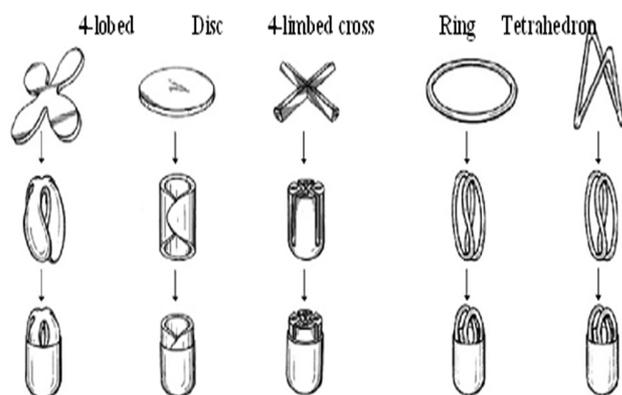


Figure 6: Different geometric forms of unfoldable systems (Bardonnnet et al., 2006).

Interestingly, the tetrahedron shaped devices were reported to remain in the stomach for longer periods of time than the other tested shapes (of similar size). The gastric retention of rigid rings was significantly affected by their size. Disk and clover leaf-shaped systems showed only poor gastric retention (Bardonnnet et al., 2006). In addition, strings and pellets were eliminated fairly rapidly.

Klausner (Klausner et al., 2002) developed unfolding, multilayer, polymeric films based on a drug containing shellac matrix as the inner layer, covered on both sides with (outer) layers composed of hydrolyzed gelatin/ Eudragit S (Rohm Pharma GmbH)/ glycerin/ glutaraldehyde. Such dosage forms placed into gelatin capsules were administered to beagle dogs and two factors were found to influence the *in vivo* gastric retention behavior: the dimensions and the mechanical properties of the films. Relatively large devices (surface $\geq 2.5 \times 2.5$ cm) and rigid frames were found to prolong the gastric residence time and improved absorption properties.

The same group studied the performance of levodopa containing multilayer films (5.0×2.5 cm

in size) in beagle dogs (Klausner et al., 2003). They developed the system consisted of an inner, drug containing film layer (EC-levodopa, 1:1), covered on both sides by (outer) shielding layers of enzymatically hydrolyzed gelatin/ Eudragit S/ glycerin/ glutaraldehyde blends (48:30:20:2), and a frame of rigid polymeric strips (L-poly(lactic acid)/EC, 9:1). Importantly, therapeutic levodopa concentrations (>500 ng/ml) could be maintained over 9 hrs following the administration of one single film. The mean absorption time of the drug was significantly extended in comparison to non-gastroretentive controlled release particles and oral solutions. Later, the performance of levodopa containing, multilayer films was also studied in humans (Klausner et al., 2003). Prolonged gastroretentivity (≥ 5 h) was achieved due to the rigidity and size of the dosage forms. The films rapidly unfolded and maintained their mechanical integrity. The absorption period of the drug was significantly prolonged in comparison to a non gastroretentive controlled release tablet.

Groning (Groning et al., 2007) develop oblong tablets which expand after contacting with gastrointestinal fluids within a few minutes to a length of 4–6 cm and which should remain in the stomach for a prolonged period of time due to their size. The tablets were prepared from riboflavin containing collagen sponges using a computer controlled single punch tablet machine. The collagen material was compressed to oblong tablets with dimensions of $3.5 \text{ mm} \times 9 \text{ mm} \times 18 \text{ mm}$. A crossover *in vivo* study with 12 healthy male and female subjects was performed. The renal excretion of riboflavin was measured after oral administration of collagen tablets and small sustained release hydrocolloid tablets as reference preparation. The amount of riboflavin excreted into the urine enhanced after administration of the expanding collagen tablets in comparison with the hydrocolloid tablets. The differences were statistically significant after 5, 6, 8, 9, 10 and 12 hrs. **Figure 8** shows the collagen oblong tablet before and after contact with water in comparison with a no. 1 hard gelatin capsule (Groning et al., 2007).



Figure 8: Comparison of collagen dosage form with an opaque hard gelatin capsule (No. 1) before and after expansion in water (Groning et al., 2007).

2.2.4 Bioadhesive Systems

A bioadhesive can be defined as a substance with the ability to interact with biological materials and is capable of being retained there. It involves the use of bioadhesive polymers which are usually macromolecular, hydrophilic gelling substances with numerous hydrogen bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups (e.g., crosslinked polyacrylic acids, sodium carboxymethyl cellulose, sodium alginate and carrageenan) that can adhere to the epithelial surface of the GIT (Andrews et al., 2009; Kharenko et al., 2009; Hooda et al., 2011). The working representation of bioadhesive drug delivery system is shown in **Figure 9**.

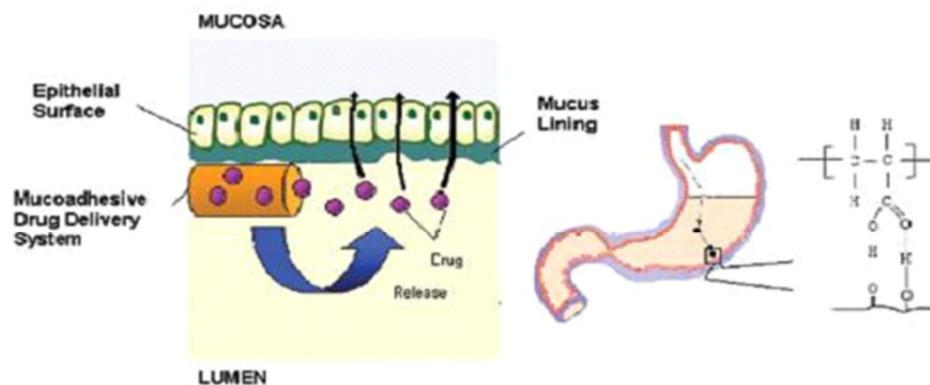


Figure 9: Schematic representation of adhesion of bioadhesive drug delivery system with mucin (Hooda et al., 2011)

Several excellent review articles have been published on fundamental aspects and potential application of bioadhesive dosage forms. The basis of adhesion is that a dosage form can stick to the mucosal surface by different mechanism (Carvalho et al., 2010; 52-53).

These mechanisms are:

- 1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
- 2) The diffusion theory which proposes physical entanglement of mucin strands with the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer

substrate.

- 3) The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- 4) The electron theory, which proposes attractive electrostatic forces between the glycol protein mucin network and the bioadhesive material.

Several types of dosage forms including tablets, microparticles and pellets have been proposed to allow prolonged residence within the stomach based on bioadhesive polymers. Some recent developments are now discussed here.

Chavanpatil (Chavanpatil et al., 2006) developed a new bioadhesive tablet of ofloxacin using various bioadhesive polymers like psyllium

husk, HPMC K100M and a swelling agent, crosspovidone in combinations were tried and optimized to get the release profile for 24 hrs. The swelling properties were found to increase with increasing crosspovidone concentration and contributed significantly in drug release from the tablet matrix. The bioadhesive property of the developed formulation was found to be significant ($P < 0.005$) in combination as compared to HPMC K100M and psyllium husk alone. The similarity factor f_2 was found to be 91.12 for the developed formulation indicating the release was similar to that of the marketed formulation (Zanocin OD).

Adhikary (Adhikary et al. 2008) prepared a bioadhesive tablet of ranitidine hydrochloride and studied the effect of mucoadhesive polymers such as Carbopol, hydroxyl propyl methyl cellulose, and dextrose. A combination of polymers CBL and HPMC in the ratio 5:1 proved to give the highest mucoadhesion. The bioadhesion was further enhanced by the presence of the alkaline pH modifiers, the effect being greatest with MgO. Recently, a three layered mucoadhesive tablet was developed by Mad Solid dispersion of Itraconazole with Eudragit E100 was prepared by spray drying method to improve dissolution and trilayered mucoadhesive tablet was prepared, with inner core containing solid dispersion of the drug and with carbopol and HPMC sandwiched between two layers of hydrophilic mucoadhesive polymer mixture of carbopol and Hydroxy propyl methyl cellulose (HPMC) (Madgulkar et al., 2008). Amounts of Carbopol 934P (CP) and Methocel K4M (HPMC) were varied in the outer coat around the solid dispersion. The drug release pattern for all the formulation combinations was found to be non-fickian, approaching zero order kinetics. Suitable combination of two polymers provided adequate bioadhesive strength and sustained release profile with zero order kinetics. Later, Deshmukh et al. (Later and Deshmukh, 2009) utilized the natural hydrophilic polymers in the preparation of bioadhesive tablets of theophylline anhydrous. Different types of natural hydrophilic polymers such as xanthum gum, locust bean gum, guar gum, karaya gum,

and their combinations were used to formulate matrix tablets. The bioadhesive strength of the tablets was measured as the force of detachment against the porcine gastric mucosa. The combination of karaya gum: guar gum (6:4) tablet showed greater bioadhesive strength as compared with a single gum and other gum combination tablets. Karaya gum: guar gum loaded tablets were not discharged from the mucous membrane and were dissolved in the gastric fluid. An increase in the gum concentration increases the drug release profile beyond 12 hrs whereas there is no significant effect of gum concentration on the bioadhesive strength of the tablet. Recently, gastroretentive mucoadhesive tablets of cephalexin were developed using variety of mucoadhesive polymers such as hydroxylpropyl methyl cellulose K4M, hydroxyl propylcellulose, chitosan, carbopol 934P and sodium carboxymethyl cellulose. It was found that the formulation containing HPMC K4M and carbopol 934P in combination exhibited maximum mucoadhesive strength of 144.42 gms, *in vitro* residence time was 8.73 hrs and *in vitro* drug release was found to be 75.03% in 10 hrs with non-Fickian diffusion mechanism. So, the optimized formulation F(2) was further subjected to *in vivo* retention time in rabbit by X-ray technique, SEM and Accelerated stability studies and was found to be the best (Sonani et al., 2010).

Due to all or nothing phenomenon associated with single unit dosage forms, a risk of premature gastric emptying is always present. In order to overcome this limitation of single unit dosage forms, multi-unit dosage forms have been developed and become popular now. These distribute uniformly within the gastric content and gradually empty from the stomach, possibly resulting in longer lasting effects and reduced intersubject variabilities (Pawar et al., 2011). Prepared microspheres loaded with tetracycline by ionic precipitation with sodium sulfate (Hejazi and Amiji, 2002). Spherical particles with an average diameter of 2.0–3.0 μm were formed. Depending on the preparation method, 8 – 69%

drug could be incorporated. At pH 1.2 and 2.0, the entire amount of tetracycline was instantaneously released whereas at pH 3.5 and 5.0, 70 and 90% of the drug was released after 3 and 8 hrs, respectively. The same authors studied the gastric residence of chitosan based microspheres and the local tetracycline concentrations following oral administration in gerbils (Hejazi and Amiji, 2003). Most of the microspheres were found in the colon 6 hrs after administration. Furthermore, the gastric residence time of the chitosan based microspheres was found to be independent of the gastric pH within the range of 1.0–4.5. The drug was predominantly found in the colon and urine 6 hrs after administration. Again, there was no significant difference in the tetracycline concentration profile when the gastric pH varied in the range of 1.0–4.5.

Prepared a tetracycline–sucralfate complex under acidic conditions and evaluated its mucoadhesive properties both *in vitro* and *in vivo*. For this purpose, a novel *in vitro* gastric mucoadhesion test using ex -vivo rat stomach was developed (Higo et al., 2004). Excellent mucoadhesive properties of the tetracycline–sucralfate complex were demonstrated. Developed the stomach targeted mini-tablets of heparin using thiolated polycarbophil as the mucoadhesive carrier material and was compared with hydroxyethylcellulose (HEC) as a non-mucoadhesive control (Schmitz et al., 2005). The *in vitro* drug release profiles were similar, and near constant release rates were observed during 4 hrs with both polymers. In a gastric transit study in rats, the HEC formulations could not be observed in the gastric lumen at 4 hrs after administration, in contrast to thiolated polycarbophil based delivery systems. Further *in vivo* evaluation in rats revealed that the relative bioavailability of oral formulations (compared with subcutaneous administration) was significantly higher in the case of thiolated polycarbophil compared with HEC.

Developed, optimized and evaluated the *in vitro* performance of mucoadhesive microspheres of

lacidipine for treatment of pylorospasm. Lacidipine microspheres containing chitosan were prepared by chemical denaturation using glutaraldehyde as a crosslinking agent (Sultana et al., 2009). A central composite design was employed to study the effect of independent variables, polymer concentration (X1), volume of glutaraldehyde (X2), stirring speed (X3) and crosslinking time (X4) on dependent variables, drug entrapment efficiency and percentage mucoadhesion. The entrapment efficiency varied from 14–40.82% depending upon the polymer concentration, volume of crosslinker and stirring speed. All batches of microspheres exhibited good mucoadhesive property (73–83%) in the *in vitro* wash off test. It was observed that polymer concentration and glutaraldehyde volume had a more significant effect on the dependent variables. Maximum entrapment (36.53%) and mucoadhesion (81.33%) was predicted at 3.5% chitosan, 3ml glutaraldehyde, 3000 rpm stirring speed and 75 mins crosslinking time under optimized process condition.

A comparative study of three types of microspheres loaded with theophylline was conducted by (Miyazaki et al., 2008). Their pharmacokinetic studies were conducted in Beagle dogs, comparing bulk powder, commercial sustained release granules (Theodur), sustained release microsp-heres, floatable microspheres and mucoadhesive microspheres. Theodur and sustained release microspheres showed lower maximum concentration (C_{max}) ($P < 0.01$) and larger values for mean residence time (MRT) ($P < 0.05$) than bulk powder, whereas area under the concentration time curve (AUC) was lower. The floatable microspheres showed a larger value for MRT than bulk powder ($P < 0.01$), and a larger AUC than Theodur ($P < 0.05$). Overall, the gastroretentive microspheres improved the extent of bioavailability of theophylline, which is absorbable from the entire gastrointestinal tract. The mucoadhesive microsphere showed a prolonged serum drug level, indicating a superior sustained release delivery system for theophylline.

Recently, a novel bioadhesive dosage form of rifampicin was developed by Pund (Pund et al., 2011). They prepared a multi-particulate formulation which consisted of rifampicin pellets for immediate release as the loading dose and a bio/mucoadhesive rifampicin tablet for extended release. For the mucoadhesive rifampicin formulation, statistical experimental strategy was utilized to simultaneously optimize the effect of

two independent variables namely amount of Carbopol and MCC. The *in vivo* gamma scintigraphy of optimized formulation was carried out in six healthy human volunteers, after radiolabeling the formulation with ^{99m}Tc . **Figure 10** shows the gamma scintigraphic images of rifampicin pellets. The transit profiles demonstrated that the dosage form was retained in the stomach for more than 320 mins.

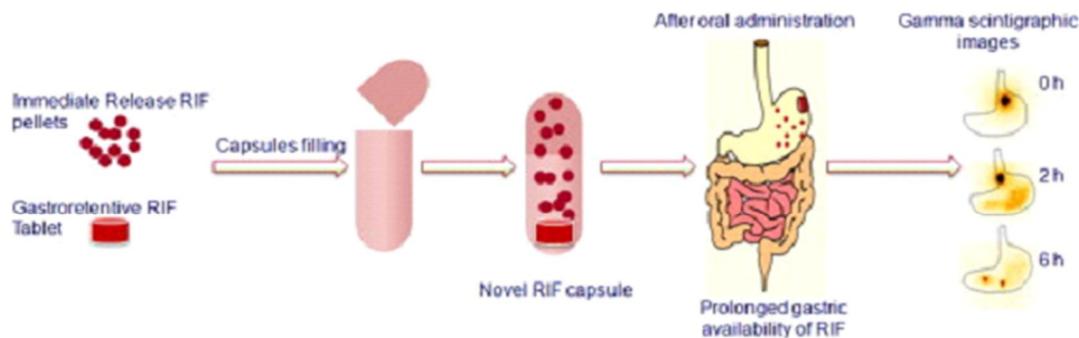


Figure 10: Representation of prolonged gastric availability in gamma scintigraphic images of rifampicin pellets in stomach (Pund et al., 2011)

2.2.5 Density controlled systems

2.2.5.1 High density systems

High density devices use their weight as a retention mechanism. When the density of the system is larger than that of the gastric juice, the device settles down to the bottom of the stomach, remaining located below the pylorus. Gastric contents have a density close to water (1.004 g/cm^3). This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content ($\sim 1.004 \text{ g/cm}^3$). These formulations are prepared by

coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc (Rouge et al., 1998; Clarke et al., 1995). The materials increase density by up to $1.5\text{-}2.4 \text{ g/cm}^3$. A density close to 2.5 g/cm^3 seems necessary for significant prolongation of gastric residence time. When the patient is upright small high density pellets sink to the bottom of the stomach (**Figure 11**) where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall.

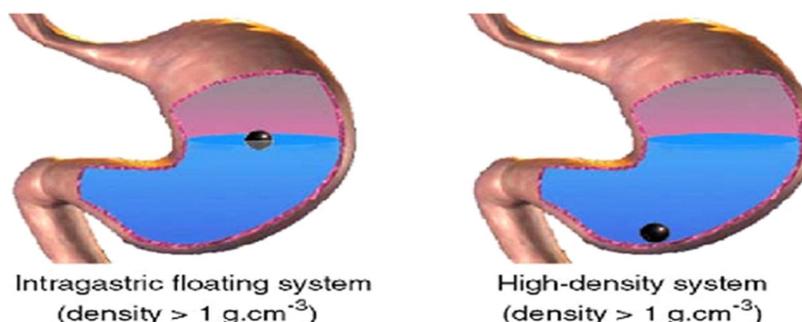


Figure 11: Schematic representation of intragastric floating (low density) system and high density system (Bardonnet., 2006)

Recently, Pan et al. (69) developed a novel famotidine gastric resident osmotic pump tablet using iron powder as a gas formation and density increasing agent. Central composite design-response surface methodology was used to investigate the influence of factors, i.e., polyethylene oxide (Mw 1,000,000) content, NaCl content, iron powder content and weight gain, on the responses including ultimate cumulative release and correlation coefficient of drug release profile. The optimized formulation displays a complete drug delivery and zero order release rate. Gamma scintigraphy was selected as the method to monitor *in vivo* gastric residence time of the ^{99m}Tc-labeled system in Beagle dogs. It was observed that the system can retain in stomach for an extended period of 7 h after administration compared with conventional tablets. The present investigation suggests that water insoluble drug can be delivered from single layer osmotic pump tablets completely due to the push power of the hydrogen gas generated by the reaction of the iron and gastric fluid. And iron powder can increase the system density which is over 2.5 g cm⁻³, making the system resident in stomach to prolong the drug delivery time in absorption zone.

However, it has been reported that such devices did not significantly extend the gastric residence time. Although encouraging results were reported in ruminant, effectiveness in human subject beings was not observed and no system has been marketed (Moes et al., 2003).

2.2.5.2 Raft forming system

Raft forming systems produce a layer on the top of gastric fluids. Here, a gel forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles (**Figure 12**) on contact with gastric fluid. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of *Helicobacter pylori* (*H. Pylori*) infections in the GIT (Shah et al., 2009). The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These

ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float.

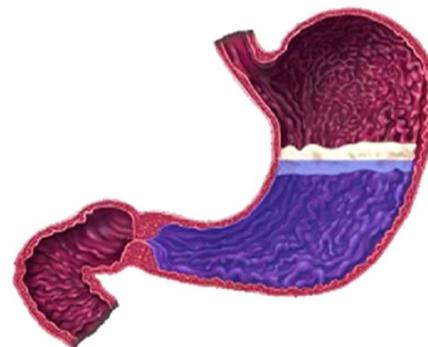


Figure 12: Representation of raft forming system (Bardonnat., 2006)

2.2.5.3 Low density systems (Floating systems)

The concept of floating DDS was first described in the literature in 1968 (Davis, 1968), when Davis developed a method for overcoming the difficulty experienced by persons of gagging or choking while swallowing medicinal pills. He suggested that such difficulty could be overcome by providing pills with a density of less than 1 g/cm³, so that the pill will float on water surface. Since then several approaches have been used to develop an ideal floating system.

They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations in some cases (Gangadharappa et al., 2007). Floating systems can be based on several principles including gas generation systems (effervescent systems), swelling systems (non effervescent systems), and inherent low density.

2.2.5.3.1 Gas generation systems (Effervescent systems)

This is a very interesting approach based on the generation of CO₂ within the system upon contact with the body fluids for which it utilizes effervescent components such as sodium

bicarbonate (NaHCO_3) or sodium carbonate and additionally citric or tartaric acid (Singh and Kim., 2000). After contact with acidic aqueous media, CO_2 is generated and entrapped which produced an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the fluid.

Floating drug delivery systems can be formulated into both single unit and multi unit systems. Various articles have been published on single

unit and multi unit systems. In single unit systems, such as capsules or tablets (Xu and Groves, 2001. Baumgartner et al., 2000), effervescent substances are incorporated in the hydrophilic polymer, and CO_2 bubbles are trapped in the swollen matrix (**Figure 13**). *In vitro*, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 hrs. *In vivo* experiments in fasted dogs showed a mean gastric residence time increased up to 4 hrs (Baumgartner et al., 2000).

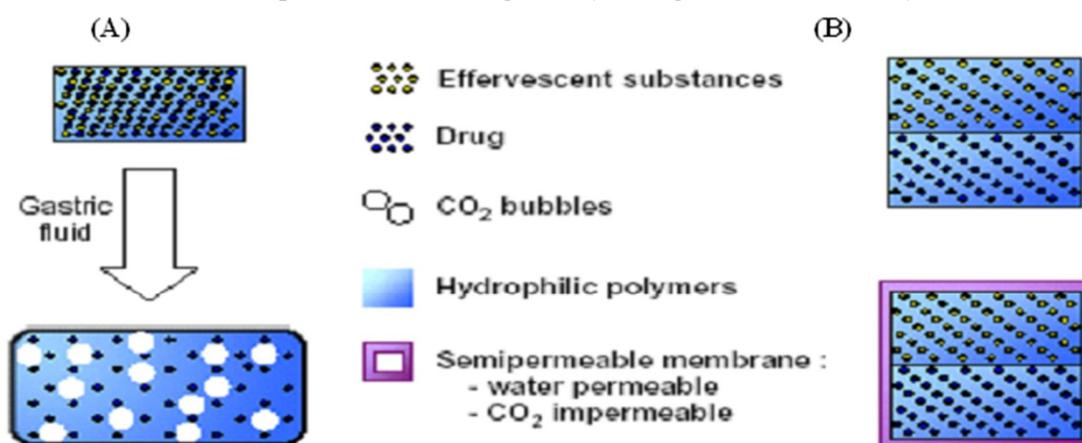


Figure 13: Example of effervescent gas generating floating systems: Monolayer drug delivery system (A) bilayer gas generating systems, (B) with or without semipermeable membrane (Singh and Kim, 2000).

Recently some novel research was carried out on single unit floating dosage forms including the development of multi layer tablets, use of factorial design for optimizing the various processing and formulation parameters. Developed a bilayer floating tablet (BFT) for captopril using HPMC, K15M and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer (Rahman et al., 2006). The release layer contained captopril and various polymers such as HPMC K15M, PVP K30 and Carbopol 934p, alone or in combination with the drug. Optimized formulation released approximately 95% drug in 24 hrs *in vitro*, while the floating lag time was 10 mins and the tablet remained floatable throughout the studies. Placebo formulation containing barium sulphate in the release layer administered to human volunteers for *in vivo* X-ray studies showed that

BFT had significantly increased the gastric residence time. Designed and evaluated a composite gastroretentive matrix for zero order delivery of highly soluble drug alfuzosin hydrochloride (Fassihi et al., 2008). Two systems containing polyethylene oxide (PEO), HPMC, sodium bicarbonate, citric acid and polyvinyl pyrrolidone were dry blended and compressed into triple layer and bilayer composite matrices (**Figure 14**). Both systems proved to be effective in providing prolonged floatation, zero order release, and complete disentanglement and erosion based on the analysis of data with “*f*₂” of 68 and 71 for PEO and HPMC based systems, respectively.

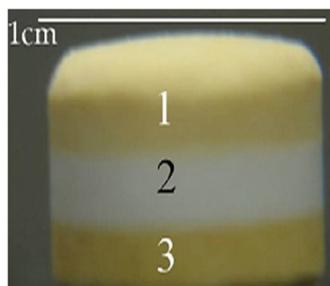


Figure 14: representation of multi-layer floating tablet of afuzosin hydrochloride (77).

Developed a floating multi-layer coated tablets based on gas formation (Sungthongjeen et al., 2008). The system consists of a drug containing core tablet coated with a protective layer (hydroxyl propyl methyl cellulose), a gas forming layer (sodium bicarbonate) and a gas entrapped membrane, respectively. Eudragit_{RL} 30D was chosen as a gas entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the CO₂ gas formation and the gas entrapment by polymeric membrane. The floating tablets using direct compressed cores had shorter time to float and faster drug release than those using wet granulated cores. The increased amount of a gas forming agent did not affect time to float but increase the drug release from the floating tablets while increasing coating level of gas entrapped membrane increased time to float and slightly retarded drug release.

Design and developed a bilayer regioselective floating tablets comprising two layers, i.e. immediate release layer of lovastatin and sustained release layer of atenolol (Kulkarni et al., 2009). The immediate release layer comprised sodium starch glycolate as a super disintegrant and the sustained release layer comprised HPMC K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All formulations floated for more than 12 h. More than 90% of lovastatin was released within 30 mins. HPMC K100M and xanthan gum sustained retarded the release of atenolol from the controlled release layer for 12 hrs. The optimized formulation was found to be buoyant for 8 h in stomach. Therefore, biphasic drug release pattern was successfully achieved

through the formulation of floating bilayer tablets in this study. Nanda developed a floating tablet of ibuprofen using HPMC K4M, HPMC K15M, C 934P by applying 2³ full factorial design (Nanda et al., 2010). It was found that sodium bicarbonate loading level was important for floating properties. HPMC provided the sustained release, but the ratio of the grades was not important. Carbopol provided the binding capacity to the tablet and maintained the integrity of the tablet.

Sheu prepared swelling and floating tablets of losartan using combination of hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate at various compression pressures for evaluating swelling characteristics and floating capacity (Sheu et al., 2010). An appropriate ratio of HEC to NaCMC, addition of sodium bicarbonate, and compression at lower pressures resulted in the tablets floating over SGF for more than 16 h and swelling to 2 cm in diameter within 3h. The release patterns of Losartan from these tablets were found to be pH dependent. Results of the clinical trials showed that the mean bioavailability from GRD-A (HEC 91.67%, sodium bicarbonate 3.33% and Losartan 8.33%) was approximately 164%, relative to the immediate release product (Cozaar). MRT and t (max) values were greater and C (max) values were lower for the GRDDS tablets compared with Cozaa.

Senyigit investigate the ability of thiolated matrix tablets of riboflavin for gastroretentive delivery systems (Senyigit et al., 2011). Poly-acrylic acid-cysteine (PAA-Cys) and chitosan-4-thiobutylamidine (chitosan-TBA) were evaluated as anionic and cationic thiolated polymers. Mucoadhesion studies showed that mucoadhesion work of PAA-Cys and chitosan-TBA tablets were 1.341 and 2.139 times higher than unmodified ones. The mucoadhesion times of PAA, PAA-Cys, chitosan, and chitosan-TBA tablets were 1.5±0.5, 21±1, 1±0.5, 17±1 hrs, respectively. A controlled release was provided with thiolated tablets for up to 24 h. These promising *in vitro* results of thiolated tablets were

proved with *in vivo* studies. The thiolated tablets showed a gastroretention time up to 6 hrs, whereas unmodified tablets completely disintegrated within 1 h in rat stomach.

Allam developed floating matrix tablets of acyclovir using hydroxypropyl methyl cellulose 4000, Compritrol 888 and sodium bicarbonate was used as a gas generating agent (Allam et al., 2011). A 3² factorial design was applied to optimize the drug release profile systematically. The results of factorial design indicated that a high level of both hydroxypropyl methyl cellulose 4000 (X₁) and Compritrol 888 (X₂) favors the preparation of floating controlled release of acyclovir tablets. Also, a good correlation was observed between predicted and actual values of the dependent variables chosen for the study. Javadzadeh prepared floating tablets of Metronidazole using HPMC, Psyllium and Carbopol for better eradication of *Helicobacter Pylori* in peptic ulcer diseases. Various formulations were designed using multifactorial design. Formulations containing HPMC as filler showed prolonged lag times for buoyancy. Adding Psyllium to these formulations had reduced relative lag times. Overall, selected formulations were able to float immediately and showed buoyancy for at least 8 hrs (Javadzadeh et al., 2011). Meanwhile, sustained profiles of drug release were also obtained.

Goswami developed a bilayer tablet formulation for prolonged gastric residence time using Metformin and Pioglitazone hydrochloride as an oral hypoglycemic agent for control of diabetes (Goswami et al., 2011). The fabrication of bilayer floating tablet was done by modified direct compression using polymer like hydroxypropyl methyl cellulose (HPMC), Carbopol, polyvinyl pyrrolidone to facilitate immediate release of Pioglitazone and sustained release of Metformin. Formulated tablets remain buoyant over a period of 12-20 hrs and released more than 80% of drug in study period.

Now days, multi unit dosage forms are gaining popularity as discussed earlier that multi unit systems are more effective in prolonging the

gastric retention as compared to single unit systems. Stops assessed the *in vivo* behavior of the radiolabelled calcium alginate beads using gamma scintigraphy under fasting conditions with water or an aqueous solution of citric acid, a potential gut transit delaying substance (Stops et al., 2006). The study was performed in healthy male volunteers who swallowed the radiolabelled calcium alginate beads after a 10 hrs overnight fast. The results indicated that prolonged gastric retention was achieved when the dosage form was administered with the citric acid solution when compared to retention in the absence of citric acid. Citric acid, therefore, has the potential to delay the gastric emptying of the calcium alginate beads when administered to fasted volunteers. Singh prepared the floating calcium alginate beads by simultaneously ionotropic gelation of alginate and sterculia gum by using CaCl₂ as cross linker (Singh et al., 2010). The swelling of beads has been carried out as a function of various reaction parameters and pH of the swelling media. In addition, *in vitro* release dynamics of anti-ulcer model drug pantoprazole from drug loaded beads in different release media has been carried out for the evaluation of the drug release mechanism and diffusion coefficients.

Stops developed the floating calcium alginate beads of riboflavin, to improve drug bioavailability compared with that from many commercially available and modified release products (Stops et al., 2008). Using SEM and ESEM, externally the calcium alginate beads were spherical in shape, and internally, air filled cavities were present thereby enabling floatation of the beads. The calcium alginate beads remained buoyant for times in excess of 13 hrs, and the density of the calcium alginate beads was <1.000 g cm⁻³. Riboflavin release from the calcium alginate beads showed that riboflavin release was slow in acidic media, whilst in more alkali media, riboflavin release was more rapid. The characterization studies showed that the calcium alginate beads could be considered as a potential gastroretentive dosage form.

Goole developed and evaluated floating minitables (MT) of levodopa prepared by melt

granulation and subsequent compression. The investigation showed that MT composition and MT diameter had the greatest influence on drug release, which was sustained for more than 8 hrs. The best floating properties were obtained with 3mm MT prepared at low compression forces

ranging between 50 and 100 N. It was found that dissolution profiles depend more on the prolonged release ability of Methocel® K15M than on the pH dependent solubility of levodopa (Goole et al., 2007).

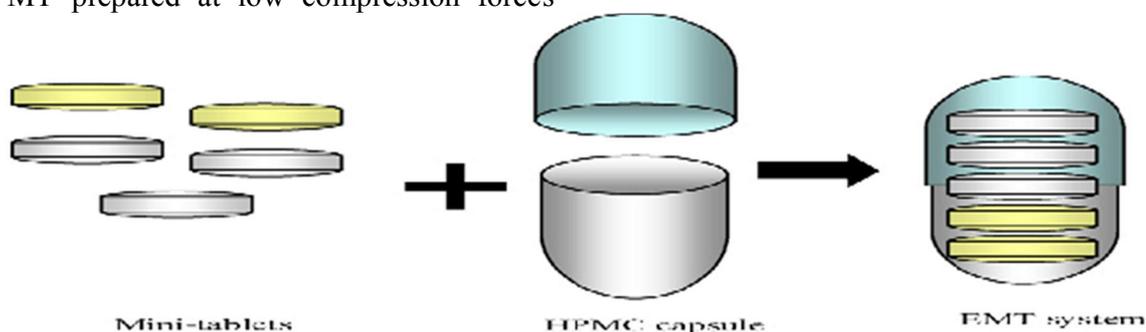


Figure 15: Schematic diagram of mini tablet system. During manufacture, two immediate release mini tablets (yellow coloured) are placed within one half of the capsule, then three sustained release mini tablets are added, and the other half of the capsule is pressed (Ishida et al., 2008).

Ishida developed and optimized a novel sustained release dosage form consist of immediate release mini-tablets (IRMT) and sustained release mini-tablets (SRMT) contained in a hydroxypropyl methyl cellulose (HPMC) capsule (**Figure 15**). The IRMT contained PSE, excipients and low substituted hydroxypropyl cellulose (a disintegrant), and the tablets were coated with HPMC, water soluble polymer (Ishida et al., 2008). IRMT prepared with varying amounts of low substituted hydroxypropyl cellulose all dissolved completely within the first 60 mins, so low substituted hydroxypropyl cellulose content does not greatly influence PSE release. The SRMT contained only PSE and excipients, and were coated with a mixture of HPMC and the water insoluble polymer ethyl cellulose. The PSE release profile for the SRMT could be controlled by varying the thickness of the coat, and the lag time could be controlled by varying the amount of ethyl cellulose present in the polymer coat. PSE was released immediately from encapsulated mini tablet system and release was sustained over an extended period of time: the PSE in the IRMT dissolved within 60 mins, whereas the PSE in the SRMT was released over 8–10 hrs.

Goole developed sustained floating minitables of levodopa and conducted the scintigraphic and pharmacokinetic studies on ten healthy fed volunteers (Goole et al., 2008). Two concepts of sustained-release floating minitables – Levo-Form 1 (matrix) and 2 (coated) were evaluated and compared to the marketed product Prolopa® HBS 125. It was shown that the three formulations offered almost the same mean gastric residence time, which was about 240 mins. Prolopa® HBS 125 and Levo-Form 2 presented intragastric disintegration, which can lead to a more pronounced “peak & valley” effect on the plasma concentration–time profile of levodopa. In contrast, the plasma concentration–time profile of levodopa following the administration of Levo-Form 1 was more evenly distributed. Moreover, Levo-Form 1 provided the lowest variations between men and women in terms of AUC and C_{max} values. Finally, when the same amount of inhibitors of extracerebral dopa decarboxylase – carbidopa and benserazide – had been administrated, the mean AUC, C_{max} and T_{max} values obtained for benserazide were lower than those obtained for carbidopa.

Meka developed a floating minitables of furosemide based on gas formation technique for

furosemide. The system consists of core units (solid dispersion of furosemide: povidone and other excipients), coated with two successive layers, one of which is an effervescent (sodium bicarbonate) layer and other one an outer polymeric layer of polymethacrylates. Only the system using Eudragit RL30D and combination of them as polymeric layer could float within acceptable time. The time to float decreased as amount of the effervescent agent increased and, when the coating level of polymeric layer decreased. The drug release was controlled and linear with the square root of time. By increasing coating level of polymeric layer decreased the drug release. The rapid floating and the controlled release properties were achieved in this present study. The *in vivo* gastric residence time was examined by radiograms and it was observed that the units remained in the stomach for about 6 hrs (Meka et al., 2009).

Belgamwar described a floating, pulsatile, multiparticulate drug delivery system intended for chronopharmacotherapy of arthritis. Cross linked beads of acefenac were prepared using low methoxyl-ated pectin (LM104AS), sodium alginate, and low methoxylated pectin (LM104AS) along with sodium alginate by acid

base reaction during ionotropic gelation. It was found that calcium pectinate beads show maximum drug entrapment. Hence, pectin containing formulation was further studied for buoyancy, DSC and radio imaging study. Drug release study was performed in acidic environment using pH 1.2 buffer solution for 6 hrs and then at 7.4 pH for 60 mins. The total drug release ranges from 5–10% and 90–94% in acidic and basic media, respectively (Belgamwar et al., 2010).

2.2.5.3.2 Swelling systems (Hydrodynamically balanced system)

Hydro dynamically balanced systems (HBS) are the systems, containing one or more gel forming hydrophilic polymers which upon contact with the gastric fluids swells and forms a colloidal gel barrier resulting in low density. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsule rapidly dissolves in the gastric fluid, and hydration and swelling of the surface polymers produces a floating mass (Bardonnnet et al., 2006). Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy (**Figure 16**) (Arora et al., 2005).

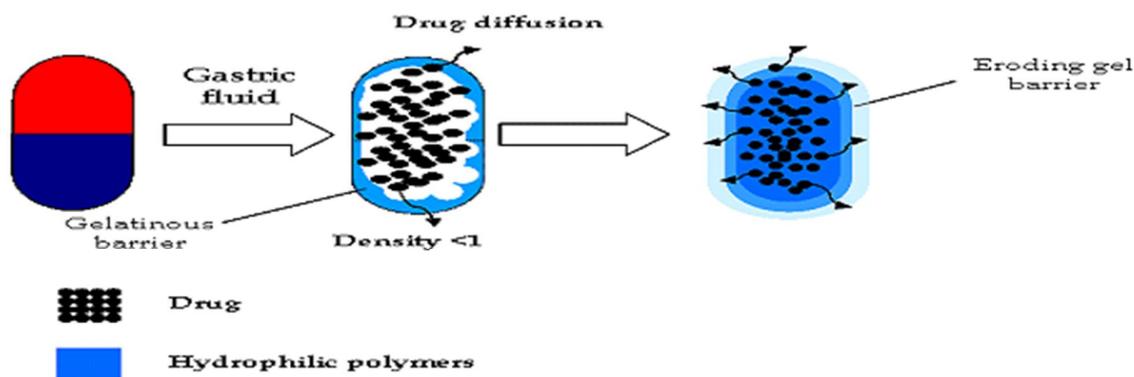


Figure 16: Hydrodynamically balanced system (HBS)-The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier (Bardonnnet et al., 2006).

Sheth & tossunian developed a floating capsule containing a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolves and a bulk density of <1 was achieved

(95-96). The floating properties of the dosage forms depended on the type of polymer used. HPMC is the most common used excipient, although HEC, HPC, sodium CMC, agar,

carrageenan are also used (Reddy and Murthy, 2002). Dorozynski conducted a comparative study of different types of polymers for preparation of floating capsule. Capsules filled with chitosans showed the lowest densities; the highest ones were observed with sodium alginate containing capsules. The maximum floating force for capsules (size 0) ranged from 26.7 (sodium alginate) to 64.7 mN (chitosan) (Dorozynski et al., 2004). Recently, Arora developed a hydrodynamically balanced system of metformin as a single unit floating capsule using various grades of low density polymers. Capsules prepared with HPMC K4M and ethyl cellulose gave the best *in vitro* percentage release and was taken as the optimized formulation. *In vivo* studies were carried out in rabbits to assess the buoyancy, as well as the pharmacokinetic parameters of the formulation using gamma scintigraphy. The formulation remained buoyant during 5 hrs of study in rabbits. The comparative pharmacokinetic study was performed by administration of the optimized HBS capsules and immediate release capsules, both with radiolabelled metformin, using gamma counter. There was an increase in AUC in optimized HBS capsules of metformin when compared with immediate release formulation (Arora et al., 2007).

In addition to the capsules, HBS tablets were also developed. Baumgartner prepared a HBS tablet based on HPMC K4M. After coming in contact with gastric fluid, the system takes up water and swells which decreased the density below 1 (Baumgartner et al., 2000). Thus, after a certain lag time, the system starts to float. Several processing and formulation parameters were found to influence the floating properties of the HBS tablets (Colombo et al., 1989; Gerogiannis et al., 1993; Rouge et al., 1997; Baumgartner et al., 1998). Veerareddy described a hydrodynamically balanced tablet of clarithromycin (CLA) for the treatment of *Helicobacter pylori* (*H. pylori*) mediated peptic ulcer. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the

desired release. The formulation developed using 66.2% clarithromycin, 12% HPMC K4M polymer, 8% sodium bicarbonate gave floating lag time less than 3 mins with a floating time of 12 hrs, and an *in vitro* release profile very near to the desired release. X-ray studies showed the enhanced gastric residence time of the tablet to 220±30 mins. *In vivo* radiographic studies suggest that the tablet has increased gastric residence time for the effective localized action of the antibiotic (clarithromycin) in the treatment of *H. pylori* mediated peptic ulcer (Veerareddy et al., 2008).

Rouge developed the floating mini tablets based on hydrophilic cellulosic polymers. These tablets tend to stick together during dissolution studies. To prevent this, antiadhesive filler was added then. Bilayer HBS tablets were also developed by some researchers in which one layer conferred the buoyancy and other controlled the drug release (Rouge et al., 1997). A bilayer formulation of misoprostol has been developed against gastric ulcers (Bardonnet et al., 2006). Both layers contained swellable polymers and only one contained drug (**Figure 17.a**) so that buoyancy and drug release could be optimized independently. They observed a mean gastric residence time >3 hrs after a single meal (breakfast) and >10 hrs after a succession of meals. Finally, an impermeable polypropylene cylinder was developed having 10–15 mm length, sealed on both sides by a matrix of hydrophilic polymer (HPMC) containing the drug. Air entrapped in the core of the cylinder provided the buoyancy (**47**) (**Figure 17.b**).



Figure 17: Improvement in HBS (43)

A glycerol monooleate (GMO) matrix was recently proposed as a gastroretentive carrier system (Kumar et al., 2004). The devices were prepared by melting GMO at 55°C in a water bath, adding the drug under stirring and pouring

the molten mass into cylindrical moulds with an inner diameter of 8.5 mm. The GMO matrices significantly swelled in water and the swollen masses floated at the surface after a certain lag time.

2.2.5.3.3 Inherent low density system

Larger values of floating lag time are always unacceptable as the housekeeper waves of the stomach may sweep out the dosage form into the intestine prior to its buoyancy (Parikh and Amin. 2008). Even gas forming systems and HBS systems take time to achieve buoyancy due to which the risk of premature gastric emptying is always exist. So, it is always desired that the drug delivery system could float immediately upon contact with gastric fluid which will reduced the risk associated with other floating systems. To achieve this, the low density should be provided from the beginning either by the entrapment of air (hollow chamber) or by the incorporation of low density material like oils or foam powder (Bardonnet et al., 2006).

A single unit floating tablet consisting of polypropylene foam powder, matrix forming polymer(s), drug and optional filler was developed by (Streubel et al., 2003). The structure of this type of tablet is shown schematically in **Figure 18**. The highly porous foam powder provides a low density of the system for at least 8 hrs in 0.1 N HCl at 37°C. Different types of matrix forming polymers were studied: HPMC, polyacrylates, sodium alginate, corn starch, carrageenan, gum guar and gum Arabic. Importantly, the release rate could be effectively adjusted by altering the matrix forming polymer: foam powder ratio, initial drug loading, tablet geometry (radius and height), type of matrix forming polymer, the use of polymer blends, and the addition of water soluble or insoluble fillers (such as lactose or microcrystalline cellulose).

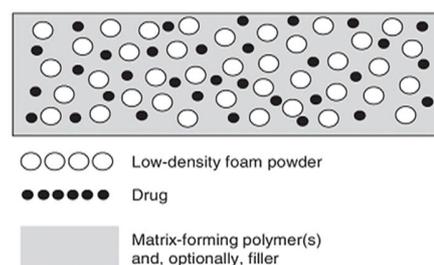


Figure 18: Schematic presentation of the structure of low density, floating matrix tablets (Streubel et al., 2003).

Further, a novel multiparticulate, gastroretentive drug delivery system based on low density foam powder has been developed and its performance demonstrated *in vitro* (Streubel et al., 2002). Floating microparticles consisting of polypropylene foam powder; verapamil HCl as the model drug; and Eudragit RS (Rohm Pharma GmbH), EC or poly (methyl methacrylate) (PMMA) were prepared with an oil-in-water solvent extraction/ evaporation method (**Figure 19.A**). The drug and release rate controlling polymer were dissolved in methylene chloride in which polypropylene foam powder was then dispersed. The resulting suspension was subsequently emulsified into an external aqueous, polyvinyl alcohol solution (adjusted to pH 12.5) and agitated with a stirrer to allow microparticle formation. The microparticles were irregular in shape and highly porous. Encapsulation efficiencies that were close to 100% could be achieved by varying either the amount of ingredients: volume of the organic phase ratio or the relative amount of Eudragit RS/EC/PMMA. In all cases, good *in vitro* floating behavior was observed. The type of polymer that was used significantly affected the resulting drug release rate, which increased in the following rank order: PMMA < EC < Eudragit RS. Importantly, a broad spectrum of release patterns could be obtained with the investigated formulations. The size of the microparticles was found to be almost independent of the drug loading, but strongly depended on the relative amount of Eudragit RS/EC/PMMA. Differential scanning calorimetry and X-ray measurements showed that the drug was partly dissolved, and partly in the amorphous form distributed throughout the system.

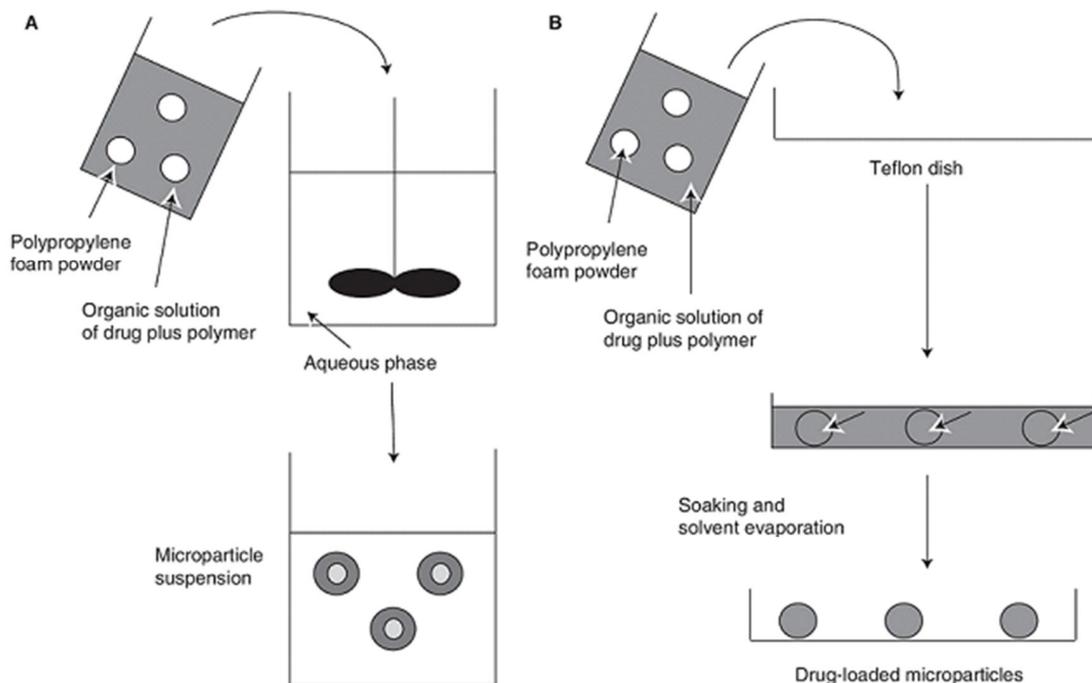


Figure 19: Schematic presentation of the preparation of floating microparticles based on low density foam powder, using: (a) a solvent evaporation method; (b) a soaking method (Streubel et al., 2006).

Further studies focused on the development of a new preparation method for this type of low density, foam based floating microparticles and on the demonstration of the systems performance *in vitro* (Streubel et al., 2003). Major advantages of a suggested novel preparation technique include short processing times, no exposure of the ingredients to high temperatures, the possibility to avoid toxic organic solvents, and high encapsulation efficiencies (close to 100%). Floating microparticles consisting of polypropylene foam powder, model drug (chlorphenamine maleate, diltiazem HCl, theophylline or verapamil HCl), and a second polymer (Eudragit RS or PMMA) were prepared by soaking the microporous foam particles with an organic solution of the drug and polymer, and subsequent drying (**Figure 19.B**). Good *in vitro* floating behavior was observed in most cases, and a broad variety of drug release patterns could be achieved by varying the drug loading and type of second polymer. In addition, the low density microparticles could be compressed into rapidly

disintegrating tablets, providing an easily administrable oral dosage form (Streubel et al., 2003).

Kawashima et al. (Kawashima et al., 1991; Kawashima et al., 1992; Sato et al., 2003) developed the hollow microspheres (microballoons) consisting of eudragit S (an enteric polymer) containing the drug in the polymeric shell. The preparation procedure and mechanism of microballoon formation is schematically illustrated in **Figure 20**. A solution of polymer and drug in ethanol/methylene chloride is poured into an agitated aqueous solution of polyvinyl alcohol. The ethanol rapidly partitions into the external aqueous phase and the polymer precipitates around the methylene chloride droplets. The subsequent evaporation of the entrapped methylene chloride leads to the formation of internal cavities within the microparticles.

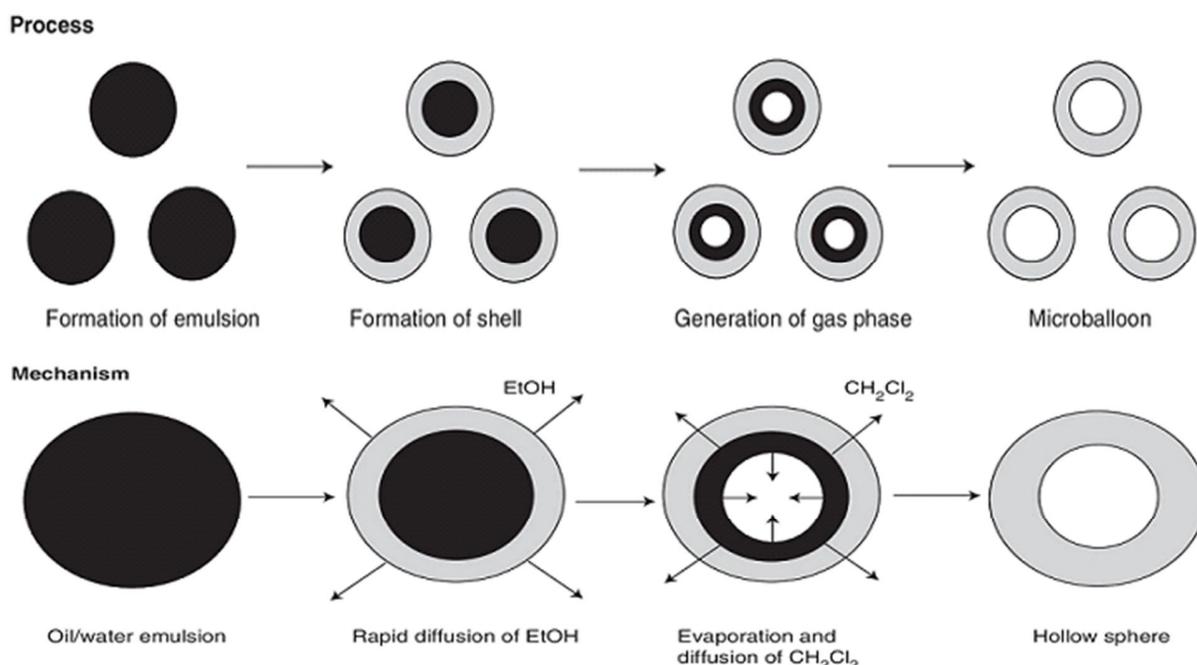


Figure 20: Preparation procedure (emulsion-solvent diffusion method) and mechanism of microballoon formation: Hollow microspheres for use as a floating controlled drug delivery system in the stomach (Streubel et al., 2006).

However, according to Lee (Lee et al., 1999), many drugs are not released in significant amounts from this type of microparticles at the pH of gastric fluids. Modifications of this system consisted of the addition of nonvolatile oil to the dispersed phase (Lee et al., 2001) or the use of Eudragit S/RL mixtures (kamel et al., 2001). The group of Kawashima also prepared hollow microspheres using mixtures of Eudragit S and other hydrophilic or hydrophobic polymers (such as Eudragit L [Röhm Pharma GmbH], hydroxypropyl methyl cellulose phthalate, HPMC or EC) (Sato et al., 2004). The incorporation of HPMC within the outer shell showed promising results concerning the control of drug release from the system at the pH of gastric fluids. With increasing HPMC contents the amount of riboflavin released also increased; however, the floating properties of the microspheres decreased. The performance of these riboflavin containing microballoons was also studied *in vivo* (Sato et al., 2004; Sato et al., 2004). After oral administration to healthy volunteers, the intragastric behavior was investigated by γ -

scintigraphy and the urinary excretion of riboflavin was followed. In the fed state, microballoons were retained in the stomach for up to 5 hrs. Interestingly, microspheres with good floating properties but low *in vitro* drug release rates showed lower urinary excretion of riboflavin in the time period of 4–8 hrs after dosing, compared with microspheres with worse floating properties and high *in vitro* drug release rates. Thus, it is important to select an appropriate balance between the floating properties and drug release rates with this type of system.

Recently, piroxicam was incorporated into this type of hollow polycarbonate microspheres with encapsulation efficiencies >95% (Joseph et al., 2002). *In vitro* drug release in simulated gastric fluid showed no significant burst effect. The system was also evaluated *in vivo* in rabbits and was found to provide sustained drug delivery during prolonged time periods, with an increased bioavailability compared with the free drug. Jain prepared and evaluated the gastroretentive performance and pharmacokinetic parameters of

optimized floating microspheres (RgFMCS4) consisting of calcium silicate (CS) as porous carrier; repaglinide (Rg), an oral hypoglycemic agent and Eudragit S (ES) as polymer. The optimized formulation demonstrated favorable *in vitro* floating and drug release characteristics (Jain et al., 2005). The gastroretentive behavior of this optimized formulation was compared with non-floating microspheres (RgNFM) prepared from the identical polymer. The gamma scintigraphy of the formulations was carried out in albino rabbits to monitor the transit of RgFMCS4 and RgNFM in the gastrointestinal (GI) tract. Prolonged gastric residence time (GRT) of over 6 hrs was achieved in all animals for calcium silicate based floating microspheres of Rg. Rg loaded optimized formulation was orally administered to albino rabbits and blood samples were used to determine pharmacokinetic parameters of Rg from floating microspheres, which were compared with pharmacokinetic parameters of the marketed tablet formulation. The relative bioavailability of Rg loaded floating microspheres was found to be increased about 3.17 times in comparison to that of the marketed tablet.

Gibaly prepared floating (F) microcapsules containing melatonin (MT) by the ionic interaction of chitosan and a negatively charged surfactant, sodium dioctyl sulfosuccinate (DOS). **Figure 21** represents the preparation method of

ionic cross linking. The characteristics of the F microcapsules generated compared with the conventional non-floating (NF) microspheres manufactured from chitosan and sodium tripolyphosphate (TPP) were also investigated (Gibaly et al., 2002). The use of DOS solution in coagulation of chitosan produced well formed microcapsules with round hollow core and 31.2-59.74% incorporation efficiencies. Chitosan concentration and drug/polymer ratio had a remarkable effect on drug entrapment in DOS/chitosan microcapsules. The dissolution profiles of most of microcapsules showed near zero order kinetics in simulated gastric fluid (S.G.F: pH 1.2). Moreover, release of the drug from these microcapsules was greatly retarded with release lasting for several hours ($t_{50\%}$ S.G.F.): 1.75-6.7 hrs, depending on processing factors), compared with NF microspheres where drug release was almost instant. Most of the hollow microcapsules developed tended to float over simulated bio fluids for more than 12 h. Talukder and Fassihi prepared beads of low methoxylated pectin and, optionally, sodium alginate crosslinked with calcium chloride. The floating properties of the devices strongly depended on the subsequent drying process (Talukder and Fassihi, 2004). Oven dried beads did not float, whereas freeze dried beads remained floating for >12 hrs in hydrochloride buffer pH 1.5 due to the presence of air filled hollow spaces within the system.

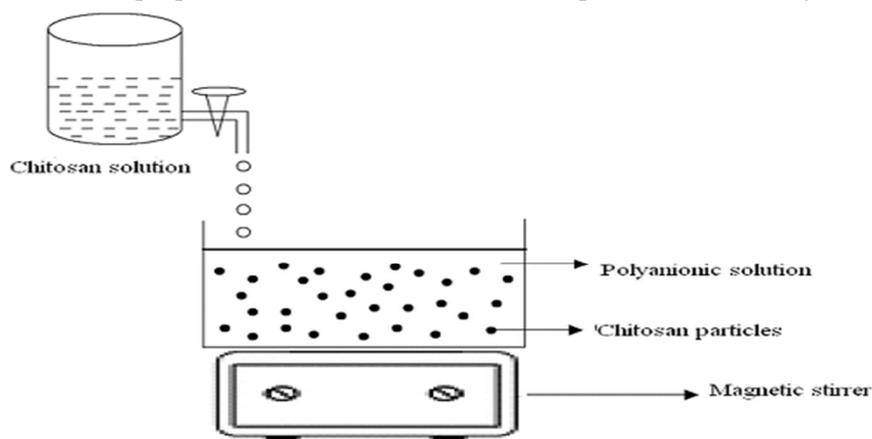


Figure 21: represents the preparation of chitosan microspheres by ionic cross linking

Pawar (Pawar et al., 2007) developed hollow calcium pectinate beads for floating pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Hollow/porous beads were prepared by simple process of acid base reaction during ionotropic crosslinking, to overcome limitations of various approaches for imparting buoyancy. The floating beads obtained were porous (34% porosity), hollow with bulk density <1 and had floating $t_{50\%}$ of 14–24 hrs. *In vivo* studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 hrs. The floating beads provided expected two phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising floating pulsatile drug delivery system for site and time specific release of drugs acting as per chronotherapy of diseases.

2.3 Current trends and advancements

2.3.1 Dual working systems

These systems are based on the two working principles of either floating and bioadhesion or swelling and bioadhesion. FDDS are formulated to persist floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3–4 hrs. Furthermore, floating systems do not always release the drug at the intended site. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semiliquid contents are churning around due to the effect of peristalsis.

A dual working system would overcome drawbacks associated with bioadhesive, swelling, and floating systems, and would have a significant effect on improving the therapeutic effect of the drug involved (Zheng et al., 2006; Chavanpatil et al., 2006; Kumar et al., 2008).

2.3.2 Floating osmotic systems

A floating osmotic drug delivery system employs the principal of osmotic pressure to float on the gastric fluid. Basically these systems comprise of three parts; an osmotic core (containing drug reservoir, osmotic agents, and other excipients), a shape retaining semipermeable membrane; and an outer compression coating consisting of gas generating and gel forming agents.

For delivery of drug an orifice is bored through both the outer layers. After administration when this system comes in contact with gastric fluid, initially CO₂ is generated due to the presence of a gas forming agent and this generated gas entraps within the bed of swelled gel, thus the system became buoyant due to diminished density. Delivery of drug then totally depends upon the osmotic pressure generated inside the osmotic core. First a saturated solution of drug is formed due to the flow of fluid through the semi-permeable membrane and second expulsion of drug through the orifice due to osmotic pressure develops within the osmotic core. A major advantage of floating osmotic drug delivery systems is that they deliver drug independent to physiological parameters like pH of gastric fluid (Zou et al., 2008).

2.3.3 Floating-pulsatile systems

Pulsatile drug delivery systems release the drug rapidly and completely after certain lag times. However an uncertainty is always associated with such systems, they may expel out from the body without releasing drug content due to the presence of lag time. Floating pulsatile systems develop to overcome this drawback and have gained increasing interest during recent years for a number of drug therapies (Badve et al., 2007; Mahale et al., 2011).

2.3.4 Floating Solid lipid microparticle systems

Solid lipid micro/nanoparticles are used for increasing permeability which may result in increased bioavailability reduction of dose and side effects. SLNs/SLMs formulates into a hydrodynamically balanced capsule, which is a gastroretentive dosage form for prolonging the release of administration. SLMs/SLNs consist of

biocompatible lipid core and an amphelic surfactant as an outer shell. Particles are micro/nano meter range, which are actually dispersed in the aqueous surfactant solution. SLMs have attracted increasing attention as a potential drug delivery carrier owing to their advantages such as possibility of simple and large production and low toxicity.

Advantages of SLMs/SLNs are possibility of controlled drug release and drug targeting, increased drug stability, high drug payload, feasibility of incorporating lipophilic and hydrophilic drugs, no biotoxicity of the carrier, avoidance of organic solvents, ease in large scale production and sterilization, surface modification can be easily performed. Ofloxacin loaded SLNs were prepared using palmitic acid as lipid matrix and polyvinyl alcohol (PVA) as emulsifier by a hot homogenization and ultrasonication method. The physicochemical characteristics of SLN were investigated by optical microscope scanning electron microscopy, and photon correlation spectroscopy.

The SLNs showed sustained release and enhanced antibacterial activity in-vitro. Pharmacokinetic results demonstrated that SLN increased the bioavailability of ofloxacin by 2.27 folds and extended the mean residence time of the drug from 10.50 to 43.44 hrs. Single oral administration of ofloxacin loaded nanoparticles at 3 drug doses, 5 mg/kg, 10 mg/kg and 20 mg/kg; all produced higher survival rates of lethal infected mice compared with native ofloxacin. These results indicate that SLN might be a promising delivery system to enhance the pharmacological activity of ofloxacin.

CONCLUSION

GRDDS are of particular interest for drugs that, act locally in the stomach, primarily absorbed in stomach, poorly soluble at an alkaline pH, have a narrow window of absorption, Unstable in the intestinal or colonic environment.

ACKNOWLEDGEMENTS

The author is grateful to the support of the Dr. Arun Garg, Director, PDM College of Pharmacy, Haryana, India and Dr. Arun Nanda, H.O.D, Department of Pharmaceutical Science, MDU, Rohtak, Haryana, India.

REFERENCE:

1. Adhikary, A., Vavia, P.R. 2008. Bioadhesive ranitidine hydrochloride for gastroretention with controlled microenvironmental pH. *Drug Dev. Ind. Pharm.* 34(8), 860-869.
2. Ali, J., Arora, S., Ahuja, A., Babbar, A., Sharma, R.K., Khar, R.K., Baboota, S. 2007. Formulation and development of hydrodynamically balanced system for metformin: *In vitro* and *in vivo* evaluation. *Eur. J. Pharm. Biopharm.* 67(1), 196-201.
3. Allam, A.N., E.I. Gamal, S.S., Nagar, V.F. 2011. Optimization of acyclovir oral tablets based on gastroretention technology: factorial design analysis and physicochemical characterization studies. *Drug Dev. Ind. Pharm.* 37(7), 855-867.
4. Andrews, G.P., Laverty, T.P., Jones, D.S. 2009. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur. J. Pharm. Biopharm.* 71, 505-518.
5. Arora, S., Ali, J., Ahuja, A., Khar, R.K., Baboota, S. 2005. Floating Drug Delivery Systems: A Review. *AAPS PharmSciTech.* 6(3), Article 47.
6. Badve, S.S., Sher, P., Korde, A., Pawar, A.P. 2007. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. *Eur. J. Pharm. Biopharm.* 65, 85-93.
7. Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C., Falson, F. 2006. Gastroretentive dosage forms: Overview and special case of *Helicobacter pylori*. *J. Control. Release.* 111, 1-18.
8. Basit, A. 2001. Colonic metabolism of ranitidine: implications for its delivery and absorption. *Int. J. Pharm.* 227(1-2), 157-165.
9. Baumgartner, S., Kristl, J., Vrecer, F., Vodopivec, P., Zorko, B. 2000. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int. J. Pharm.* 195, 125 - 135.
10. Baumgartner, S., Smidkorbar, J., Vrecer, F., Kristl, J. 1998. Physical and technological parameters influencing floating properties of matrix tablets based on cellulose ethers. *STP Pharm. Sci.* 8, 285-290.

11. Carvalho, F.C., Bruschi, M.L., Evangelista, R.C., Gremião, M.P. 2010. Mucoadhesive drug delivery systems. *Braz. J. Pharm. Sci.* 46(1).
12. Chavanpatil, M.D., Jain, P., Chaudhari, S, Shear, R., Vavia, P.R. 2006. Novel sustained release swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. *Int. J. Pharm.* 316,86-92.
13. Chavda, H.V., Patel, C.N. 2010. A newer formulation approach: superporous hydrogel composite-based bioadhesive drug delivery system. *Asian J. Pharm. Sci.* 5 (6), 239-250.
14. Chavda, H.V., Patel, C.N. 2010. Preparation and Characterization of swellable polymer based superporous hydrogel composite of poly (acrylamide-co-acrylic acid). *Trends Biomater. Artif. Organs.* 24(1),83-89.
15. Chavda, H.V., Patel, CN. 2011. Effect of crosslinker concentration on characteristics of superporous hydrogel. *Int. J. Pharm. Inves.* 1(1), 17-21.
16. Chawla, G., Gupta, P., Koradia, V., Bansal, A. 2003. Gastroretention: A means to address regional variability in intestinal drug absorption. *Pharm. Technol.* 50-58.
17. Chen, J., Blevins, W.E., Park, H., Park, K. 2000. Gastric retention properties of superporous hydrogel composites. *J. Control. Release.* 64, 39-51.
18. Chen, J., Park, K. 2000. Synthesis of fast-swelling, superporous sucrose hydrogels. *Carbohydrate Polymers.* 41, 259-268.
19. Clarke, G.M., Newton, J.M., Short, M.B. 1995. Comparative gastrointestinal transit of pellet systems of varying density. *Int. J. Pharm.* 114, 1-11.
20. Colombo, P., Provasi, D., Borazzo, M.G., Maggi, L., Catellani, L. 1989. The role of compression force in floating tablet formula optimization. *Acta Pharm. Technol.* 35, 168-170.
21. Dave, B., Amin, A., Patel, M.M. 2004. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation. *AAPS PharmSciTech.* 5(2), Article 34.
22. Deshmukh, V.N., Jhadav, J.K., Sakarkar, G.M. 2009. Formulation and *in vitro* evaluation of theophylline anhydrous bioadhesive tablets. *Asian J. Pharm.* 3(1), 54-58.
23. Dorozynki, P., Jachowiz, R., Kulinowski, P., Kwiecinski, S., Szybinski, K., Skorka, T., Jasinski, A. 2004. The macromolecular polymers for the preparation of hydrodynamically balanced systems – methods of evaluation. *Drug Dev. Ind. Pharm.* 30, 947-957.
24. E.I. Gibaly, I. 2002. Development and *in vitro* evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres. *Int. J. Pharm.* 249(1-2), 7-21.
25. E.L kamel, A.H., Sokar, M.S., Gamal, S.S, Naggar, V.F. 2001. Preparation and evaluation of ketoprofen floating oral delivery system. *Int. J. Pharm.* 220:13-21.
26. Fell, J.T. 1996. Targeting of drugs and delivery systems to specific sites in the gastrointestinal tract. *J Anat.* 189 (3), 517-519.
27. Gaikwad, M., Belgamwar, V., Tekade, A., Gattani, S., Surana, S. 2010. Formulation and evaluation of floating, pulsatile, multiparticulates using pH-dependent swellable polymers. *Pharm. Dev. Technol.* 15(2), 209-216.
28. Gangadharappa, H.V., Kumar, P., Kumar, S. 2007. Gastric floating drug delivery systems: A review. *Ind. J. Pharm. Educ. Res.* 41, 295-305
29. Garg, S., Sharma, S. 2003. Gastroretentive drug delivery systems. *Pharm. Tech.* 160-166.
30. Gerogiannis, V.S., Rekkas, D.M., Dallas, P.P., Choulis, N.H. 1993. Floating and swelling characteristics of various excipients used in controlled release technology. *Drug Dev. Ind. Pharm.* 19, 1061-1081.
31. Goole, J., Gansbekeb, B., Pilcer, G., Deleuzea, P., Blocklet, D., Goldman, S., Pandolfod, M., Vanderbist, F., Amighia, K. 2008. Pharmacoscintigraphic and pharmacokinetic evaluation on healthy human volunteers of sustained-release floating minitables containing levodopa and carbidopa. *Int. J. Pharm.* 364, 54-63.
32. Goole, J., Vanderbist, F., Amighi, K. 2007. Development and evaluation of new multiple-unit levodopa sustained release floating dosage forms. *Int. J. Pharm.* 334, 35-41.
33. Goswami, L., Mukhopadhyay, S., Durgapal, S. 2011. Formulation and evaluation of combined floating bilayer tablet of metformin and pioglitazone. *J. Pharm. Res.* 4(3), 645-646.
34. Gröning, R., Cloer, C., Georgarkis, M., Müller, R.S. 2007. Compressed collagen sponges as gastroretentive dosage forms: *In vitro* and *in vivo* studies. *Eur. J. Pharm. Sci.* 30, 1-6.
35. Hejazi, R., Amiji, M. 2002. Stomach specific anti-*H. pylori* therapy. I. Preparation and characterization of tetracycline loaded chitosan microspheres. *Int. J. Pharm.* 235, 87-94.
36. Hejazi, R., Amiji, M. 2003. Stomach specific anti-*H. pylori* therapy. II. Gastric residence studies of tetracycline-loaded chitosan microspheres in gerbils. *Pharm. Dev. Technol.* 8, 253-262.

37. Higo, S., Ori, K., Takeuchi, H., Yamamoto, H., Hino, T., Kawashima, Y. 2004. A novel evaluation method of gastric mucoadhesive property *in vitro* and the mucoadhesive mechanism of tetracycline-sucralfate acidic complex for eradication of *Helicobacter pylori*. Pharm. Res. 21, 413-419.
38. Hoffman, A., Stepensky, D., Lavy, E., Eyal, S., Klausner, E., Friedman, M. 2004. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int. J. Pharm. 277, 141-153.
39. Hoffmann-LA Roche. 1976. Sustain release formulations. DE2611041.
40. Hoffmann-LA Roche. 1984. Hydrodynamically balanced controlled release compositions containing L-dopa and a decarboxylase inhibitor. US4424235 .
41. Hooda , A., Jain, M., Rathee, P., Garg, A., Nanda, A. 2011. Gastrointestinal mucoadhesive drug delivery system: A review. J. Pharm. Res. 4(5), 448-1453.
42. Hwang, S., Park, H., Park, K. 1998. Gastric retentive drug delivery system. Crit. Rev. Ther. Drug Carrier Syst. 15(3), 243-284.
43. Ishida, M., Abe, K., Hashizume, M., Kawamura, M. 2008. A novel approach to sustained pseudoephedrine release: Differentially coated mini-tablets in HPMC capsules. Int. J. Pharm. 359, 46-52.
44. Jain, S.K., Awasthi, A.M., Jain, N.K., Agrawal, G.P. 2005. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and *in vitro* characterization. J. Control. Release. 107, 300-309.
45. Javadzadeh, Y., Asnaashari, S., Khoei, N.S., Zarrintan, M.H., Adibkia, K. 2011. Preparation and evaluation of novel metronidazole sustained release and floating matrix tablets. Pharm. Dev. Technol. 16(4), 400-407.
46. Joseph, N.J., Lakshmi, S., Jayakrishnan, A. 2002. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: *in vitro* and *in vivo* evaluation in rabbits. J. Control. Release. 79, 71-79.
47. Joshi, A., Vasu, K., Nivsarkar, M., Shishoo, C. 2011. Gastroretentive delivery of rifampicin: *In vitro* mucoadhesion and *in vivo* gamma scintigraphy. Int. J. Pharm. 411(1-2), 106-112.
48. Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., Ito, Y. 1991. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (*in vitro*) and floating behavior (*in vivo*). J. Control. Release. 16, 279-290.
49. Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., Ito, Y. 1992. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J. Pharm. Sci. 81, 135-140.
50. Kharenko, E.A., Larionova, N., Demina, N.B. 2009. Mucoadhesive drug delivery systems (review). Pharm. Chem. J. 43(4), 200-208.
51. Kim, D., Park, K. 2004. Swelling and mechanical properties of superporous hydrogels of poly (AAm-co-AAc) polyethyleneimine interpenetrating polymer networks. Polymer. 45, 189-196.
52. Klausner, E.A., Eyal, S., Lavy, E., Friedman, M., Hoffman, A. 2003. Novel levodopa gastroretentive dosage form: *in vivo* evaluation in dogs. J. Control. Release. 88, 117-126.
53. Klausner, E.A., Lavy, E., Barta, M., Cserepes, E., Friedman, M., Hoffman, A. 2003. Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharm. Res. 20, 1466-1473.
54. Klausner, E.A., Lavy, E., Friedman, M., Hoffman, A. 2003. Expandable gastroretentive dosage forms. J. Control. Release. 90, 143-162.
55. Klausner, E.A., Lavy, E., Stepensky, D., Cserepes, E., Barta, M., Friedman, M., Hoffman, A. 2003. Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration to healthy volunteers. J. Clin. Pharmacol. 43, 711-720.
56. Klausner, E.A., Lavy, E., Stepensky, D., Friedman, M., Hoffman, A. 2002. Novel gastroretentive dosage forms: Evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. Pharm. Res. 19, 1516-1523.
57. Kulkarni, A., Bhatia, M. 2009. Development and evaluation of regioselective bilayer floating tablets of atenolol and lovastatin for biphasic release profile. Iranian J. Pharm. Res. 8(1), 15-25.
58. Kumar, M.K., Shah, M.H., Ketkar, A., Mahadik, K.R., Paradkar, A. 2004. Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices. Int. J. Pharm. 272, 151-160.
59. Kumar, P., Singh, S., Mishra, B. 2008. Floating osmotic drug delivery system of ranitidine hydrochloride: development and evaluation-a technical note. AAPS PharmSciTech. 9, 480-485.
60. Lee, J.H., Park, T.G., Choi, H.K. 1999. Development of oral drug delivery system using

- floating microspheres. *J. Microencapsul.* 16,715-729.
61. Lee, J.H., Park, T.G., Lee, Y.B., Shin, S.C., Choi, H.K. 2001. Effect of adding non-volatile oil as a core material for the floating microspheres prepared by emulsion solvent diffusion method. *J. Microencapsul.* 18, 65-75.
 62. Liu, Q., Fassih, R. 2008. Zero-order delivery of a highly soluble, low dose drug alfuzosin hydrochloride via gastro-retentive system. *Int. J. Pharm.* 348, 27-34.
 63. Madgulkar, A., Kadam, S., Pokharkar, V. 2008. Development of trilayered mucoadhesive tablet of itraconazole with zero-order release. *Asian J. Pharm.* 2(1), 57-60.
 64. Mahale A.M, Panigrahy R.N, Sreenivas S.A. 2011. Formulation and *in vitro* evaluation of gastroretentive drug delivery system for acyclovir. *Pharmacie Globale.* 5 (12), 1-4.
 65. Meka, L., Kesavan, B., Kalamata, V.N., Eaga, C.M., Bandari, S., Vobalaboina, V., Yamsani, M.R. 2009. Design and evaluation of polymeric coated minitables as multiple unit gastroretentive floating drug delivery systems for furosemide. *J. Pharm. Sci.* 98(6), 2122-2132.
 66. Merck and Co. 1986. Drug delivery device which can be retained in the stomach for a controlled period of time. EP 0202159.
 67. Merck and Co. 1988. Drug delivery device which can be retained in the stomach for a controlled period of time. US 4735804.
 68. Merck and Co. 1988. Drug Delivery Device Which Can Be Retained In The Stomach For A Controlled Period Of Time - US 4758436.
 69. Merck and Co. 1988. Drug delivery device which can be retained in the stomach for a controlled period of time. US 4767627.
 70. Miyazaki, Y., Yakou, S., Takayama, K. 2008. Comparison of gastroretentive microspheres and sustained-release preparations using theophylline pharmacokinetics. *J. Pharm. Pharmacol.* 60(6), 693-698.
 71. Moes, A.J. 2003. Gastric retention systems for oral drug delivery. *Business Briefing: Pharmatech.* 157-59.
 72. Nama, M., Gonugunta, C.S., Veerareddy, P.R. 2008. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. *AAPS PharmSciTech.* 9(1), 231-237.
 73. Nanda, A., Ola, M., Bhaskar, R., Sharma, C.K., Nayak, S. 2010. Formulation and evaluation of an effervescent, gastroretentive drug-delivery system. *Pharm. Technol.*, 60-71.
 74. Nayak, A.K., Maji, R., Das, B. 2010. Gastroretentive drug delivery systems: A review. *Asian J. Pharm. Clin. Res.* 3(1), 2-10.
 75. Omidian, H., Park, K., Rocca, J.G. 2007. Recent developments in superporous hydrogels. *J. Pharm. Pharmacol.* 59, 317-327.
 76. Omidian, H., Qiu, Y., Yang, S., Kim, D., Park, H., Park, K. 2005. Hydrogels having enhanced elasticity and mechanical strength properties. US Patent.6960617.
 77. Omidian, H., Rocca, J.G., Park, K. 2006. Elastic superporous hydrogel hybrid of polyacrylamide and sodium alginate. *Macromol. Biosci.* 6, 703-710.
 78. Omidian, H., Rocca, J.G., Park, K. 2005. Advances in superporous hydrogels. *J. Control. Release.* 102, 3-12.
 79. Ozdemir, N., Ordu, S., Ozkan, Y. 2000. Studies of floating dosage forms of furosemide: *in vitro* and *in vivo* evaluations of bilayer tablet formulations. *Drug Dev. Ind. Pharm.* 26 (8), 857- 866.
 80. Pan, W., Guan, J., Zhou, L., Nie, S., Yan, T., Tang, X. 2010. A novel gastric resident osmotic pump tablet: *In vitro* and *in vivo* evaluation. *Int. J. Pharm.* 383, 30-36.
 81. Parikh, D., Amin, A. 2008. *In vitro* and *in vivo* techniques to assess the performance of gastroretentive drug delivery systems: a review. *Expert Opin. Drug Deliv.* 5(9), 951-965.
 82. Parikh, D., Amin, A. 2008. *In vitro* and *in vivo* techniques to assess the performance of gastroretentive drug delivery systems: a review. *Expert Opin. Drug Deliv.* 5(9), 951-965.
 83. Park, H., Park, K., Kim, D. 2006. Preparation and swelling behavior of chitosan based superporous hydrogels for gastric retention application. *J. Biomed. Mat. Res.* 76(1), 144-150.
 84. Park, K., Chen, J., Park, H. 2001. Hydrogel composites and superporous hydrogel composites having fast swelling, high mechanical strength, and superabsorbent properties US 6271278.
 85. Pawar, V., Kansal, S., Garg, G., Awasthi, R., Singodia, D., Kulkarni, G. 2011. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. *Drug Del.* 18(2), 97-110.
 86. Rahman, Z., Ali, M., Khar, R.K. 2006. Design and evaluation of bilayer floating tablets of captopril. *Acta Pharm.* 56, 49-57.

87. Reddy, V.H., Murthy, R.S.R. 2002. Floating dosage systems in drug delivery. *Crit. Rev. Ther. Drug. Carrier Syst.* 19(6), 553-585.
88. Robles, L.V., Martínez, I., Barreda T.Q. 2008. Sustained delivery of captopril from floating matrix tablets. *Int. J. Pharm.* 362, 37-43.
89. Rocca, J., Omidian, H., Shah, K. 2004. Progresses in gastroretentive drug delivery systems. *Pharm. Tech.* 152-156.
90. Rocca, J.G., Omidian, H., Shah, K. 2005. Gastric retention technologies: commercial status of gastric retention technologies. *Drug Deliv. Technol.* 5, 40-46.
91. Rouge, N., Allemann, E., Gexfabry, M., Balant, L., Cole, E.T., Buri, P., Doelker, E. 1998. Comparative pharmacokinetic study of a floating multiple unit capsule, a high density multiple unit capsule and an immediate release tablet containing 25mg atenolol. *Pharm. Acta. Helv.* 73, 81-87.
92. Rouge, N., Cole, E.T., Doelker, E., Buri, P. 1997. Screening of potentially floating excipients for minitablets. *STP Pharm. Sci.* 7, 386-392.
93. Rouge, N., Leroux, J.C., Cole, E.T., Doelker, E., Buri, P. 1997. Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules. *Eur. J. Pharm. Biopharm.* 43, 165-171.
94. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. 2004. *In vitro* and *in vivo* evaluation of riboflavin- containing microballoons for a floating controlled drug delivery system in healthy humans. *Int. J. Pharm.* 275, 97-107.
95. Sato, Y., Kawashima, Y., Takeuchi, H., Yamamoto, H. 2003. Physicochemical properties to determine the buoyancy of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. *Eur. J. Pharm. Biopharm.* 55, 297-304.
96. Sato, Y., Kawashima, Y., Takeuchi, H., Yamamoto, H. 2004. *In vitro* evaluation of floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. *Eur. J. Pharm. Biopharm.* 57, 235-243.
97. Sato, Y., Kawashima, Y., Takeuchi, H., Yamamoto, H., Fujibayashi, Y. 2004. Pharmacoscintigraphic evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. *J. Control. Release.* 98, 75-85.
98. Schmitz, T., Leitner, V.M., Schnürch, A. 2005. Oral heparin delivery: design and *in vivo* evaluation of a stomach-targeted mucoadhesive delivery system. *J. Pharm. Sci.* 94(5), 966-973.
99. Senyigit, Z.A., Vetter, A., Guneri, T., Schnürch, A.B. 2011. A comprehensive *in vitro* and *in vivo* evaluation of thiolated matrix tablets as a gastroretentive delivery system. *Drug Del.* 18(6), 405-414.
100. Shah, S.H., Patel, J.K., Patel, N.V. 2009. Stomach specific floating drug delivery system: A review. *Int. J. PharmTech Res.* 1(3), 623-633
101. Sheu, M.T., Chen, R.N., Ho, H., Yu, C.Y. 2010. Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 Polymorphism. *Eur. J. Pharm. Sci.* 39, 82-89.
102. Singh, B., Sharma, V., Chauhan, D. 2010. Gastroretentive floating sterculia-alginate beads for use in antiulcer drug delivery. *Chem. Eng. Res. Des.* 88(8), 997-1012.
103. Singh, B.N., Kim, K.H. 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J. Control. Rel.* 63, 235-259.
104. Singh, S., Joshi, V., Kumar, P. 2009. Gastroretentive drug delivery system: Current approaches. *J. Pharm. Res.* 2(5), 881-886.
105. Soani, N.G., Hiremath, S.P., Dasonkoppa, F.S., Jamakandi, V.G., Sreenivas, S.A. 2010. Design and evaluation of gastroretentive mucoadhesive cephalixin tablets. *Pharm. Dev. Technol.* 15(2), 178-83.
106. Soppimath, K.S., Kulkarni, A.R., Aminabhavi, T.M. 2001. Development of hollow microspheres as floating controlled release systems for cardiovascular drugs: preparation and release characteristics. *Drug Dev. Ind. Pharm.* 27, 507-515.
107. Srivastava, A.K., Wadhwa, S., Ridhurkar, D., Mishra, B. 2005. Oral sustained delivery of atenolol from floating matrix tablets- formulation and *in vitro* evaluation. *Drug Dev. Ind. Pharm.* 31, 367-374.
108. Stops, F., Fell, J.T., Collett, J.H., Martini, L.G. 2008. Floating dosage forms to prolong gastro retention-The characterisation of calcium alginate beads. *Int. J. Pharm.* 350, 301-311.
109. Stops, F., Fell, J.T., Collett, J.H., Martini, L.G., Sharma, H.L., Smith, A.M. 2006. The use of citric acid to prolong the *in vivo* gastro-retention of a floating dosage form in the fasted state. *Int. J. Pharm.* 308, 8-13.
110. Streubel, A., Siepmann, J., Bodmeier, R. 2003. Floating matrix tablets based on low density foam powder: effects of formulation

- and processing parameters on drug release. Eur. J. Pharm. Sci. 18, 37-45.
111. Streubel, A., Siepmann, J., Bodmeier, R. 2003. Multiple unit gastroretentive drug delivery systems: a new preparation method for low density microparticles. J. Microencapsul. 20, 329-347.
112. Streubel, A., Siepmann, J., Bodmeier, R. 2006. Drug delivery to the upper small intestine window using gastroretentive technologies. Curr. Opin. Pharmacol. 6(5), 501-508.
113. Streubel, A., Siepmann, J., Bodmeier, R. 2006. Gastroretentive drug delivery systems. Expert Opin. Drug Deliv. 3(2), 217-233.
114. Streubel, A., Siepmann, J., Bodmeier, R. 2002. Floating microparticles based on low density foam powder. Int. J. Pharm. 241, 279-292.
115. Sultana, S., Bhavna, Iqbal Z., Panda, B.P., Talegaonkar, S., Bhatnagar, A., Ahmad, F.J. 2009. Lacidipine encapsulated gastroretentive microspheres prepared by chemical denaturation for pylorospasm. J. Microencapsul. 26(5), 385-393.
116. Sungthongjeen, S., Sriamornsak, P., Puttipipatkachorn, S. 2008. Design and evaluation of floating multi-layer coated tablets based on gas formation. Eur. J. Pharm. Biopharm. 69, 255-263.
117. Talukder, R., Fassihi, R. 2004. Gastroretentive delivery systems: a mini review. Drug Dev. Ind. Pharm. 30, 1019-1028.
118. Talukder, R., Fassihi, R. 2004. Gastroretentive delivery systems: hollow beads. Drug Dev. Ind. Pharm. 30, 405-412.
119. Whitehead, L., Collett, J.H., Fell, J.T. 2000. Amoxicillin release from a floating dosage form based on alginates. Int. J. Pharm. 210, 45-49.
120. Xu, G., Groves, M.J. 2001. Effect of FITC-dextran molecular weight on its release from floating cetyl alcohol and HPMC tablets. J. Pharm. Pharmacol. 53(1), 49 - 56.
121. Yang, S., Park, K., Rocca, J.G. 2004. Semi-interpenetrating polymer network superporous hydrogels based on poly (3-sulfopropyl acrylate, potassium salt) and poly (vinyl alcohol): Synthesis and characterization. J. Bioactive Compatible Polymers. 19, 81-100.
122. Zheng, J., Liu, C., Bao, D., Zhao, Y., Ma, X. 2006. Preparation and evaluation of floating bioadhesive microparticles containing clarithromycin for the eradication of *Helicobacter pylori*. J. Appl. Polym. Sci. Symp. 102, 2226-2232.
123. Zou, H., Jing, X., Kong, L., Gao, S. 2008. Design and evaluation of a dry coated drug delivery system with floating-pulsatile release. J. Pharm. Sci.; 97, 263-273.