3. PREVIOUS WORKS ON GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Past works reported on the gastroretentive drug delivery systems includes floating tablets, floating bioadhesive tablets, floating capsules, multi-particulate systems, hollow micro spheres and floating beads etc. Few reports that are available are briefly reviewed.

Sheth *et al.*, 1984, have reported gastric retentive characteristics of hydrodynamically balanced systems of diazepam and chlordiazepoxide as well as the blood level profile for both drugs, the hydrodynamically balanced systems was retained in the stomach for a longer period of time than conventional tablets swallowed concurrently, and slowed gastric retention time upto 6 hours. The *in vivo* blood level time profile of diazepam from hydrodynamically balanced system was three times from conventional tablets.

Inouye *et al.*, 1989, prepared sustained release floating granules of prednisolone using chitosan of different degrees of deacetylation (Chitosan H and L). The granules were prepared by a method involving deacidification, had internal cavities, were immediately buoyant in both acidic and neutral fluids and gave sustained release of prednisolone.

Babu *et al*., 1990, formulated the sustained release floating capsules of salbutamol sulfate using different combination of hydrocolloids of natural and synthetic origin. The floating capsules showed a Higuchian release profile. The *in- vivo* X- ray studies of the abdomen were carried out to locate floating dosage form at various time intervals.

Yuasa *et al.*, 1996, prepared the intragastric floating granules using calcium silicate (Florite, FLR) as a floating carrier which has floating ability due to air included in the pores when they are covered with a polymer. The granules showed a longer floating time and they suggested that the FLR is a useful carrier for the development of a floating and sustained release preparation.

Takashima *et al*., 1998, investigated the preparation of floating granules using hollow glass beads (G.B) as carrier and oxprenolol hydrochloride as model drug. The prepared granules were evaluated for density, floating property and drug release profile. The density of all type of formulations containing G.B was less than 1 gm/cm^3. These granules floated for long time in test fluid and rate of drug release from the granules was decreased with decreased G.B contents.

Whitehead *et al.*, 1998, investigated the *in vivo* behavior of multiple units floating drug delivery system compared to a non floating dosage form manufactured from identical material. They performed the study on seven healthy volunteers, who swallowed the radiolabelled formulations after a standard breakfast and reported that prolonged gastric residence of over 5.5 hours were achieved in all subjects for the floating formulations and in contrast, the non floating formulations showed short gastric residence time, with a mean onset emptying time of 1 hour.

Iannuccelli, *et al.*, 1998, formulated air compartment multiple unit systems and optimized their *in vitro* floating ability. They showed that the floating ability increased with increased in PVA concentration and molecular weight and it was found to be excellent when using PVA 100000 at a concentration of at least 5 %.

Iannuccelli, *et al.*, 1998a, assayed the intragestric behavior of floating multiple unit system. The floating units used in this study composed of a calcium alginate core separated by an air compartment from a calcium alginate/polyvinylalcohol membrane. They conducted the *in vivo* study by administering to each subject at the same time both floating and control systems, loaded with barium sulphate, and monitored them in the gastric region at determined time intervals using X- ray apparatus and reported that the floating system remained buoyant on gastric content under both fastened and fed state.

Nurten *et al.*, 2000, reported floating dosage forms of furosemide by *in vitro* and *in vivo* evaluations. Because of the lower solubility of drug in the gastric medium, it was first enhanced by preparing an inclusion complex of furosemide with beta-cyclodextrin (B-CD) in a 1:1 proprtion using the kneading method. Bilayered HPMC 4000, HPMC 100 and CMC were employed for the control of furosemide and for matrix formation. An efferscent mixture of sodium bicarbonate and citric acid was added for floating. Dissolution rate studies were performed using the continuous flow through cell method. The *in vivo* evaluation of the formulation that provided delivery of active material (near the targeted profile, formulation with release layer containing furosemide- B-CD (1:1), HPMC 100, 30 mg and the floating layer containing 250 mg HPMC 400, 30 mg sodium bicarbonate and 28 mg of citric acid) in 6 healthy male volunteers. The floating tablets prepared by adding barium sulphate stayed in stomach for 6 hours. The plasma concentration time curve obtained with the floating dosage of form was about 1.8 times those of the conventional furosemide tablet in blood analysis. Maximum and minimum plasma concentrations were also found to be between desired limits. In urine analysis, the peak diuretic effect seen in classical preparations was decreased and

prolonged in floating design forms. A considerable significant correlation was detected between *in vivo* results and *in vitro* data of the dissolution rate.

Nur and Zhang, 2000, prepared the captopril floating and/or bioadhesive tablets using two viscosity grades of hydroxypropylmethyl cellulose (HPMC 4000 and 15,000 cps) and carbopol 934P. The tablets were evaluated for *in vitro* dissolution in simulated gastric fluid (enzyme free) at 37 °C ± 0.1 °C using the USP apparatus II basket methods and compared to conventional tablets. It was found that release of captopril from these floating tablets was apparently prolonged up to 24 hours. The drug release followed both the Higuchi model and the Korsmeyer and Peppas equation. It was also observed that the tablet hardness and stirring rate had no or little effect on the release kinetics.

Shoufeng *et al.*, 2002, evaluate the contribution of formulation variable HPMC and carbopol on the properties of tablets using a continuous monitoring system which consist of an electric balance interfacing with a PC, was designed to perform the continuous monitoring of floating kinetics of GRDDS. It was found that HPMC of higher viscosity generally exhibited a greater floating capacity and carbopol appeared to have a negative effect on the floating properties and incorporation of hydrophobic agents like magnesium stearate could significantly improve the floating ability of GRDDS.

Choi *et al.*, 2002, prepared floating beads from a sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas-forming agents and investigated the effects of gas-forming agents on bead size and floating properties. They reported that the size, porosity and pore diameter of the beads depends upon the amount of gas-forming agents used in the preparation of beads. Gel strength analysis indicated that the bead strength decreased from 9 to 4 N with increase in gas-forming agent. Release rate of riboflavin from the beads increased proportionally with addition of $NaHCO_3$. However, increased weight ratios of $CaCO_3$ did not appreciably accelerate drug release. The results of these studies indicated that $CaCO_3$ was superior to $NaHCO_3$ as a gas forming agent in alginate bead preparations. The enhanced buoyancy and sustained release properties of $CaCO_3$ containing beads made them an excellent candidate for floating drug dosage systems.

Streubel *et al.*, 2003, developed low density foam (polypropylene) based microparticles using diltiazem hydrochloride, theophylline or verapamil hydrochloride as model drug and eudragit RS or polymethyl methacrylate as polymer. The floating micro particles showed a good *in-*

vitro floating behavior and a broad variety of drug release pattern depending upon the drug loading and polymer used.

Dave *et al*., 2004, reported preparation of gastroretentive drug delivery system containing ranitidine hydrochloride using guar gum, xanthum gum, HPMC and sodium bicarbonate as gas generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties were investigated. The results indicated that a low amount of citric acid and a high amount of stearic acid favored sustained release of ranitidine hydrochloride.

Shimpi *et al.*, 2004, prepared floating granules of diltiazem hydrochloride using Gelucire 43/01 by melt granulation technique. The granules were retained in stomach for 6 hours and approximately 65 to 85 % drug was released over 6 hours with initial fast release from the surface.

Basak *et al*., 2004, developed five batches of floating matrix tablets of ciprofloxacin using hydrophilic polymer HPMC and gas generation agent sodium bicarbonate and citric acid in varying amount. The two batches of tablets showed desired floating time (8 hours) and released 80 - 89 % of drug in 8 hours. Hence, It was evident that gas powered floating matrix tablet could be promising delivery system for ciprofloxacin with sustained release action.

Pornsak *et al*., 2004, prepared oil-entrapped calcium pectinate gel (CaPG) beads capable of floating in the gastric condition. The gel beads containing edible oil were prepared by either being gently mixed or homogenized an oil phase with water phase containing pectin, and then extruded into calcium chloride solution with gentle agitation at room temperature. The gel beads formed were then separated, washed with distilled water, and dried at 37 °C for 12 hours. The effect of selected factors, such as type of oil, percentage of oil, and type of pectin on morphology and floating properties was investigated. The results suggested that oil-entrapped calcium pectinate gel beads floated if a sufficient amount of oil was used. Scanning electron photomicrographs demonstrated very small pores, ranging between 5 and 40 μm, dispersed all over the beads. The type and percentage of oil played an important role in controlling the floating of oil-entrapped CaPG beads.

Srivastav *et al.*, 2005, prepared floating microspheres of cimetidine for prolongation of gastric residence time. The microspheres were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. The prepared microspheres exhibited prolonged drug release up to 8 hours and

remained buoyant for > 10 hours. The mean particle size increased and the drug release rate decreased at higher polymer concentration of polymers No significant effect of the stirring rate during preparation on drug release was observed. *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres.

Chauhan *et al.*, 2005, prepared the single and multiple unit floating matrices of residronate sodium using gelicure 43/01 by melt solidification and melt granulation technique. Both single and multiple unit systems showed increase in drug release on aging due to changes in the properties of gelicure 43/01.

Choudhury and Kar, 2005, prepared gel beads for a highly water-soluble drug metformin hydrochloride using sodium alginate as the polymer and oil by gently mixing or homogenizing of oil and water phase containing sodium alginate which was then extruded into calcium chloride solution to produce gel beads. The effects of factors like type of oil and percentage of oil on the morphology and release characteristics were investigated and reported that the mean diameter of beads increased with increase in the amount of the oil phase and the pore size of oil-entrapped beads was affected by concentration of the oil. The beads showed excellent sustaining properties.

Chavanpatil *et al*., 2005, designed the sustained release formulations, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems using different polymers, such as psyllium husk, HPMC K100M, crospovidone and its combinations to get the desired sustained release profile over a period of 24 hours. The prepared formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and *in vitro* drug release profile. It was found that dimensional stability of the formulation increased with the increasing psyllium husk concentration and *in vitro* drug release rate increased with increasing amount of crospovidone due to the increased water uptake, and hence increased driving force for drug release. *In vivo* studies of the optimized formulation were carried out in 24 healthy human volunteers and compared the pharmacokinetic parameters with the marketed once. Based on the *in vivo* performance, the optimized formulation showed promise to be bioequivalent to the marketed product with percent relative bioavailability 97.55 %.

Al-Saidan *et al*., 2005, developed guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride using various viscosity grades of guar gum, i.e., 30 % wt/wt low viscosity (LM1), 40 % wt/wt medium-viscosity (MM2), or 50 % wt/wt high-

viscosity (HM2) by wet granulation method. The drug release from HM2 tablets provided controlled release comparable with marketed sustained release diltiazem hydrochloride tablets. Guar gum matrix tablets HM2 showed no change in physical appearance, drug content, or in drug release pattern after storage at 40 °C relative humidity 75 % for 6 months. When subjected to *in vivo* pharmacokinetic evaluation in healthy volunteers, the HM2 tablets provided a slow and prolonged drug release when compared with D-SR tablets. Based on the results of *in vitro* and *in vivo* studies it was concluded that that guar gum matrix tablets provided oral controlled release of water-soluble diltiazem hydrochloride.

Varshosaz *et al*., 2006, developed effervescent floating-bioadhesive tablets of Ciprofloxacin to lengthen the stay of drug in its absorption area using sodium carboxymethyl cellulose, hydroxypropyl methylcellulose (HPMC), polyacrylic acid (AA), polymetacrylic acid (MAA), citric acid, and sodium bicarbonate. The results demonstrated that the tablets with 5 % effervescent base had longer lag time than 10 %, the type of polymer had no significant effect on the floating lag time and formulations showed a Higuchi, non-Fickian release mechanism.

Jain *et al*., 2006, evaluated the gastro-retentive performance and pharmacokinetic parameter of optimized floating microspheres consisting calcium silicate (CS) a porous carrier, repaglinide (Rg) and Eudragit S (ES). The optimized microspheres showed prolong gastric residence time (6 hours) in all animals and the relative bioavailability of Rg loaded microspheres were found to be 3.17 times in comparison with marketed tablets.

Jain *et al.*, 2006a, reported the floating microspheres of Orlistat an oral anti obesity agent using calcium silicate as porous carrier and Eudragit S as polymer by solvent evaporation technique. The microspheres were found to be regular in shape and highly porous. The microspheres containing 200 mg calcium silicate, showed the best floating ability in simulated gastric fluid.

Patel *et al*., 2006, prepared the floating microspheres of metformin hydrochloride by non-aqueous emulsification solvent evaporation technique using ethycellulose as rate controlling polymer. The drug release from the microspheres was found to be 47 to 85 % in 8 hours.

Patel *et al.*, 2006a, developed intra gastric floating drug delivery systems of cefuroxime axetil using 3^2 full factorial design and evaluated the contribution of HPMC K4M / HPMC K100 LV and SLS on the drug release. It was found that all formulations had floating lag time less

than 2 minutes, remained floating up to 8 hours and polymer bland and SLS significantly affect the time required for 50% drug release as well as percentage drug release in 12 hours.

Xiaoqiang *et al.*, 2006, prepared floating matrix dosage forms of Phenoporlamine hydrochloride based on gas generation technique using HPMC K4M, Carbopol 971 P NF and sodium bicarbonate. The dissolution profile of all the tablets showed non-Fickian diffusion in simulated gastric fluid and *in vivo* study in six healthy human volunteer suggested that floating matrix tablets containing more carbapol was capable of sustained delivery of the drug for longer periods with increased bioavailability.

Rahman *et al*., 2006, developed bilayer floating tablets of captopril using HPMC, PVP K 30, and carbopol as release layer in combination or alone and sodium bicarbonate and citric acid formed floating layer. The floating behavior and *in vitro* dissolution studies were carried out in USP XXIII apparatus II in simulated gastric fluid. The final formulation followed Higuchi release model and showed no significant change in physical appearance, *in vitro* drug release pattern and floating behavior after storage at 45 °C and 75 % RH for three months.

Chavanpatil *et al.*, 2006, developed floating, swellable and bioadhesive sustained release gastroretentive dosage forms for drugs having absorption from upper gastrointestinal tract. Various release retarding polymers like psyllium husk, HPMC K100M and a swelling agent, crosspovidone in combinations were tried and optimized to get the release profile for 24 hours. Formulations were evaluated for *in vitro* drug release profile, swelling characteristics and *in vitro* bioadhesion property. The *in vitro* drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type. For the developed formulation, the value of *n* was found to be 0.5766. The high water uptake leading to higher swelling of the tablet supported the anomalous release mechanism of ofloxacin. The swelling properties were increased 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.

Shishu *et al.*, 2007, developed multiple-unit oral floating dosage forms of 5- fluorouracil to prolong gastric residence time by dispersing 5- fluorouracil together with calcium carbonate into a mixture of sodium alginate and hydroxypropyl methylcellulose solution and then dripping the dispersion into an acidified solution of calcium chloride. The evolving gas permeated through the alginate matrix, leaving gas bubbles or pores, which provided the

beads buoyancy. The formulations were optimized for different weight ratios of gas-forming agent and sodium alginate. The results demonstrated that beads containing higher amounts of calcium carbonate demonstrated instantaneous, complete, and excellent floating ability over a period of 24 hours. The optimized formulation was subjected to *in vivo* antitumor studies to check the therapeutic efficacy of the floating dosage forms containing 5-flurouracil against benzo (a) pyrene-induced stomach tumour in albino female mice (Balb/C strain) and it was found that floating beads reduced the tumour incidence in mice by 74 %, while the conventional tablet dosage form reduced this incidence by only 25 %.

Goole *et al.,* 2007, developed multiple unit floating drug delivery systems (minitablets) by melt granulation and subsequent compression and evaluated the importance of composition and manufacturing parameter on the floating and dissolution properties of minitablets. They reported that the composition and diameter of minitablets had the great influence on the drug release, which was sustained for more than 8 hours.

Jain *et al*., 2007, prepared the porous carrier (calcium silicate) based floating granular drug delivery systems of Repaglinide and evaluated for gastroretentive and controlled release properties. The optimized formulation demonstrated favorable *in- vitro* floating and release characteristics. Prolonged gastric residence time of over 6 hours was achieved in all subjects and the relative bioavailability of repaglinide loaded floating granules increased 3.8 times in comparison to that of its marketed capsule.

Sonar *et al*., 2007, developed a bilayer and floating-bioadhesive tablets of rosiglitazone maleate using HPMC and sodium bi carbonate in the floating layer and 5% (w/v) PVP in ethanol in the sustained layer. It was observed that the *in vitro* drug release from the tablets was controlled by the amount of HPMC in the sustained release layer and followed the matrix first-order release model. The concentration of HPMC significantly affected the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablets were buoyant for up to 8 hours in the human stomach studied by gamma scintigraphy.

Kale and Tayade, 2007, developed floating drug delivery systems of piroxicam in the form of microspheres by emulsification solvent-evaporation method. The developed microspheres remained buoyant continuously over the surface of acidic media containing surfactant for a period of 8-12 hours. It was found that the *in vitro* drug release behaviour of the floating microspheres was characterized as an enteric property. Polymer being soluble above pH 7.0,

the drug release rates from microspheres changed dramatically above and below pH 7.0. At intestinal pH the drug release was faster and continuous as compared to the amount released at gastric pH.

Gambhire *et al*., 2007, prepared floating drug delivery systems of diltiazem hydrochloride to prolong gastric residence time and increase its bioavailability by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC, Methocel K100M CR), compritol 888 ATO, alone or in combination as independent variables and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate and succinic acid on drug release profile and floating properties were investigated. The time required for 50 % and 85 % drug dissolution was selected as dependent variables. The results of factorial design indicated that a high level of both Methocel K100M CR and Compritol 888 ATO favoured the preparation of floating controlled release of diltiazem hydrochloride tablets. The linear regression analysis and model fitting showed that all these formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r) while tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

Mishra and Pathak, 2008, formulated oil entrapped floating microbeads of loratidine by emulsion gelation method to increase residence time in stomach. The formulations were optimized by 2^3 factorial designs using a polymer ratio of 2.5:1.5 (pectin/sodium alginate) by mass, 15% (m/v) of oil (mineral oil or castor oil) and 0.45 mol L^{-1} calcium chloride solution for the desired buoyancy and physical stability. The results demonstrated that the i*n vitro* drug release in the fed state followed zero order release profile with value of $n < 0.45$.

Gattani *et al*., 2008, prepared floating microspheres of diltiazem hydrochloride by non-aqueous emulsification solvent evaporation technique, using ethyl cellulose and Eudragit RS-100 as the rate controlling polymer. The floating microspheres were evaluated for drug-polymer compatibility, (%) yield, particle size analysis, drug entrapment efficiency, surface topography, *in vitro* floatability and release studies. Results showed that the mixing ratio of components in the organic phase affected the size, size distribution (199-320 µm), drug content (59-84%), % yield (57-77%) and drug release of microsphere (45-99% after 12 hours) and floating time >12 hours. The best results were obtained at the ratio of drug: polymer Eudragit RS-100 (1:3). Stability studies showed no significant change in the drug content in the formulation even after 3 months.

Jain *et al.*, 2008, prepared floating granular delivery systems for the treatment of mucosal ulcer consisting of (i) calcium silicate (CS) as a porous carrier; (ii) ranitidine hydrochloride (RH), an antiulcer agent; and (iii) hydroxypropyl methylcellulose K4M (HPMC) and ethylcellulose (EC) as matrix-forming polymers and studied effect of various formulation and process variables on the particle morphology, particle size, micromeritic properties, percent drug content, *in vitro* floating behavior, and *in vitro* drug release from the floating granules. Scanning electron microscopy (SEM) of the granules revealed that that more pores of CS in secondary coated granules (SCG) were covered by the polymer solution than those in primary coated granules (PCG). The formulation demonstrated favourable *in vitro* floating and sustained drug release characteristics. The *in vivo* pharmacokinetic studies in albino rats indicate that higher plasma concentration was maintained throughout the study period from the floating granules of RH.

Khan *et al*., 2008, prepared gastroretentive floating tablets of theophylline using hydrophilic polymer methocel K4M gel forming agent and sodium bicarbonate and citric acid as gas generating agents and investigated the effects of soluble sodium bicarbonate, citric acid, Methocel K4M and dose variation on drug release profile and floating properties of tablets. It was observed that in all cases increase of the amount of floating agent caused a decrease of the floating lag time. Increase of theophylline load showed an increase of the floating lag time, which was independent of floating agent content. The release rate, extent and mechanisms were found to be governed by the content of polymer and floating agent. It was found that polymer content and amount of floating agent significantly affected the time required for 50 % of drug release, percentage drug release after 8 hours, release rate constant, and diffusion exponent (n). Kinetic modeling of dissolution profiles revealed that the drug release mechanism could range from diffusion controlled to case II transport, which was mainly dependent on presence of relative amount of theophylline, polymer and floating agent.

Nama *et al.*, 2008, developed the hydrodynamically balanced delivery systems of Clarithromycin to prolong gastric residence time with the desired *in vitro* release profile for the localized action in the stomach for the treatment of *Helicobacter pylori* mediated peptic ulcer by applying wet granulation technique. The proportion of sodium bicarbonate and polymer was varied to get the least possible lag time and desired release rate respectively. The formulation developed using 66.2 % Clarithromycin, 12 % HPMC K4M polymer, 8 % sodium bicarbonate gave floating lag time less than 3 min with a floating time of 12 hours, 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 minutes. The mechanism of release of Clarithromycin from the floating tablets was anomalous diffusion transport and followed zero order kinetics. *In vivo* radiographic studies suggest that the tablet had increased gastric residence time for the effective localized action of the antibiotic (Clarithromycin) in the treatment of *Helicobacter pylori* mediated peptic ulcer.

Hiremath *et al*., 2008, developed oral controlled release matrix tablet formulations of isoniazid using hydroxypropyl methylcellulose (HPMC) as a hydrophilic release retardant polymer using wet granulation technology. The *in vitro* release studies were performed using US Pharmacopoeia type I apparatus (basket method) in 900 ml of pH 7.4 phosphate buffer at 100 rpm. The release kinetics was analyzed using korsmeyer– peppas model. The results in the present investigation confirmed that the release rate of the drug from the HPMC matrices was highly influenced by the drug/HPMC ratio and viscosity grade of the HPMC. Also, the effect of compression force and release media was found to be significant on the release profiles of isoniazide from HPMC matrix tablets. The release mechanism was found to be anomalous non-Fickian diffusion in all the cases.

Prajapati *et al.*, 2008, developed and optimized gastric floating drug delivery systems (GFDDS) containing domperidone as a model drug by employing Box-Behnken design with three polymers: hydroxypropyl methylcellulose K4M (HPMC K4M), carbopol 934P and sodium alginate, as independent variables. Floating lag time (FLT), total floating time (TFT), time required to release 50 % of the drug and diffusion exponent (*n*) were selected as dependent variables. The result showed that HPMC loading was found to be significant for floating properties. Carbopol loading had a negative effect on floating properties but was found helpful in controlling the release rate of the drug. No significant effect of sodium alginate on floating properties was observed but it was important for gel formation.

Das *et al*., 2008, designed mucoadhesive microspheres of diltiazem hydrochloride to prolong the residence time at the absorption site by emulsification-internal gelation technique with a maximum incorporation efficiency of 93.29 ± 0.26 %. The scanning electron microscopic study indicated that the microspheres were spherical in shape and the drug remained dispersed in the polymer matrix at amorphous state, which was further confirmed by x-ray diffraction analysis. The *in vitro* wash-off test indicated that the microspheres had good mucoadhesive properties. The *in vitro* drug release mechanism was non-Fickian type controlled by swelling and relaxation of polymer. There was no significant change in drug

content and cumulative drug release of drug-loaded microspheres stored at different storage condition after eight weeks of study.

Lingam *et al.*, 2008, developed gastro retentive floating minitab's based on gas generation technique in order to prolong the gastric residence time and to increase the overall bioavailability of the drug. The floating minitab prepared by direct compression process, were coated with three successive layers of an inner seal coat, effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of an polymethacrylates (eudragit RL30D, RS30D, and combinations of them). The optimum system floated completely within 3 minutes and maintained the buoyancy over a period of 12 hours. The drug release was controlled and linear with the square root of time. Both the rapid floating and the controlled release properties were achieved in the multiple-unit floating drug delivery system and on storage at 40 °C and 75 % RH for 3 months showed no significant change found in dissolution profiles.

Lingam *et al.*, 2008a, prepared biphasic multiple units floating minitablets based on gas formation technique to maintain constant plasma level of a drug concentration within the therapeutic window by direct compression process. The floating minitablets consisted of loading dose as uncoated core units, and prolonged-release core units coated with three successive layers, one of which was seal coat, an effervescent (sodium bicarbonate) layer, and an outer polymeric layer of polymethacrylates. The system using eudragit RL30D and combination of them as polymeric layer could float within acceptable time. The drug release from the mini tablets was linear with the square root of time. The rapid floating and the controlled release properties were achieved in this present study.

Kulkarni and Bhatia, 2008, prepared bilayer floating tablets of diltiazem hydrochloride and lovastatin to give immediate release of lovastatin and controlled release of diltiazem hydrochloride using sodium starch glycolate as super disintegrant for lovastatin in the immediate release layer and hydroxypropyl methylcellulose (HPMC) K4M and xanthan gum as release-retarding agents for diltiazem hydrochloride in the controlled release layer and sodium bicarbonate was used as the gas generating agent by direct compression method. All the formulations showed good matrix integrity and released lovastatin within 30 minutes and released diltiazem hydrochloride for 12 hours. The floating bilayer tablets followed the Higuchi model and the release of one drug remained unaffected in presence of the other drug.

Mastiholimath *et al*., 2008, developed oral controlled release dosage forms of ranitidine hydrochloride to prolong the presence of dosage forms in the stomach in order to improve the bioavailability of drugs with a 'narrow absorption window' by solvent evaporation technique with modification using an ethanol co-solvent system. The formulated microspheres were free flowing with good packability and encapsulation efficiencies up to 96 %. Microspheres showed excellent buoyancy and a biphasic controlled release pattern up to 12 hours. *In vivo* bioavailability studies performed on rabbits indicated significant improvement in bioavailability.

Ramji *et al.*, 2009, developed swellable, floating, and sustained release tablets by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (crosspovidone, sodium starch glycolate, and crosscarmelose sodium) and effervescent substance (sodium bicarbonate). Formulations were evaluated for percentage swelling, *in vitro* drug release, floating lag time, total duration of floating, and mean residence time (MRT) in the stomach. The drug release from optimized formulation followed the Higuchi kinetic model, and the mechanism was found to be non-Fickian/anomalous according to krosmeyer–peppas (n = 0.68). *In vivo* nature of the tablets was observed at different time intervals in the radiographic pictures of the healthy volunteers.

Rao *et al.*, 2009, formulated and optimized an effervescent floating tablets formulation of salbutamol sulfate using 3^2 full factorial design (eight runs). The content of hydroxylpropyl methyl cellulose (HPMC) (X1) and sodium bicarbonate (X2) were taken as independent variables and % drug release after 6 hours (Y1), t 50 % (Y2), and buoyancy lag time (BLT) (Y3) were taken as the dependent variables. The release data were evaluated by the model-dependent (curve fitting) method using the PCP Disso v2.08 software. Optimization studies were carried out using the Design Expert Software. The result demonstrated that the *in vitro* drug release mechanism showed anomalous transport. An increase in the concentration and viscosity grade of the polymer resulted in a decrease in the release rate, but it was found that at a higher concentration of HPMC, the viscosity grade did not significantly affect the drug release. Concentration of both HPMC and sodium bicarbonate had a significant effect on the bilayer tablets.

Havaldar *et al.*, 2009, prepared floating tablets of Atenolol to study the influence of different polymers on its release rate by direct compression method. The prepared tablets were evaluated for physicochemical parameters such as hardness, floating properties (floating lag time and floating time), matrix integrity, swelling studies and drug content. All the

formulations showed floating lag time within the prescribed limit (< 10 minutes) and retarded the release of drug for eight hours. Diffusion exponent (n) value was found in the range of 0.52 - 0.99 indicating diffusion as a release mechanism. The swelling studies of all the formulations showed that formulations containing xanthan gum has higher swelling indices than HPMC K100M and HPMC K4M.

Singh *et al.*, 2009, developed oral bioadhesive hydrophilic matrices of hydralazine hydrochloride using 3^2 central composite designs and optimized their *in vitro* drug release profile and *ex vivo* bioadhesion against porcine gastric mucosa. Response surface plots were drawn and optimum formulations were selected. The optimum formulation was selected by trading off various response variables. Upon comprehensive evaluation of grid searches, the formulation (CP: 50.0 mg and HPMC: 68.4 mg) fulfilled the optimal criteria of best regulation of the release rate and bioadhesive strength with t_{50} of 5.29 hours, Q_{18} of 91.51 %, *n* of 0.6302 and BS of 254.9 N.

Kulkarni *et al.*, 2009, designed bilayer region selective floating tablets of atenolol and lovastatin to give immediate release of lovastatin and sustained release of atenolol using sodium starch glycollate as a super disintegrant (immediate release layer), HPMC K100M and xanthan gum as the release retarding polymers (sustained release layer) and sodium bicarbonate as a gas generating agent by direct compression method. All prepared formulations floated for more than 12 hours and released more than 90 % of lovastatin within 30 minutes and atenolol from the controlled release layer upto 12 hours. Diffusion exponents (n) were determined for all the formulations (0.53-0.59). The release of atenolol was found to follow a mixed pattern of korsmeyer-peppas, hixson-crowell and zero order release models. The optimized formulation was found to be buoyant for 8 hours in stomach.

Azad *et al.*, 2009, prepared gastroretentive floating tablets of theophylline by direct compression technique and investigated the effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount of theophylline on drug release profile and floating properties. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent. The release mechanisms were explored and explained with zero order, first order, Higuchi and korsmeyer equations.

Patel *et al.*, 2009, formulated novel gastro retentive controlled release drug delivery system of verapamil HCl to increase the gastric retention time of the dosage form by using

Hydroxypropyl methylcellulose (HPMC), carbopol, and xanthan gum for gel forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The optimized intragastric floating tablet composed of 3:2 of HPMC K4M to xanthan gum exhibited 95.39 % drug release in 24 hours and followed zero-order and non-Fickian release transport *in vitro*, while the buoyancy lag time was 36.2 seconds, and the intragastric floating tablet remained buoyant for >24 hours. X-ray studies showed that total buoyancy time was able to delay the gastric emptying of verapamil hydrochloride intragastric floating tablet in mongrel dogs for more than 4 hours. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or *in vitro* dissolution pattern after storage at 40 °C / 75 % relative humidity for 3 months.

Belgamwar *et al*., 2009, developed sustained release gastroretentive dosage forms using the novel effervescent systems with floating, swellable and bioadhesive properties using various release retarding polymers like psyllium husk, HPMC K15M, and a swelling agent crosspovidone in different combinations to get the release profile for 12 hours. The formulations were evaluated for physicochemical characteristics, *in vitro* drug release profile, swelling characteristics, floating capacity, and *in vitro* bioadhesive property. Result showed that the *in vitro* drug release followed Higuchi kinetics and the release mechanism was found to be of a non-Fickian type. The swelling properties increased with increasing crosspovidone concentration and contributed to the drug release from the tablets matrix.

Khan *et al.*, 2009, prepared gastroretentive floating tablets of theophylline using two hydrophilic cellulose derivatives, methocel K100M and K15MCR, sodium bicarbonate and citric acid as gas generating agents by direct compression technique. The floating tablets were evaluated for their gel forming and release controlling properties. Formulations were evaluated for *in vitro* buoyancy and drug release study using USP XXII paddle-type dissolution apparatus and 0.1N HCl as dissolution medium. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent.

Jain *et al.*, 2009, prepared floating microspheres of famotidine by the solvent evaporation method using different polymers, i.e. acrycoat S100 and cellulose acetate. The prepared microspheres exhibited prolonged drug release (18 hours) and remained buoyant for more than 12 hours. The mean particle size increased and the drug release rate decreased at a higher polymer concentration. The mean particle size of the prepared floating microspheres

increased but the drug release rate from the microspheric-coated layer decreased as the polymer concentration increased.

Patel and Chavada, 2009, formulated mucoadhesive amoxicillin microspheres containing carbopol-934P as mucoadhesive polymer and ethyl cellulose as carrier polymer by emulsion-solvent evaporation technique. A 3^2 full factorial design was employed to study the effect of independent variables, drug-to-polymer-to-polymer ratio (amoxicillin-ethyl cellulose-carbopol-934P) (X1) and stirring speed (X2) on dependent variables, i.e. percentage mucoadhesion, drug entrapment efficiency, particle size and t_{80}. Results of preliminary trials showed that quantity of emulsifying agent, time for stirring, drug-to-polymers ratio and speed of rotation affected the characteristics of microspheres. The best batch exhibited a high drug entrapment efficiency of 56 %; mucoadhesion percentage after 1 hour was 80 % and the particle size was 109 µm. A sustained drug release was obtained for more than 12 hours. The drug-to-polymer-to-polymer ratio had a more significant effect on the dependent variables. *In vivo* H. pylori clearance tests were also carried out by administering amoxicillin powder and mucoadhesive microspheres to *H. pylori* infected wistar rats under fed conditions at single dose or multiple dose(s) in oral administration. The results showed that amoxicillin mucoadhesive microspheres had a better therapeutic effect than amoxicillin powder.

Maravajhala *et al*., 2009, prepared Niacin-ethyl cellulose microspheres by water-in-oil-in-oil double emulsion solvent diffusion method and determined the effect of polymer-drug ratio, surfactant concentration for secondary emulsion process and stirring speed of emulsification process on *in vitro* drug release behavior and particle size. The result demonstrated that the *in vitro* release profile could be altered significantly by changing various processing and formulation parameters to give a controlled release of drug from the microspheres for 10 hours which followed Higuchi model, indicating diffusion controlled principle.

Gattani *et al.*, 2010, developed alginate/hydroxypropyl methylcellulose (HPMC) based floating-mucoadhesive beads of clarithromycin by ionic gelation technique. Prepared beads were evaluated extensively for particle size, drug entrapment; swelling and surface morphology by using scanning electron microscopy. X-ray radioimaging study in rabbits, *in vitro* mucoadhesion using rat stomach mucosal membrane and *in vitro* drug release studies were carried out. *Ex vivo* performance of alginate-HPMC beads were studied using albino rats in comparison to simple alginate-calcium beads. Alginate-HPMC beads were suitable floating-muco-adhesive drug delivery system for delivering clarithromycin to treat stomach ulcers.

Bhardwaj *et al*., 2010, prepared and evaluated floating microballoons of indomethacin to increase its residence time in the stomach by the emulsion solvent diffusion technique using different ratio of acrylic polymers (eudragit RS100 and eudragit S100) as carriers. On the basis of optical microscopy, particle size range was found to be ranging from 130.90 ± 12.10 to 170.58 ± 17.50 µm. Microballoons exhibited floating properties for more than 10 hours. *In vitro* drug studies were performed in 0.1 M HCl with 0.1% SLS and phosphate buffer (pH 6.2). Different drug release kinetics models were applied for selected batches.

Tadros, 2010, developed controlled release effervescent floating matrix tablets of ciprofloxacin hydrochloride using HPMC and sodium alginate as release retarding polymer and sodium bi carbonate as gas generating agents. The prepared tablets showed acceptable physicochemical properties and all the formulations followed non-Fickian drug release mechanism. The *in vivo* studies carried out by X- ray imaging in six healthy human volunteers revealed a mean gastric retention period of 5.5 hours.

Patel and Chavda, 2010, formulated effervescent floating-bioadhesive tablets to lengthen the stay of glipizide in its absorption area using chitosan (CH), hydroxypropyl methylcellulose (HPMC), carbopol P934 (CP), polymethacrylic acid (PMA), citric acid, and sodium bicarbonate. The results showed that the tablets containing 5 % effervescent base had longer lag time than 10 % and the type of polymer had no significant effect on the floating lag time. All tablets floated atop the medium for 23-24 hours and followed a Higuchi, non-Fickian release mechanism.

Tripathi and Singh, 2010, developed pH-sensitive controlled release oil-entrapped calcium pectinate microgel bead of clarithromycin by ionic gelation technique. The gel beads were formed instantly after adding the liquid formulation mixture drop wise into calcium chloride solution and evaluated for their diameter, floating lag time, encapsulation efficiency and drug release. The results showed that the particle size, encapsulation efficiency and buoyancy were significantly affected by the concentration of the polymer and calcium chloride. The formulation exhibited sustained release profile and fitted to the peppas model with $n < 0.45$.

Kharia *et al*., 2010, prepared floating tablets by wet granulation method using 3^2 full factorial design for optimization of drug release profile. The amount of psyllium husk (X1) and hydroxypropyl methylcellulose K4M (X2) were selected as independent variables and the times required for 50% ($t_{50\%}$) and 70% ($t_{70\%}$) drug dissolution were selected as dependent variables. These studies indicated that the proper balance between psyllium husk and

hydroxypropylmethyl cellulose K4M could produce a drug dissolution profile similar to the predicted dissolution profile. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix.

Vedha *et al.*, 2010, developed multiple-unit floating drug delivery system based on gas formation technique in order to prolong the gastric residence time by dispersing nevirapine together with calcium carbonate in a mixture of sodium alginate and hydroxypropyl methylcellulose solution and then dripping the dispersion into an acidified solution of calcium chloride. The obtained beads were found to float due to entrapment of CO_2 in the polymeric membrane. The prepared beads were evaluated for percent drug loading, drug entrapment efficiency, morphology, surface topography, buoyancy, *in vitro* release, and release kinetics. The results showed that beads containing higher amounts of calcium carbonate demonstrated an instantaneous, complete, and excellent floating ability over a period of 24 hours. The increased amount of the gas forming agent did not affect the time to float, but increased the drug release from the floating beads, while increasing the coating level of the gas-entrapped membrane, increased the time to float, and slightly retarded the drug release.

Shinde *et al.*, 2010, formulated oral floating tablets of cephalexin using the hydrophilic polymer hydroxypropyl methylcellulose (HPMC), gas generating agent sodium bicarbonate and citric acid. A 3^2 factorial design was applied systematically; the amount of citric acid and amount of HPMC K100M were selected as independent variables. The time required for 50 % drug release, percent drug release at 12 hours and percent drug release at 6 hours were selected as dependent variables. The results of factorial design indicated that high level of HPMC K100M and citric acid favoured sustained release of cephalexin.

Singh *et al.*, 2010, formulated floating-bioadhesive tablets of tramadol using varying amounts Carbopol 971P (CP) and hydroxypropyl methylcellulose (HPMC), along with other requisite excipients and evaluated for i*n vitro* drug release profile, floating characteristics and *ex vivo* bioadhesive strength using texture analyzer. The studies indicated the formulation of floating bioadhesive compressed matrices with excellent controlled release, mucoadhesion and hydrodynamic balance. Comparison of the dissolution profiles of the optimized formulation, with optimal composition of CP: HPMC: 80.0:125.0, with that of the marketed controlled release formulation indicated analogy of drug release performance with each other.

Optimization study was validated using eight confirmatory experimental runs indicated very high degree of prognostic ability of CCD.

Satishbabu *et al*., 2010, developed multiple units oral floating drug delivery system of famotidine to prolong gastric residence time and increase drug bioavailability. The gel beads were prepared by emulsion gelation method by employing sodium alginate alone and mixture of sodium alginate and hydrophilic copolymers such as carbopol 934P and hydroxypropyl methylcellulose K15M grade in three different ratios with cod liver oil. The effect of selected factors, such as percentage of oil and amount of copolymers on floating properties was investigated. The *in vitro* drug release study of the beads was carried out in simulated gastric media employing a modified Rosette-Rice test apparatus; the apparatus was further modified by incorporating a water jacket to the apparatus to circulate hot water to maintain 37 ± 2° for throughout the release study. The results suggested that beads formulated by employing sodium alginate alone could not sustain the drug release up to 8 hours, whereas beads formulated with mixture of sodium alginate and copolymers demonstrated sustained release of famotidine up to 8 hours.

Rajab *et al*., 2010, formulated novel gastro retentive controlled release drug delivery system of verapamil hydrochloride using hydroxypropyl methylcellulose (HPMC), carbopol, and xanthan gum as gel forming agents and sodium bicarbonate and anhydrous citric acid as gas forming agents. The optimized intragastric floating tablet composed of 3:2 of HPMC K4M to xanthan gum exhibited 95.39 % drug release in 24 hours followed zero-order and non-Fickian release mechanism, while the buoyancy lag time was 36.2 seconds, and the intragastric floating tablets remained buoyant for >24 hours. X-ray studies showed that total buoyancy time was able to delay the gastric emptying of verapamil hydrochloride intragastric floating tablets in mongrel dogs for more than 4 hours. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or *in vitro* dissolution pattern after storage at 40 °C / 75 % relative humidity for 3 months.

Khan and Dehghan, 2011, prepared gastro-retentive floating tablets of atrovastatin calcium to enhance bioavailability using hypromellose, sodium bicarbonate, polyethylene oxide, docusate sodium, mannitol, crosscarmellose sodium, and magnesium stearate. The floating tablets showed floating lag time of 56 ± 4.16 seconds and good matrix integrity with *in vitro* dissolution of 98.2 % in 12 hours. After stability studies, no significant change was observed in stability, solubility, floating lag time, total floating duration, matrix integrity, and sustained

drug release rates. *In vivo* pharmacokinetic study performed in rabbits revealed enhanced bioavailability of floating tablets, about 1.6 times than conventional tablet.

Negi *et al*., 2011, investigated effect of bioadhesion on the initial *in vitro* buoyancy behaviour of effervescent matrix tablets of ciprofloxacin hydrochloride. Tablets were prepared by direct compression using HPMC K4M and carbopol 971P as hydrophilic-controlled release polymers, sodium bicarbonate as gas-generating agent, polyplasdone XL, Explotab and Ac-Di-Sol as swelling agents. Tablets were evaluated for normal and modified initial *in vitro* floating behavior, floating duration, swelling behavior and *in vitro* drug release studies. The results showed that the initial buoyancy was depended on bioadhesion ability of tablets and floating duration was also dependent on concentration of sodium bicarbonate and swelling agents.

Arora and Budhiraja, 2011, prepared stomach-specific floating tablets of metronidazole based on the buoyancy and bioadhesion concept to study the effects of various polymeric blends of bioadhesive polymers namely chitosan and carbopol 971P with low density polymer-methocel K100LV to get the desired *in vitro* drug release profile in the stomach, buoyancy, swelling index, and mucoadhesion. It was observed that the chitosan and carbopol 971P significantly influenced the *in vitro* drug release and bioadhesion strength. An increase in buoyancy was observed with increase in Methocel K100LV concentration in the polymeric blend. The optimum formulations provided desired high drug concentration (~35%) during 1 hour and sustained the release up to 12 hours. The mechanism of release of metronidazole from the floating bioadhesive tablets was anomalous diffusion transport.

Gangurde *et al*., 2011, designed sustained release bioadhesive gastroretentive dosage forms of ofloxacin using 3^2 full factorial design to systematically study the drug release profile and bioadhesive strength. Tablets were prepared by direct compression technique and were evaluated for tablets characteristics, swelling study, adhesion strength, percent drug released, radiographic imaging study and stability study. The optimized formulations showed good tablet characteristics, swelling property and excellent adhesion strength with high detachment force. The drug release mechanism was found to be anomalous and followed Higuchi kinetics. Radiographic image proved that tablet remained intact in its structural integrity and shape in stomach up to 24 hours.

Haithem *et al*., 2011, prepared a gastroretentive floating tablets of captopril which is an angiotensin converting enzyme inhibitor used in the treatment of hypertension and heart

failure by direct compression and wet granulation technique, using the polymers hydroxypropylmethyl cellulose (HPMC) as the primary retarding polymer together with carboxymethylcellulose (CMC), ethyl cellulose (EC) and pectin as a secondary release modifying polymers in different ratios. The results indicated that the wet granulation method showed a good flow and compressibility characteristics and a better dose uniformity in comparison with direct compression technique. Pectin together with HPMC in the ratio of 1:1 was found to meet the requirement for a good matrix formation and floating characteristics and the drug release was sufficiently sustained for 12 hours with floating time >24 hours and floating lag time of 2 minutes. Kinetic modelling of the release data for the selected formulations showed that the mechanism of drug release pattern followed anomalous or non –Fickian diffusion.

Chavda and Patel, 2011, designed drug-delivery systems based on superporous hydrogel composite for sustained delivery of ranitidine hydrochloride and characterized for measurement of apparent density, porosity, swelling studies, mechanical strength studies and scanning electron microscopy. The prepared system floated and delivered the ranitidine hydrochloride for about 17 hours. The release profile of ranitidine hydrochloride was studied by changing the retardant polymer in the system. The *in vitro* drug release profile followed korsmeyer-peppas model with diffusion exponent values in between 0.48 ± 0.01 and 0.70 ± 0.01, indicated an anomalous non-Fickian transport.

Kshirsagar *et al*., 2011, developed and optimized floating-bioadhesive gastroretentive drug delivery systems of hydrochlorothiazide (HCTZ) by 3^2 factorial design using HPMC K15M Carbopol 974P as independent variables and percentage of HCTZ release at 8 hours and time required to release 80 % of drug as dependent variables. The main effect and interaction terms were quantitatively evaluated using a mathematical model. The gastroretentive ability of the tablets studied by X-ray studies in healthy human volunteer confirmed the buoyancy of dosage form in the stomach up to 16 hours. The optimized formulation released the drug for 24 hours in sustained manner. The predicted values agreed well with the experimental values demonstrating the feasibility of the model in the development of gastroretentive drug delivery systems.

Pandya *et al*., 2011, developed controlled-release floating microspheres to increase residence time in the stomach by the emulsion solvent diffusion technique, using (i) calcium silicate (CS) as porous carrier; (ii) glipizide, an oral hypoglycemic agent; and (iii) eudragit S as polymer. The prepared microspheres were found to be regular in shape and highly porous,

exhibited prolonged drug release up to 8 hrs and remained buoyant for >10 hours. *In vitro* studies demonstrated diffusion-controlled drug release from the microspheres and followed the Higuchi matrix model and the peppas-korsmeyer model.

Kotagale *et al*., 2011, prepared floating microspheres of ranitidine hydrochloride by solvent evaporation technique with ethyl cellulose, eudragit RS100 alone or in combination and evaluated for percent yield, drug entrapment, percent buoyancy and drug release. The results showed that the release of ranitidine hydrochloride from the microsphere influenced by changing ranitidine hydrochloride-polymer and ranitidine hydrochloride-polymer-polymer ratio. *In vitro* release of ranitidine hydrochloride from microspheres into simulated gastric fluid at 37 °C exhibited no significant burst effect and rate of release increased with time and significantly enhanced by pH modifiers. A 15% w/w concentration of fumaric acid provided significant drug release from ranitidine hydrochloride microspheres prepared with ranitidine hydrochloride:ethyl cellulose (1:3), ranitidine hydrochloride:eudragit RS100 (1:2) and ranitidine hydrochloride:ethyl cellulose:Eudragit RS100 (1:2:1) whereas citric acid, tartaric acid showed significant cumulative release at 20 % w/w.

Rathi *et al*., 2012, developed gastroretentive sustained release floating and bioadhesive drug delivery systems to prolong the gastric retention time of Metoprolol succinate by employing hydroxypropyl methylcellulose (HPMC K100M) as hydrophilic gel material, sodium bicarbonate as gas-generating agent and Sodium CMC (SCMC) as bioadhesive polymer. Tablets were prepared using 3^2 full factorial design and amounts of HPMC K100M and SCMC were taken as independent variables while floating lag time (FLT), bioadhesive strength, time taken to release 50 % of drug and time taken to release 90 % of drug were selected as dependent variables. Tablets were also evaluated for physical properties, swelling and matrix erosion. Optimized formulations followed Higuchi kinetics with short buoyancy lag time, total floating time of more than 24 hours and could maintain drug release for 24 hours. Content uniformity, hardness, friability, weight variation of the formulations was lying within limits.

Tomuta *et al.*, 2012, investigated the possibility of obtaining hydroxypropyl methylcellulose (HPMC) hydrophilic matrix extended-release dosage forms of metoprolol using aqueous dispersions of Eudragit NE, as binders in fluid bed granulation and evaluated the influence of formulation variables (levels of HPMC-Methocel K100 M and Surelease E7 19010) on drug release during a period of time of 12 hours. The formulation factors were the granulation polymer concentration and the matrix-forming polymer concentration. The obtained results

showed that the percentage of the drug released during the 12 hours was influenced both by the Methocel ratio and the Eudragit NE ratio; increasing the ratios of Eudragit and Methocel leading to the decrease of the percentage of the released drug. The influence of Eudragit NE percentage was maximum at four and six hours, but the influence of Methocel K100 M concentration was almost the same at all sampling times; all studied formulations showed a kinetic release that fitted best with the Peppas model.

Malakar and Nayak, 2013 investigated the development and optimization of floating bioadhesive matrix tablets of ondansetron HCl for gastroretentive delivery using 2 3 factorial design. And analyzed the effects of xanthan gum, guar gum and carbopol 934 P as hydrophilic polymer-blends on drug release. The optimized tablets were floated well in simulated gastric fluid (SGF) (>8 h) with no lag-time and also showed a good bioadhesion time (5.23 ± 0.25 min) on goat intestinal mucosa in SGF. The in vitro drug release of these tablets showed sustained ondansetron HCl release over 8 h, which correlated well with controlled-release (zero order) pattern with super case-II transport mechanism.

Chen *et al*., 2014 developed gastroretentive dosage form tablets of alendronate, the most commonly used biphosphonate for treating osteoporosis, to enhance its oral bioavailability. Tablets were characterized with the effects of different molecular weights (MWs) of chitosan (CS) and hydroxyethyl cellulose (HEC) at various ratios on swelling, floating, and physical integrity. The CS component was formed using various acids: acetic, lactic, malic, succinic, and citric, and a high viscosity grade of HEC was selected. The results demonstrated that the swelling ratios of the formulations comprising high MW CS were lower than those of low or medium MW CS when salts were formed with any countering acids except for acetic acid. The decreasing ranking of the swelling rates was: CS-citrate > CS-malate > CS-lactate > CS-succinate > CS-acetate. A negative correlation was found between the pKa of the respective countering acid and the swelling rate.

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