3.1. LITERATURE REVIEW OF EARLIER WORK

Kikendall et al., (1983) reported that it is difficult to specifically target the gastric mucus with bioadhesive polymers. For example, polycarbophil and carbopol have the tendency to stick with the surfaces of contact resulting in to the risk of esophageal adherence which may cause drug-induced injuries.

Sheth and Tossounian (1984) developed a HBS system containing a mixture of a drug and hydrocolloids. When it comes in contact with gastric fluids, the capsule shell dissolved and the mixture after swelling formed a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time. Pharmaceutical products, using the same principle, containing APIs had been developed, containing L-DOPA, combined with a de-carboxylase inhibitor.

Ch’ng et al., (1985) and Longer et al., (1985) reported the use of various polymers in bioadhesive system as in the case of local treatment of gastric disorders, it would also be beneficial to achieve close adherence of a DDS to the mucosal surface of the stomach. The use of bioadhesive polymers as gastroretentive materials had been well reviewed in the pharmaceutical literature and is the subject of patent applications.

Ingani et al., (1987) worked on double layered matrix tablets, containing an effervescent layer loaded with carbonate and optionally citric acid, using HPMC K4M and K15M as gelling hydrocolloid and release controlling polymer. After contact with acidic aqueous media, CO\(_2\) was generated and entrapped within the gelling hydrocolloid, causing the system to float. Meanwhile the drug was released in a sustained manner.

Inouye et al., (1988 and 1989) investigated CT based sustained release floating tablets using a mixture of NaHCO\(_3\) and citric acid. Two types of CT with different degrees of de-acetylation, CT H and L, and prednisolone as a model drug were used and two types of preparations were examined. The first one was directly compressed tablets using a mixture of sodium hydrogen carbonate and citric acid, while the second one was composed of a directly compressed layer coated with CT layer enclosing CO\(_2\). Both formulations imparted quick buoyancy to the preparations, but the drug release from the preparation using CT L was slower than that of CT H. In a further study, the release properties were controlled by regulating the CT content of the granules, or the CT L membrane thickness of the laminated preparations.
Ichikawa et al., (1991a) and Ichikawa et al., (1991b) developed a multiple unit effervescent floating pills. The system consisted of sustained release pills as seeds surrounded by double layers. The inner layer was a double effervescent layer containing both NaHCO₃ and tartaric acid to avoid direct contact between sodium bicarbonate and tartaric acid. The outer swellable membrane layer contains mainly PVA and purified shellac. Following contact with aqueous media, it formed swollen balloon like pills, with a density much lower than 1 g/ml, due to the carbon dioxide generated by the neutralization reaction in the inner effervescent layers with the diffusion of water through the outer swellable membrane layer. Around 20 % of this system was found to float completely within 10 min. and approximately 80 % remained floating over a period of 5 h irrespective of pH and viscosity of the test medium, meanwhile, the drug was released.

Shalaby and Park (1990, 1992) explained size increasing enzyme-digestible hydrogels consisting of poly (vinyl pyrrolidone) cross linked with albumin. These gastroretentive hydrogels, swells to a significant extent depending on the albumin content and degree of albumin alkylation and were degrade in the presence of pepsin. Even under fasted conditions, the GRT in dogs exceeded 24 h. These hydrogels were used to deliver flavin mononucleotide, which is known to be absorbed only from the upper part of the small intestine, where the drug could be detected up to 50 h after administration in the blood, suggesting its efficient retention in the stomach.

Hyon and Ikada (1992) prepared and reported controlled release microspheres for administration by the oral route and comprising polylactic acid and a water soluble physiologically active substance and having a mean particle size, from about 0.01 mµ to 300 mµ including active substances such as the antidiabetic agents glipizide, glymidine sodium, phenformin hydrochloride, methformin, buformin hydrochloride. This report was in US Patent 5,100,669.

Clarke et al., (1993) formulated high density pellets and studied GI transit of four multiple unit pellet dosage forms of different sizes and densities by gamma scintigraphy. The pellets were prepared by the processes of extrusion and spheronisation and radiolabelled with ⁹⁹ᵐTc or ³¹¹In. Small pellets of normal and high density were examined on one occasion and large pellets of normal and high density on another. The small and large pellet data from each
administration were analysed separately, and then pooled to determine the overall effects of size and density on GI transit. The data indicated that the increase in density caused a delay in gastric emptying \((p < 0.05)\) but the prolongation of small intestinal residence time was not significant. Gastric emptying of the pellets was not affected by their size, although small intestinal residence time was prolonged by the large pellets \((p < 0.05)\).

Thanoo et al., (1993) developed a drug loaded polycarbonate microspheres using a solvent evaporation method. The microspheres were found to float on simulated gastric and intestinal fluid. It was observed that increase in drug to polymer ratio in the microspheres increased the release rate of the drugs. It was concluded that sustained drug delivery could be obtained using this matrix system.

Desai and Bolton (1993) developed floating moulded gel tablets of theophylline for controlled release, using agar and light mineral oil. Light mineral oil was used for the floating of the tablet. Additionally, it served to prevent the air entrapped within the gel matrix from escaping in the acidic environment of the stomach, due to its hydrophobicity. However, the mechanisms are not yet clear.

Menon et al., (1994) reported the formulation of a monolithic floating dosage form for Furosemide using factorial design keeping the drug to polymer ratio, polymer to polymer ratio and polymer grade as the three factors. The optimized formulation thus obtained was found to have a good in-vitro / in-vivo correlation.

Lim et al., (1994) prepared CT beads containing sulfadiazine by ionotropic gelation and studied to determine drug loading and release. The efficiency of drug loading, bead size (BSI), opacity and sphericity increased with drug loading. A longer period of contact with counter ions decreased BSI and efficiency of loading. Release depended on drug loading and dissolution medium. In acid medium, beads containing less than 34% drug showed a slower release rate with increasing drug content.

Simoni et al., (1995) formulated a new enteric-coated ursodeoxycholic acid (UDCA) formulation which sinks in the stomach and releases the drug only at a \(pH > or = 6.5\). They measured the activity in 12 healthy subjects, using a specific enzyme immunoassay, the serum levels of UDCA after a single oral dose of 450 mg of UDCA in three different formulations; enteric coated sinking tablet,
stomach-floating enteric coated hard gelatin capsule and conventional gelatin capsule. The effect following oral administration of enteric-coated, sinking UDCA was significantly higher than that obtained after both conventional UDCA and floating enteric coated UDCA.

Atyabi et al., (1996a, 1996b) used the ion exchange resin Dowex for developing a floating tablet. The resin beads were loaded with bicarbonate and theophylline which were bound to the resin. Drug loaded resin beads were coated with a semi-permeable membrane to overcome rapid loss of CO₂. After exposure to gastric media, exchange of bicarbonate and chloride ions took place and lead to the formation of CO₂ which was trapped within the membrane, causing the particles to float. GRT was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of sustaining the drug release.

Chun (1996) developed alginate microspheres of Ampicillin sodium (AMP-Na) by the emulsification process, acetone was used as hardening agent. Different parameters such as the concentration of calcium chloride, the stirring time and the amount of AMP-Na were investigated. The preparation parameters had no significant effect on the release of AMP-Na from the alginate microspheres, although they had some effects on the physical properties and morphology of the microspheres had some effects on the physical properties and morphology of the microspheres.

Deshpande et al., (1997) prepared a controlled-release gastric retention system composed of a swellable core, consisting of the drug, chlorpheniramine maleate or riboflavin 5’ phosphate, and the expanding agents polyvinyl pyrolidone (PVP), Carbopol 934P and calcium carbonate. The tablet core was coated with a permeable coating, consisting of blends of Eudragit RL® 30 D and NE 30 D in different ratios. The prepared tablets swelled to 2-4 times their original volume, and releasing the drug in a controlled manner. The optimal ratio of Eudragit® RL 30 D: NE 30 D was reported to be 70:30, which was optimum for sufficient elasticity to withstand the pressure of expansion during the initial swelling phase, and allowing the breakdown of the tablet following release of the drug.

Bhagwat et al., (1997) reported a novel solid matrix controlled release, oral dosage form where the dosage form contains a therapeutically effective amount of a sulfonylurea or a salt or derivative thereof in the matrix. Further, the use of an
aqueous alkalizing medium afforded substantially complete bioavailability of the drug from the matrix of the tablet. The core tablets could optionally be coated with a coating material in the range of 2% to 10% with an enteric material or with a water insoluble material like ethyl cellulose.

Ahuja et al., (1997) reported that muco-adhesion in DDS had gained interest among pharmaceutical scientists as a means of promoting dosage form residence time as well as improving intimacy of contact with various absorptive membranes of the biological system. Besides acting as platforms for sustained-release dosage forms, bioadhesive polymers could themselves exert some control over the rate and amount of drug release, and thus contribute to the therapeutic advantage of such systems.

Ponchel and Irache (1998) reported that the concept of bio-adhesion beside its increasing popularity in alternative routes of administration (e.g., nasal, buccal, ocular, vaginal and rectal), the systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucous present in the stomach. High turnover rate of the gastric mucous leads to difficulties in retaining a mucoadhesive system at the desired site.

Whitehead et al., (1998) formulated multiple unit floating calcium alginate beads by freeze drying. These beads maintained a positive floating force for over 12 h, and the density measurement was done by using a helium pycnometer, found to be less than 1 g/cm³. The in-vivo behavior of this system compared to non-floating multiple-unit dosage forms manufactured from identical material was done using γ-scintigraphy in the fed state. Prolonged GRTs of over 5.5 h were achieved for the floating formulations, while the non-floating beads displayed short GRTs, with a mean onset emptying time of 1 h.

Nagahara et al., (1998) augmented the anti- H. pylori effect of amoxicillin, by making mucoadhesive microspheres, which had the ability to reside in the GI tract for an extended period. The microspheres contained the antimicrobial agent and an adhesive polymer (carboxyvinyl polymer) powder dispersed in waxy hydrogenated castor oil. The percentage of amoxicillin remaining in the stomach both 2 and 4 h after oral administration of the mucoadhesive microspheres to Mongolian gerbils under fed conditions was about three times higher than that after administration in the form of a 0.5% methylcellulose suspension.
Rouge and Allemann (1998) studied the factors which improves the in-vitro buoyancy and drug release profile of floating minitablets containing either Piretinide or Atenolol as the model drug. The buoyancy of the minitablets was achieved either by the swelling of the excipients or by incorporating gas generating agent, sodium bicarbonate. The study concluded that it was possible to produce minitablets containing either Piretinide or Atenolol, which have a positive resultant weight during more than 6 hr and satisfactory release profile.

Iannuccelli et al., (1998a) and Iannuccelli et al., (1998b) developed a multiple-unit gastroretentive DDS which contained air compartments. The units forming the system were composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate or calcium alginate/polyvinyl acetate. Floating in-vitro and in-vivo of drug-free systems was observed. (Iannuccelli et al., 1998a; Iannuccelli et al., 1998b)

Krogel and Bodmeier (1999) formulated a floating device consisting of two drug-loaded HPMC matrix tablets, placed within an open impermeable, hollow polypropylene cylinder. Each matrix tablet closed one of the ends of the cylinder so that an air-filled space was created between them, which in turn provided a low, overall density of the system. The device was expected to remain floating until at least one of the tablets has dissolved.

Kulkarni et al., (1999) developed and optimized, controlled release SA beads containing Diclofenac sodium by precipitation of SA in alcohol followed by crosslinking with glutaraldehyde in acidic medium. Beads were optimized by considering the percentage entrapment efficiency, swelling capacity of beads in water and their release data. The beads produced at higher temperatures and longer times of exposure to the crosslinking agent had shown the lower entrapment efficiency, but extended release of DS from the beads.

Yohko and Nagahara (1999) formulated muco-adhesive microspheres containing drug and Carbopol 934P, which were dispersed within a waxy matrix of polyglycerol esters of fatty acids. The microspheres were reported to prolong the GI residence of the drug after oral administration, by adhering to the stomach mucosa in rats and Mongolian gerbils, which was due to the hydration and swelling of the Carbopol in the microspheres on contact with water.

Chen et al., (2000) described superporous hydrogels, having gastroretentive
properties due to rapid swelling and superabsorbent properties. Equilibrium swelling was reached in less than 1 m. Improved mechanical strength was achieved by adding a composite material, such as croscarmellose sodium. *In-vivo* experiments in dogs, even under fasting conditions showed gastric retention for 2 – 3 h, after which they emptied into the intestine. On the other hand, in the fed state, the superporous hydrogel composites stayed in the stomach for > 24 h.

Lynne *et al.*, (2000) prepared floating alginate beads from alginate solutions containing either dissolved or suspended Amoxicillin. Drug release studies showed that beads prepared with the drug in solution provided some sustained release characteristics and that these could be improved by the addition of amylose. The beads retained their buoyancy when amylose and Amoxicillin were incorporated, exhibiting resultant weight values greater than zero after 20 h. Preparation of the beads from alginate solutions containing the drug in suspension allowed higher drug loadings, at the expense of faster release and lower buoyancy.

Foster *et al.*, (2000) reported that glipizide extended release produced better cost outcomes than metformin and acarbose in a model of 3 years' treatment of type-2 diabetes mellitus. Glipizide extended release had pharmacoeconomic and quality of life was advantageous, but more clinically relevant comparisons with other antidiabetic agents were needed. There were limitations to the present data, but the available pharmacoeconomic data have been favourable for glipizide extended release.

Giunchedi *et al.*, (2000) have prepared matrix tablets of Ketoprofen for prolonged release by employing direct compression method using polymers like Sodium alginate, Calcium gluconate and Hydroxypropyl methyl cellulose. *In-vitro* release tests and erosion studies of the matrix tablets were carried out in USP phosphate buffer pH 7.4. Matrices consisting of SA alone or in combination and HPMC gave a prolonged drug release at a fairly constant rate. Only the matrices containing the highest quantity of HPMC maintained their capacity to release ketoprofen for a prolonged period of time.

Jackson *et al.*, (2000) reported extended GRTs of the positively charged ion-exchange resin cholestyramine, an anionic resin, due to adhering to and coating of the gastric mucosa. On the other hand, the oppositely charged cationic-exchange resin Amberlite IRP-69 did not possess the same characteristics. Such
behaviors lead to concluding that the surface charge of the resin might play a significant role in mucoadhesion and subsequent retention.

Shoufeng et al., (2001) developed an optimized gastric floating DDS for oral controlled delivery of calcium. A central composite Box-Wilson design for the controlled release of calcium was used with three formulation variables; HPMC loading, citric acid loading and magnesium stearate loading. All three formulation variables were found to significantly affect release properties. Only HPMC loading was found to be significant for floating properties.

Takeuchi (2001) reported that mucoadhesive drug delivery devices offer several advantages over traditional dosage forms including the ability to optimize the therapeutic effects of a drug by controlling its release into the body. It has been shown that various types of poly (acrylic acid) (PAA) hydrogels were able to inhibit the hydrolytic activity of GI enzymes, such as trypsin, resulting in an increase of the bioavailability of the drug. Acrylic-based polymers could be used for the attachment of mucoadhesive delivery systems to the mucosa. Polymer hydrogels modified by grafting mucophilic copolymers such as poly (ethylene glycol) (PEG) onto the back-bone chains of the polymer can promote the adhesive process. Mucoadhesive nanoparticles have been used by Takeuchi for the oral administration of peptide drugs, and have been shown to be more effective with a more prolonged action as compared to non-coated system.

Streubel et al., (2002) developed floating microparticles based on low-density foam powder. Oil-in-water solvent extraction/evaporation method was adopted for formulation of the floating microparticles which were composed of polypropylene foam powder. verapamil HCl as the model drug and a controlled release polymer, Eudragit® RS, EC or polymethyl methacrylate (PMMA). The microparticles were found irregular in shape and highly porous. Good in-vitro floating behavior was observed. The increase in drug release was proportional to the drug loading and inversely proportional to the amount of polymer and the release profile varied with varying the polymer type.

Shoufeng, et al., (2002) studied and evaluated the contribution of formulation variables on the floating properties of gastric floating drug delivery using a continuous floating monitoring system and statistical design. several formulation variable such as different types of HPMC, varying HPMC/carbopol ratio, and addition of magnesium stearate, were evaluated using Taguchi design, and the
effect of these variables are subjected to statistical analysis.

Chung et al., (2002) evaluated and compared the pharmacokinetics and pharmaco-dynamics of immediate-release glipizide and the glipizide extended release formulation in a short-term, 5-day study. Five days of treatment with either glipizide extended release or immediate release glipizide produced similar reductions in glucose and increases in insulin and C-peptide levels. However, the pharmacokinetic profile of the glipizide extended release tablet was significantly different from that of the immediate-release glipizide tablet in that the extended release formulation resulted in lower glipizide $C_{\text{max}}$ and $AUC_{0-24}$ values. Thus, with short-term treatment, the delivery of a low steady-state concentration of the drug provided similar efficacy to that seen with higher concentrations obtained with twice-daily dosing of the immediate release formulation.

Klausner et al., (2002) developed an unfolding system which was composed of multilayer, polymeric films based on a drug-containing shellac matrix as the inner layer, with outer shielding layers on both sides composed of hydrolysed gelatin/ Eudragit S/ glycerine/ glutaraldehyde. This system was optionally framed with rigid polymeric strips composed of L-poly(lactic acid)/ ethyl cellulose. Such type of dosage forms were administered to beagle dogs, after encapsulation in gelatin capsules shell. The dimensions and the mechanical properties of the films influenced the in-vivo gastric retention behavior. Prolonged residence times and improved absorption properties could be achieved with the model drug riboflavin using a ≥ 2.5 × 2.5 cm large device.

Tonnesen and Karlsen (2002) studied alginate and their use in DDS and reported that naturally occurring alginate polymers have a wide potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. Alginate can be tailor-made to suit the demands of applicants in both the pharmaceutical and biomedical areas. This group of polymers possesses a number of characteristics that make them useful as pharmaceutical aid both as a conventional excipient and more specifically as a tool in polymeric-controlled drug delivery.

Chan and Heng (2002) studied cross-linking mechanisms of calcium and zinc in production of alginate microspheres prepared by emulsion cross-linking method. The microspheres cross-linked by a combination of these two salts showed
different morphology and slower drug release compared with those cross-linked by the calcium salt alone. It was found that alginate microspheres could be successfully produced by the emulsification method using calcium chloride, but not zinc sulphate as the sole cross-linking agent.

Chan et al., (2002) also studied the effect of aldehydes and methods of cross-linking on properties of calcium alginate microspheres prepared by emulsification. Aldehydes produced varying effects on the properties of calcium alginate microspheres loaded with sulphaguanidine.

Chowdary and Rao (2003) worked on mucoadhesive microspheres of glipizide for oral controlled release. Microspheres containing glipizide were prepared by orifice ionic gelation process using SA in combination with four mucoadhesive polymers such as sodium CMC, Mehylcellulose, Carbopol and HPMC. The microspheres so prepared exhibited good mucoadhesive property, slow release of drug and followed zero order kinetics after a lag period of 1 h.

Garg and Sharma (2003) described a number of gastroretentive systems which were in use like FDDS, gas-generating (effervescent) systems, non-effervescent systems, bio-adhesive systems, high - density systems, large single - unit dosage forms, co - administration of gastric - emptying delaying drugs (Garg S et al., 2003).

CT/alginate microcapsules were prepared by Tian, et al., (2003) by continuous air extrusion method. The influences on loading efficiency and release, such as air flow-rate, chitosan molecular weight and concentration, alginate concentration, pH of chitosan solution, ethyl cellulose, and freezing drying the capsules were studied.

Adikwu et al., (2003) worked on development of bioadhesive delivery of Metformin using Prosopis Gum. The bioadhesive value of the gum was commensurate with those of Carbopol 974-P and sodium carboxymethyl cellulose. The release of the drug was higher from prosopis gum based bioadhesive formulations than from sodium carboxymethyl cellulose and Carbopol 974-P products. This was shown by the shorter time required to reach \( t_{50} \) (the time required for 50 % of the drug to be released) or \( t_{20} \) (time required for 20 % of the drug to be released) for the release of metformin.

Qurrat-ul-Ain (2003) developed oral sustained delivery alginate microparticles
for antitubercular drugs in order to improve patient compliance. In the study, pharmacokinetics and therapeutic effects of alginate encapsulated microparticulate antitubercular drugs, i.e., isoniazid, rifampicin and pyrazinamide were examined in guinea pigs. Alginate microparticles containing antitubercular drugs were evaluated for \textit{in-vitro} and \textit{in-vivo} release profiles. These microparticles exhibited sustained release of isoniazid, rifampicin and pyrazinamide for 3–5 days in plasma and up to 9 days in organs.

Streubel \textit{et al.}, (2003) developed floating controlled DDS consisting of polypropylene foam powder. The highly porous foam powder provided low density and, thus, excellent \textit{in-vitro} floating behavior of the tablets. Polymer studied in formulation of different types of matrix were, hydroxypropyl methylcellulose (HPMC), polyacrylates, SA, corn starch, carrageenan, gum guar and gum arabic. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former. Variation in the matrix-forming polymer/ foam powder ratio may effectively modify the release rate.

Shoufeng \textit{et al.}, (2003) worked on the effect of formulation variables on drug release and floating properties of the delivery system. Hydroxypropyl methylcellulose (HPMC) of different viscosity grades and Carbopol 934P (CP934) were used to formulate the Gastric Floating Drug Delivery System (GFDDS) employing 2 ×3 full factorial design. Main effects and interaction terms of the formulation variables were evaluated quantitatively by a mathematical model. The research concluded that both HPMC viscosity and the presence of carbopol and their interaction had significant effect on the release and floating properties of the delivery system. It was observed that release rate decreases with increase in the viscosity of the polymeric system.

Holte \textit{et al.}, (2003) worked on the sustained release of water soluble drug from directly compressed alginate tablets. In different formulations, the effect of the amount and type of alginate (Protanal LF 120 L, Protanal LF 120M, Protanal LV 120D, Protanal SF 120) on the drug release rate was evaluated. The \textit{in-vitro} release studies were done in dissolution medium 0.1M HCl for 2 h followed by phosphate buffer pH 6.8. Among the grades of alginate investigated, no significant difference in the resulting drug release profiles from the tablets was
found. Sustained drug release up to 16 h was achieved using SA in combination with dibasic calcium phosphate.

Kubo et al., (2003) developed oral sustained delivery of paracetamol from \textit{in-situ} gelling gellan and SA formulations. The potential for the oral sustained delivery of paracetamol of two formulations with \textit{in-situ} gelling properties was evaluated. \textit{In-vitro} studies demonstrated diffusion-controlled release of paracetamol from the gels over a period of six h. The bioavailability of paracetamol from the gels formed \textit{in-situ} in the stomachs of rabbits following oral administration of the liquid formulations was similar to that of a commercially available suspension containing an identical dose of Paracetamol.

Pandey and Khuller (2004) evaluated chemotherapeutic potential of alginate–CT microspheres as anti-tubercular drug carriers and found that administration of a single dose of alginate-CT microspheres to guinea pigs resulted in sustained drug level in plasma for 7 days and in organs for 9 days. The half life and mean residence time of the drugs were increased 13-15 fold by microspheres encapsulation, along with an enhanced relative/absolute bioavailability. Sustained release and increase in bioavailability were also observed with a sub therapeutic dose of the microspheres (Pandey R et al., 2004).

Chowdary and Rao (2004) worked on mucoadhesive microspheres and reported a unique carrier system for many pharmaceuticals, which could be tailored to adhere to any mucosal tissue, including those found in eyes, oral cavity and throughout the respiratory, urinary and GI tract. The mucoadhesive microspheres could be used not only for controlled release but also for enhancing bioavailability, for targeted delivery of the drugs to specific sites in the body. Drug delivery through mucoadhesive microspheres was a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability over longer periods of time, and for drug targeting to various sites in the body.

Dorozynski et al., (2004) evaluated the macromolecular polymers used as excipients for the preparation of HBS. Capsule shells were filled with various polymers such as CT, HPMC, and SA are investigated for density, hydration, erosion, and floating force. They reported that the size of the HBS influenced the floating force value. The mechanism of erosion and swelling of polymers played a dominant role in floating.
Verma and Garg (2004) formulated and evaluated extended release formulation of glipizide based on osmotic technology. The effect of different formulation variables, namely, level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane, were studied. Drug release was found to be affected by the level of solubility modifier in the core formulation. Glipizide release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP) in the membrane. Burst strength of the exhausted shells increased with the weight gain of the membrane. On the other hand, burst strength decreased with an increase in the level of pore former in the membrane. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane. The manufacturing procedure was found to be reproducible and formulations were stable after 3 months of accelerated stability studies.

Chaumeila et al., (2004) controlled the drug release rate of Indomethacin, through reduction of diffusion rate of the drug within the particle by impregnation of calcium alginate inside the porous microspheres. Studied parameters were alginate concentration, alginate diffusion time and calcium concentration. Indomethacin was loaded into the microspheres by eluting an aqueous indomethacin solution through a chromatographic column packed with impregnated microspheres. Indomethacin loading was reduced by alginate.

Higo et al., (2004) developed Tetracycline–sucralfate complex under acidic conditions its mucoadhesive properties both in-vitro and in-vivo were evaluated. The complex showed excellent mucoadhesive properties, where higher amounts of the complex were retained on the gastric mucosa compared with the physical mixtures of tetracycline and sucralfate.

Sinha et al., (2004) reported the great potential of a biodegradable natural polymer CT for pharmaceutical applications due to its biocompatibility, high charge density, non-toxicity and mucoadhesion. It had been shown that it not only improved the dissolution of poorly soluble drugs but also exerted a significant effect on fat metabolism in the body. Various techniques used for preparing CT microspheres and evaluations of these microspheres had also been reviewed.
Dave et al., (2004) developed a GRDDS of ranitidine with guar gum, xanthan gum and hydroxypropyl methylcellulose K4M. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. Results indicate that the addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A $3^2$ full factorial design was applied to systemically optimize the drug release profile. The amounts of citric acid anhydrous ($X_1$) and stearic acid ($X_2$) were selected as independent variables. The time required for 50% ($t_{50}$) and 80% drug dissolution ($t_{80}$), and the similarity factor were selected as dependent variables. The results of the full factorial design showed that a less amount of citric acid and a more amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation.

Dawan and Singhal (2004) in US Patents. No. 6,703,045 described a composition useful for reducing serum glucose levels by an oral controlled release system and a method for treating diabetes in a human being by controlling the blood glucose level (BGL) and reducing the complications associated with diabetic hyperglycemia and also the long term management of Non-Insulin Dependent Diabetes Mellitus (NIDDM) by avoiding the problems associated with the tight control of BGL, i.e., hypoglycemia tolerance and seizures. The composition was directed to a solid, hydrophilic matrix controlled release oral dosage form where the dosage form contains a therapeutically effective amount of antidiabetic drug in the matrix ensuring complete bioavailability of the drug from the matrix of the tablet. The formulation undergoes substantially or approaches zero order release of active drug and the concentration of the excipients and the water swellable polymers was chosen in such a way that the erosion or dissolution rate of the polymer was equal to the swelling rate of the polymer to get a constant release.

Dhawan et al., (2004) studied the mucoadhesive properties of CT microspheres prepared by different methods and evaluated by studying the interaction between mucin and microspheres in aqueous solution. The interaction was determined by the measurement of mucin adsorbed on the microspheres. A strong interaction between CT microspheres and mucin was detected. The intensity of the interaction was dependent upon the method of preparation of CT microspheres and the amount of mucin added. The extent of mucus adsorption was proportional to the absolute values of the positive zeta potential of CT microspheres.
Hejazi and Amiji (2004) developed intra-gastric floating DDS by using HPMC K4M, CT and found that the developed delivery system has potential to increase the efficacy of the therapy and improve patient compliance.

Bosch and Ryde (2005) invented nano-particulate compositions comprising glipizide. The glipizide particles of the composition preferably have an effective average particle size of less than about 2 µ.

Patel et al., (2005) prepared glipizide microspheres containing CT by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicated that volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. Microspheres were discrete, spherical, and free flowing. The microspheres exhibited good mucoadhesive property in the in-vitro wash-off test and also showed a high percentage drug entrapment efficiency.

Mutalik et al., (2006) prepared glipizide matrix transdermal systems using the combinations of ethyl cellulose/polyvinyl pyrrolidone and Eudragit RL-100/Eudragit RS-100. The systems were evaluated for various in-vitro (drug content, drug permeation, scanning electron microscopy and drug-polymer interactions) and in-vivo (acute and long-term hypoglycemic activity, biochemical and histo-pathological studies, skin irritation and pharmacokinetic studies in mice) parameters. Drug content of the patches was found to be more than 98 %. Variations in drug permeation profiles were observed among various formulations. The in-vivo results revealed that the patches successfully prevented the severe hypoglycemia in the initial hours and they were also effective on chronic application. The transdermal route exhibited negligible skin irritation and produced better improvement with all the tested in-vivo parameters compared to oral administration.

Tadakazu and Yoshiharu (2006) formulated an intra-gastric buoyant sustained-release tablet (IGB-T) containing Amoxicillin (AMX) to eradicate gastric H. pylori. Tablets were prepared by compressing the mixture of Hydroxypropyl cellulose-H, citric acid, sodium hydrogen carbonate and AMX was employed as the basic system for preparing IGB-T. IGB-T containing AMX and HPC-H was buoyant. This system showed a sustained-release pattern in water. However, this was confirmed to be buoyant for 24 h while maintaining a tablet shape and showed a
sustained-release pattern in water and buffer solutions of pH 1.2 and 6.8.

Bhagwat et al., (2005) had taken a patent on once a day controlled release sulfonylurea anti-diabetic formulation suitable for 24 hour administration and was formulated in to solid sustained release matrix that included an alkalizing or an acidifying medium affording substantially complete bioavailability from the sustained release matrix. This method gave an improved and more economical method for stable and convenient treatment of diabetes of the type that is responsive to control by sulfonylurea anti-diabetic agents, here glipizide controlled release 24 hours formulation was developed. Ammar, et al., (2006) developed a transdermal delivery system for glipizide as a potential for convenient, safe and effective antidiabetic therapy. For this purpose, inclusion complexes of the drug in β-cyclodextrin (β-CyD), dimethyl-β-cyclodextrin (DM-β-CyD), hydroxypropyl-β-cyclodextrin (HP-β-CyD), and hydroxypropyl-γ-cyclodextrin (HP-γ-CyD) were prepared. And according to authors transdermal delivery system might be used for treatment of type-2 diabetes with the aim of improving both patient compliance and pathophysiology of the disease.

Fan et al., (2005) in U S Pat. 6,972,284 described about CT and method of preparing CT.

Choudhury and Kar (2005) worked on a new emulsion gelation method to prepare gel beads for a highly water-soluble drug metformin hydrochloride using SA as the polymer. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing SA 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. A variety of oils were used to study the effect on the sustaining property of the formed beads. The oil entrapped calcium alginate gel beads showed good sustained release.

Bardonnet et al., (2006) suggested that gas-generating system inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density system (<1 g/cm³) with immediate buoyancy were therefore developed. They were made of low-density materials, entrapping oil or air. Most are multiple unit systems, and were also called “microballoons” because of low-density core.
Lewis et al., (2006) designed and evaluated matrix type and membrane controlled transdermal systems of Nicotine suitable for use in the smoking cessation. The solvent-casting technique was used to formulate the SA patches containing Nicotine. Two types of patches, mono-layered and bi-layered, were prepared. The mono-layered patch bore a rate controlling membrane, whereas the bi-layered, served as matrix type. The physical characteristics of the patches were evaluated by standard techniques. The drug content was found to be uniform in the patches. *In-vitro* release studies of transdermal patches showed a biphasic release pattern, with diffusion as the dominating mechanism of drug release for the matrix type, while the membrane controlled released nicotine, gradually over the 24 h study.

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

Omidian et al., (2005 and 2006) formulated superporous hydrogel hybrids which were prepared by crosslinking a water-soluble or water-dispersible polymer to the formed superporous hydrogel. Examples for hybrid agents were polysaccharides, such as SA, pectin, CT or synthetic water-soluble hydrophilic polymers, e.g., poly (vinyl alcohol). Superporous hydrogels and superporous hydrogel composites, superporous hydrogel hybrids which cannot be easily broken when stretched due to their highly elastic properties in the swollen state might be very useful for developing gastrointestinal DDS.

CT (obtained by deacetylation of chitin) is a cationic polymer that has been proposed for use in microspheres systems by a number of authors. CT was selected by Patel et al., (2006), as a polymer in the preparation of mucoadhesive microspheres because of its good mucoadhesive and biodegradable properties.

Jain et al., (2006) developed floating microspheres of calcium silicate as porous carrier, orlistat as an oral anti-obesity agent and Eudragit S as polymer. For this purpose solvent evaporation method was adopted and evaluated for their gastrointestinal and controlled-release properties. The effect of various formulation and process variables on the particle morphology, micromeritic properties, *In-vitro* floating behavior, percentage drug entrapment, and *In-vitro* drug release was studied. The gamma scintigraphy was performed in albino rabbits to monitor the
transit of floating microspheres in the GI tract. The orlistat-loaded optimized formulation was orally administered to albino rabbits, and blood samples collected were used to determine pharmacokinetic parameters of orlistat from floating microspheres. The microspheres were found to be regular in shape and highly porous. Microspheres formulation CS4 which contain 200 mg calcium silicate was found to be having best floating ability (88% ± 4% buoyancy) in simulated gastric fluid as compared with other formulations. Prolonged GRT of over 6 hours was achieved in all rabbits for calcium silicate–based floating microspheres of orlistat.

Pasparakis and Bouropoulos (2006) had studied swelling and in-vitro release of Verapamil from calcium alginate and calcium alginate–CT beads. The swelling ability of the beads in different media was found to be dependent on the presence of the polyelectrolyte complex between alginate and CT, the pH of the aqueous media and the initial physical state of the beads. The presence of CT was found to decrease significantly the release from wet beads.

Tanwar et al., (2007) formulated by solvent diffusion-evaporation method and evaluated floating microspheres of verapamil hydrochloride for improving the drug bioavailability by prolongation of GRT. Cellulose acetate, acrycoat S100 and eudragit S100 microspheres loaded with verapamil hydrochloride were prepared. The microspheres had smooth surfaces, with free-flowing and good-packing properties. The yield of the microspheres was up to 70.51% and cellulose acetate microspheres entrapped the maximum amount of the drug. Scanning electron microscopy was done to confirm their hollow structures with sizes in the range 251.80 to 350.75 mm. The formulated microspheres exhibited prolonged drug release and remained buoyant for more than 12 h. Radiographic images of dog stomach revealed that cellulose acetate microspheres loaded with barium sulphate floated on the gastric fluid for about 3.2 h. In-vitro release studies demonstrated non-fickian diffusion of drug from the microspheres.

Gupta et al., (2007) worked on interpenetrating polymeric network hydrogels of glipizide using gelatin and methacrylic acid. Methacrylic acid was polymerized using potassium persulfate. Methacrylic acid was crosslinked with methylene bisacrylamide and gelatin was crosslinked using glutaraldehyde. Four formulations were prepared by varying the concentrations of methacrylic acid, methylene bisacrylamide and glutaraldehyde. The amounts of gelatin and
potassium persulfate were kept constant in all the formulations. The release data showed that, as the concentration of methacrylic acid was increased, swelling increased resulting in increased release of the drug. Among all the formulations they prepared some showed almost complete release over a period of 12 h.

Zhang et al., (2007) produced spherical composite magnetic microspheres using a very cheap biopolymer (i.e., tamarind gum and CT). The composite magnetic microspheres were evaluated based on morphology, size/size distribution, magnetic properties, functional groups, thermal stability, anti-acid, and anti-alkali stability. The results show that composite magnetic microspheres can be produced in the size range 230–460 mm by changing the operational parameters (i.e., stirring rate and Fe₃O₄ chitosan ratio).

Patel (2007) suggested that alginate obtained a “generally recognized as safe” (GRAS) status as a food and pharmaceutical ingredient by the U.S. Food and Drug Administration (FDA) in the early 1970’s. It is generally regarded as a nontoxic and non-irritant material. Calcium alginate gels are found to be nontoxic to cells and hence are suitable for drug delivery.

Bravo-Osuna, et al., (2007) prepared CT and thiolated CT (CT-TBA) coated nanoparticles of poly (isobutyl cyanoacrylates), prepared by radical emulsion polymerization. Mucoadhesion was evaluated ex vivo on rat intestinal mucosal surfaces. The presence of either CT or thiolated CT in the nanoparticle surface promoted the mucoadhesion behaviour of the colloidal system. Moreover the presence of thiol groups on the nanoparticle surface at high concentration further increased the mucoadhesion capacity of nanoparticles by forming covalent bonds with the cysteine residues of the mucus glycoproteins. On the other hand, changes in the polymeric shell composition (molecular weight of CT, presence of a cross-linked structure, density of active thiol groups on the surface) can clearly influence the bioadhesive behaviour of these colloidal systems. (Bravo-Osuna I et al., 2007)

Waterman (2007) reported that due to the strong contractions of the IMMC the ingested dosage form may possibly pass the stomach. Expandable gastroretentive devices may also imply the risk of unfolding in the esophagus during swallowing and therefore potentially causing serious complications. In contrary, systems expanding too slowly may pass the pylorus before being completely expanded and thus fail gastric retention.
Pandit (2007) developed different types in-situ gelling system of Indomethacin with SA vehicle. These were evaluated for their pharmaceutical properties including viscosity, sterility and drug content uniformity. The gelling efficacy of the prepared system was evaluated by using an in house fabricated gelation cell. The in-vitro release kinetics of the prepared system was determined in simulated tear. The gelling time and nature of the gel formed were found to be dependent on the concentration of SA present in the systems. The drug release from this system was extended upto 8 h and predominantly followed zero-order release kinetics.

Das and Ahmed (2007) formulated Rofecoxib gel for topical application using hydroxy propyl methyl cellulose (HPMC), SA and Carbopol 940. The anti-inflammatory activity of the rofecoxib gel formulation was evaluated using the rat hind paw edema model. The formulated gels which consist of 4% w/w SA-Carbopol 940 at 3:1 ratio was found to be suitable for topical application based on in-vitro evaluation and ex vivo permeation studies. The anti-inflammatory activity of 4% w/w SA-Carbopol 940 gel containing 25% w/w rofecoixb in the rat hind paw edema model revealed that the drug was delivered to the inflammation site at a controlled level over a period of 6 h.

Kassas et al., (2007) had prepared biodegradable beads of anti-diabetic drug Gliclazide with SA by ionotropic gelation method for improving the oral delivery of the anti-diabetic agent Gliclazide. The study showed that the ionic gelation of alginate molecules offers a flexible and easily controllable process for manipulating the characteristics of the beads which are important in controlling the release rate and consequently the absorption of Gliclazide from the GI tract. The in-vitro release experiments revealed that the swelling is the main parameter controlling the release rate of Gliclazide from the beads.

Amitava et al., (2007) prepared Frusemide loaded calcium alginate micro pellets by ionotropic gelation technique and studied the effect of different polymers. Here gelation of anionic sodium alginate was achieved with oppositely charged counter ion to form microparticles which were further made sustained by using different polymers namely Methocel K-15M (Hydroxy propyl methyl cellulose), Surelease (Ethyl Cellulose) and Acrycoat E30D (poly [ethyl acrylate methyl methacrylate]). The size of the micropellets ranged between 600 µm to 800 µm and increased significantly with the concentration of the
copolymers. All the formulated batches showed the sustained release of the drug for more than 8 hours. Both water soluble and insoluble copolymers were tested and found that acrylic colloidal polymer dispersion (Acrycoat E30D) was having the high encapsulation efficiencies and highest prolongation of drug release.

Rastogi (2007) had prepared alginate microspheres of Isoniazide for oral sustained drug delivery by a modified emulsification method. Maximum particles had an average size of 3.719 µm. The release profiles of INH from microspheres were examined in simulated gastric fluid (SGF pH 1.2) and simulated intestinal fluid (SIF pH 7.4). In-vitro bioadhesion was determined using rat small intestine. Isoniazid alginate microspheres were found to possess good bioadhesion (72.25 ± 1.015 %). The bioadhesive property of the particles resulted in prolonged retention in the small intestine. Increased drug loading (91 %) was observed for the optimized formulation suggesting the efficiency of the method. Nearly 26 % of INH was released in SGF pH 1.2 in 6 h and 71.25 % in SIF pH 7.4 in 30 h.

Balasubramaniyam et al., (2008) formulated intra ocular implants of SA alone and in combination with HPMC were formulated with Indomethacin as a model drug. Evaluation of drug release from the implants was done using static method, continous flow through apparatus (developed in house), USP dissolution, agar diffusion. Except in the static method, Indomethacin particle size did not impart any effect on the drug release. In agar diffusion method, an increase in agar concentration from 1 to 2 % resulted in significant decrease in the amount of drug release. Inclusion of HPMC showed decreased release of Indomethacin.

Razavi (2008) reported the therapeutic effect of SA in a rat model of trinitrobenzene sulfonic acid (TNBS)-induced inflammatory bowel disease. Sodium alginate solution was administered orally as drinking water at concentration of 0.5 % (w/v) for six weeks. Results showed that pre-treatment (in prophylactic group) and treatment with SA solution were significantly able to reduce colonic damage score, serum level and colonic mucosal production of TNF-alpha, IL-6, LTB4 and PGE$_2$ in pre- treated and treated animals compared with non-treated controls.

Mishra and Pathak (2008) prepared controlled release gastroretentive floating gel beads of loratadine increase the residence time in stomach and modulate the
release behavior of the drug. Oil (mineral or castor oil) entrapped floating microbeads prepared by the emulsion gelation method were optimized by factorial design, and a polymer ratio of 2.5,1.5 (pectin/SA) and 15\% of mineral or castor oil dropped in calcium chloride solution was found to be an optimum ratio for the desired buoyancy and physical stability. *In-vitro* drug release demonstrated sustained release of loratadine for 8 h and the gel beads floated in all test media without any lag time and remained buoyant for 12 h.

Goole *et al.*, (2008a); Goole *et al.*, (2008b) developed floating mini-tablets, using tartaric acid, NaHCO$_3$ and calcium carbonate as effervescent components and glycercyl palmitostearate as meltable binder. The system consisted of a drug-containing gas-generating core, prepared by melt granulation and subsequent compression, and coated with a flexible polymeric membrane of Eudragit® RL 30 D. The mini-tablets were able to float within 10 min and remained buoyant for more than 13 h, independent of the pH. In addition, the drug release was sustained for more than 12 h.

Khazaeli *et al.*, (2008) have prepared Ibuprofen beads by ionotropic Gelation technique with different cross-linking agents like Ca$^{2+}$, Ba$^{2+}$, Mn$^{2+}$, Co$^{2+}$, Sn$^{2+}$ and Pb$^{2+}$ were used for bead preparation. Results showed that only Ca$^{2+}$ ion were suitable for the formation of ibuprofen beads. A good swelling profile for beads in phosphate buffer pH 7.4 and the lack of swelling in hydrochloric acid pH 1.2, showed the suitable nature of the beads. In addition, formulation of Na-alginate and Calcium chloride beads resulted in an encapsulation efficacy of around 90%. The drug release studies showed controlled Ibuprofen release from the beads specially those prepared from SA and Ca-chloride in phosphate buffer medium.

Altaf and Charyulu (2008) had developed captopril microcapsules with a coat consisting of alginate and mucoadhesive polymer such as hydroxyl propyl methyl cellulose, carbopol 934P, CT and cellulose acetate phthalate using emulsification ionic gelation process. The resulting microcapsules were discrete, large, and spherical and free flowing. All alginate carbopol 934p exhibited good mucoadhesive property in the *in-vitro* wash off test. Drug release pattern for all formulation in was diffusion controlled, gradually over 8 h and followed zero order kinetics.

Builders (2008) prepared and evaluated mucinated SA microparticles for oral
delivery of Insulin. Insulin loaded microparticles for oral delivery were prepared with mucin and SA combined using a novel method based on polymer coacervation and diffusion filling. Average particle size was found to be 200-300 µm. The microparticles were filled into hard gelatin capsules and the in-vitro insulin release as well as the blood glucose reduction after oral administration to diabetic rabbits were determined. The various insulin-loaded microparticles prepared with the mucinated SA when encapsulated exhibited lag time before insulin release.

Singh et al., (2009) developed mucoadhesive microcapsules of Pioglitazone by orifice ionic gelation process using sodium alginate as a shell forming polymer and carbopol 974P, HPMC, sodium CMC as a mucoadhesive polymers for the potential use of treating acute and chronic diabetes mellitus. The microcapsules exhibited good mucoadhesive properties and drug release from the mucoadhesive microcapsules was slow and extended over long period of time depending on the composition of the coat.

Patil, et al., (2009) developed floating microspheres by emulsion solvent diffusion technique, of acyclovir with ethylcellulose and triethyl citrate. The microspheres were evaluated for particle size analysis, drug entrapment, floating ability, in-vitro drug release and characterized by scanning electron microscopy and x-ray diffractometry. The mean particle size of all formulations was found in the range of 135.103 – 229.418 µm. Drug entrapment efficiency was in the range of 63 % - 84 % w/w. The floating microspheres were spherical with no visible major surface irregularity. The x-ray pattern of a formulation showed a combined pattern of those of the polymer and drug, i.e., amorphous and crystalline respectively. Dissolution study indicated that as the polymer concentration was increased and the drug loading was decreased, the release of drug from microspheres was decreased.

Fursule et al., (2009) formulated floating calcium alginate beads of amoxicillin trihydrate containing different concentration of oil (0 % - 40 %) by emulsion, ionotropic gelation method. Spherical gel beads were formed instantaneously, because of intermolecular crosslinks formed between the divalent calcium ions and the negatively charged carboxyl group of alginic acid. The emulsifying property was limited when the oil concentration was increased. As a consequence oil began to leak from the beads at 40 % w/w of oil. The beads were
spherical, smooth and yellowish in color. Percentage buoyancy was found between 84.66% - 95.33 %, size distribution was found between 0.56 mm to 1.36 mm.

Havaldar et al., (2009) designed various (nine) formulations of floating matrix tablets of atenolol by direct compression method, containing differing concentrations of polymers. The prepared tablets were evaluated for various physicochemical parameters such as hardness, floating properties (floating lag time ‘T_{lag’}, total buoyency ‘T_{b’} and matrix integrity), swelling studies and drug content. A significant difference in drug release (P < 0.0001) and T_{lag} (P < 0.005) at 0.5, one, four and eight hours were observed. The T_{lag} of all the formulations was within the prescribed limit (<10 minutes). All the formulations showed good matrix integrity and retarded the release of drug for eight hours. The release pattern of atenolol was fitted to different models based on coefficient of correlation (r).

Soumik (2010) develop sustained release matrix tablets of water soluble Nifedipine hydrochloride using multi-unit CT treated alginate. Sustained release formulation is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Here the release of orally administered drug depends on the residence time of dosage form in the GIT. In the sustained release formulation of nifedipine as the dose administration is reduced, increases patient compliance. The sustained release formulation of nifedipine is absorbed uniformly from the entire gastro-intestinal tract. The addition of CT increased the swelling of multiple unit systems (MUS) in acidic conditions and reduced the drug release from MUS. The MUS retained in GI tract for more than 12 h and distributed throughout the GI tract.

Chaudhary and Areefulla (2012) prepared effervescent floating tablet of Gliclazide employing HPMC K100M and HPMC K4M as matrix formers and containing sodium bicarbonate as gas generating agent exhibited floating over 35 to 48 h with a T_{lag} of less than 1 m. These floating tablets also gave slow and controlled release of gliclazide over 24 h and were found suitable for once a day administration (24 h). HPMC K100M and HPMC K4M were found better suitable as matrix formers than Carbopol 934P, in the same study, for floating tablets of gliclazide.

Kapil et al., (2012) systematically formulated effervescent floating-bioadhesive
hydrophilic matrices using a face-centered cube design (FCCD) and evaluated for in vitro drug release, floatation and ex vivo bioadhesive strength. Optimal composition of polymer blends systematically chosen using brute-force methodology, overlay plots and desirability function exhibited excellent bioadhesive and floatational characteristics besides possessing adequate drug release control (T60 > 5 h). Pharmacokinetic studies carried out in rabbits showed the absence of any sharp peaks or troughs in the plasma drug levels, and various levels of in vitro/in vivo correlation (IVIVC) were successfully established. In vivo gamma scintigraphic studies in human volunteers ratified the gastroretentive characteristics of the optimized formulation with retention time of 6 h or more.

Singh et al., (2013) developed Effervescent floating-bioadhesive hydrophilic matrices and evaluated for in-vitro drug release, floatation and ex-vivo bioadhesive strength. Where the optimized formulation exhibited excellent bioadhesive and floatational characteristics besides possessing adequate drug-release control and pharmacokinetic extension of plasma levels. The successful establishment of various levels of IVIVC substantiated the judicious choice of in-vitro dissolution media for simulating the in-vivo conditions. In-vivo gamma scintigraphic studies ratified the gastroretentive characteristics of the optimized formulation with a retention time of 5 h or more.

Raju et al., (2013) developed hydrodynamically balanced systems for site specific oral drugs with low bulk density than gastric fluids for buoyancy and increased residence time of the drug. The investigator used HPMC K4M and HPMC K15M. The various batches of matrix tablets of Pioglitazone were prepared with varying concentrations of the polymers under direct compression method, using different compression forces. From the in vitro drug release studies, the matrix tablets containing HPMC K15M, which was compressed at 6 Kg/cm², showed 77.90% drug release in 12 hrs and showed better control of drug release. The in vitro release data was treated with mathematical equations, and was concluded that Pioglitazone released from the tablet followed Peppas model with non-Fickian diffusion.

Patel et al., (2013) developed Metformin HCl-loaded microparticles of ethyl cellulose, prepared by the emulsion solvent evaporation technique. Microparticles evaluated for various characteristic properties such as encapsulation efficiency, particle size & size distribution, surface morphology and drug release pattern. The optimized formulation parameters were used to prepare porous, spherical micro particles (67 µm to 127 µm) with high encapsulation efficiency (93 to 97%). Drug release over a period of 12 hrs ranged
from 85.7 % to 98.3 %. Microspheres were more spherical in shape in their manufacture with ethyl cellulose E10 and higher ratio of both polymers. Thus, in the case of ethyl cellulose, the viscosity and ratio of the polymer in dispersion medium were found to be the controlling factors of drug release.

Thakkar et al., (2014) developed gastroretentive tablets of clarithromycin to provide increased residence time in stomach for delivery of antibiotic to treat H. pylori induced gastric ulcers. Hydroxypropylmethylcellulose K4M (HPMC) was used as a mucoadhesive polymer and Avicel PH101 was used as the release modifier. Tablets containing drug, HPMC and Avicel PH101 were prepared using wet granulation technique. The tablets were evaluated for in vitro drug release profile and ex vivo bioadhesion property. A $3^2$ factorial design was employed to study the influence of amount of HPMC (X1) and amount of Avicel PH101 (X2) on drug release at the end of 2nd hour (Y1), 6th hour (Y2) and 10th hour (Y3) from the mucoadhesive tablets. Target release profile was generated for a 12 hour dosage regimen and dissolution profile of the best batch was compared using similarity factor $f_2$. Results of multiple regression analysis indicated that HPMC reduced the drug release at all time points while Avicel PH101 increased the amount of drug release. The dissolution profile of the optimum batch had the similarity factor value of 61 indicating that the release profile was similar to that of target release profile. No significant interaction was found between the drug and the polymer as indicated by DSC and FTIR study. The in vitro drug release followed Korsmeyer and Peppas model kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type ($n = 0.837$). Gastroretentive tablets for twice a day dosing could be developed for clarithromycin.

Patil et al., (2014) developed mucoadhesive sustained release drug delivery system of lafutidine a newly developed histamine H2-receptor antagonist having biological half-life of 1.92 ± 0.94 h which favours mucoadhesive sustained release drug delivery system due to its selective absorption from upper part of gastrointestinal tract in order to enhance the bioavailability. A mucoadhesive tablets was developed using the natural polymer, sodium alginate, xanthan gum and karaya gum. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. The prepared tablets of various formulations were evaluated for a total mucoadhesion time, buoyancy lag time and percentage drug released. The formulation with xanthan gum showed better results. Thus, it may be useful for prolonged drug release in stomach to improve the bioavailability and reduced dosing frequency. Non-fickians release transport was confirmed as the drug release mechanism from the
optimized formulation by Korsmeyer-Peppas. The optimized formulation (B3) showed a mucoadhesive strength >35 g. In vivo study was performed using rabbits by X-ray imaging technique. Radiological evidences suggest that, a formulated tablet was well adhered for >10 h in rabbit's stomach. Optimized lafutidine mucoadhesive tablets showed no significant change in physical appearance, drug content, mucoadhesive properties and in vitro dissolution pattern after storage at 40 °C temperature 75 ± 5% relative humidity for 3 months.

Brahmandam et al., (2014) investigated to formulate a novel gastro retentive system, floating tablets of Sitagliptin Phosphate, an anti diabetic agent by direct compression technique using lactose as diluent. The drug-excipients interaction was ruled out through FTIR studies. Nine formulations of Sitagliptin Phosphate tablets were prepared using HPMC K100 and HPMC K4M as release retarding agents in different concentrations of 10, 15 and 20% w/w. The prepared batches were evaluated for organoleptic properties, hardness, friability, weight variation and in vitro drug release. All the formulations showed low weight variation with rapid dispersion time and rapid in vitro dissolution. One amongst nine promising formulations, the formulation prepared by using 15% of HPMC K100 emerged as overall the best formulation. This optimized formulation showed good release profile with complete drug release within 24 hours. It was concluded that floating tablets of Sitagliptin

John et al., (2014) developed floating tablets of ciprofloxacin to increase the gastric residence time. Tablets were prepared by dry granulation technique. Different grades of hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M), sodium alginate and sodium bicarbonate were used for the formulation. Tablets were evaluated for their physical characteristics, viz., hardness, thickness, friability, and weight variation, drug content and floating properties. Further tablets were studied for in vitro drug release pattern over the dissolution medium. Non-Fickian diffusion was confirmed as the drug release mechanism from these tablets, indicating that water diffusion and polymer rearrangement proved as the essential role in drug release. The ideal formulation was selected based on in vitro characteristics and was preceded with in-vivo radiographic studies by incorporating barium sulphate. The in-vivo x-ray studies revealed that the tablets were in floating stage in the rabbit stomach up to 8 hours. Thus it was concluded that the sustained release formulation containing Ciprofloxacin hydrochloride was found to improve patient compliance, minimize the side effect and decrease the frequency of administration. Table 11 shows a consolidated literature report on gastroretentive drug delivery systems.
Table 11: Recent literature reports on gastroretentive drug delivery systems

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Constituent(s)</th>
<th>Dosage form(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. FLOATING DDS</strong></td>
<td></td>
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<tr>
<td>A. HYDRODYNAMICALLY BALANCED SYSTEMS</td>
<td></td>
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<tr>
<td>Pioglitazone</td>
<td>HPMC K4M, HPMCK15M</td>
<td>Tablet</td>
<td>(Raju and Narayan 2013)</td>
</tr>
<tr>
<td>Trimetazidine Dihydrochloride</td>
<td>Chitosan, SLS</td>
<td>Microspheres</td>
<td>(El-Nahas and Hosny 2012)</td>
</tr>
<tr>
<td>L-dopa</td>
<td>HPMC, carrageenan</td>
<td>Tablet</td>
<td>(Dorozynski 2011)</td>
</tr>
<tr>
<td>Metroprolol succinate</td>
<td>Sodium alginate, sodium CMC, magnesium alumino metasilicate</td>
<td>Tablet</td>
<td>(Boldhane and Kuchekar 2010)</td>
</tr>
<tr>
<td>Labetalol hydrochloride</td>
<td>HPMC K4M CR, HPMC K15M CR, Poloxamer</td>
<td>Tablet</td>
<td>(Garse et al. 2010)</td>
</tr>
<tr>
<td>Metformin</td>
<td>Sodium alginate, sodium CMC, Eudragit</td>
<td>Tablet</td>
<td>(Boldhane and Kuchekar 2009)</td>
</tr>
<tr>
<td>Propanolol hydrochloride</td>
<td>HPMC, HPC, xanthan gum, sodium alginate</td>
<td>Tablet</td>
<td>(Jagdale et al. 2009)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>HPMC K4M</td>
<td>Tablet</td>
<td>(Nama et al. 2008)</td>
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<tr>
<td>L-dopa</td>
<td>HPMC 2208</td>
<td>Capsule</td>
<td>(Dorozynski et al. 2007)</td>
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<tr>
<td>Metformin</td>
<td>HPMC K4M, ethyl cellulose</td>
<td>Capsule</td>
<td>(Ali 2007)</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>HPMC, ethyl cellulose</td>
<td>Microspheres</td>
<td>(Srivastava et al. 2005)</td>
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<tr>
<td>–</td>
<td>Sodium alginate, Chitosan</td>
<td>Hard gelatin capsule</td>
<td>(Dorozynski et al. 2004)</td>
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<tr>
<td><strong>B. EFFERVESCENT DDS</strong></td>
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<tr>
<td>Lamivudine</td>
<td>HPMC, Carbopol</td>
<td>Tablet</td>
<td>(Singh et al. 2012)</td>
</tr>
<tr>
<td>Zolpidem tartarate</td>
<td>Sodium bicarbonate, Eudragit NE 30D</td>
<td>Layered pellets</td>
<td>(Amrutkar et al. 2012)</td>
</tr>
<tr>
<td>Cefuroxime Axetil</td>
<td>HPMC K4M and HPMC K100M</td>
<td>Tablet</td>
<td>(Bomma and Veerabraham 2012)</td>
</tr>
<tr>
<td>Tizanidine hydrochloride</td>
<td>HPMC K4M, K15M and K100M</td>
<td>Tablet</td>
<td>(Someshwar et al. 2011)</td>
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<tr>
<td>Drug(s)</td>
<td>Constituent(s)</td>
<td>Dosage form(s)</td>
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</tr>
<tr>
<td>Metronidazole</td>
<td>Carrageenan (CG) and Eudragit E, Na bicarbonate</td>
<td>Tablet</td>
<td>(Bani-Jaber et al. 2011)</td>
</tr>
<tr>
<td>Liquorice</td>
<td>HPMC K100M, liquorice extract, sod. bicarbonate, talc, and magnesium stearate</td>
<td>Tablet</td>
<td>(Ram et al. 2010)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>HPMC K15M, sodium alginate, sodium bicarbonate or calcium carbonate</td>
<td>Tablet</td>
<td>(Tadros 2010)</td>
</tr>
<tr>
<td>DA-6034</td>
<td>HPMC, CP 934P, Kollidon CL, sodium bicarbonate</td>
<td>Tablet</td>
<td>(Jang et al. 2008)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>HPMC, sodium bicarbonate, Eudragit® RL 30D</td>
<td>Tablet</td>
<td>(Sungthongjeen et al. 2008)</td>
</tr>
<tr>
<td>Ranitidine hydrochloride</td>
<td>HPMC, sodium bicarbonate</td>
<td>Tablet</td>
<td>(Hassan 2007)</td>
</tr>
<tr>
<td>Phenylproponolamine</td>
<td>HPMC K4M, CP 971P, sodium bicarbonate</td>
<td>Tablet</td>
<td>(Xu et al. 2006)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>HPMC K15M &amp; K4M, Guargum, Sod. CMC</td>
<td>Tablet</td>
<td>(Srivastava 2005)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>PMMA</td>
<td>Coated pellets</td>
<td>(Sawicki and Glod 2004)</td>
</tr>
</tbody>
</table>

C. FLOATING BEADS AND MICROPARTICLES

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Constituent(s)</th>
<th>Dosage form(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin hydrochloride</td>
<td>Ethyl cellulose</td>
<td>Microparticles</td>
<td>(Patel et al. 2013)</td>
</tr>
<tr>
<td>Ginger extract (Zingiber officinale)</td>
<td>Calcium carbonate and sodium alginate</td>
<td>Beads</td>
<td>(Kumar Singh and Pal Kaur 2011)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Calcium carbonate sodium alginate, HPMC, calcium chloride</td>
<td>Beads</td>
<td>(Vedha et al. 2010)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Chitosan</td>
<td>Beads</td>
<td>(Sahasathian et al. 2010)</td>
</tr>
<tr>
<td>Riboflavin-5′-phosphate</td>
<td>Sodium alginate, anhydrous citric acid, calcium chloride</td>
<td>Beads</td>
<td>(Stops et al. 2008)</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>HPMC K15M, Sod. Alginate</td>
<td>Beads</td>
<td>(Shishu et al. 2007)</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Eudragit S, calcium silicate</td>
<td>Microspheres</td>
<td>(Jain et al. 2007)</td>
</tr>
<tr>
<td>Drug(s)</td>
<td>Constituent(s)</td>
<td>Dosage form(s)</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------</td>
<td>----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Calcium pectinate</td>
<td>Beads</td>
<td>(Sriamornsak et al. 2005)</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>HPMC, EC</td>
<td>Microspheres</td>
<td>(Srivastava 2005)</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Calcium Silicate, Eudragit S</td>
<td>Microspheres</td>
<td>(Jain 2005)</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Calcium pectinate</td>
<td>Beads</td>
<td>(Sriamornsak 2005)</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Chitosan, SLS, DOS</td>
<td>Microcapsules</td>
<td>(El-Gibaly et al. 2003)</td>
</tr>
<tr>
<td>Verapamil hydrochloride</td>
<td>Polypropylene foam powder, Eudragit RS, EC, PMMA</td>
<td>Microparticles</td>
<td>(Streubel 2002)</td>
</tr>
</tbody>
</table>

D. HOLLOW MICROSPHERES

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Constituent(s)</th>
<th>Dosage form(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine hydrochloride</td>
<td>Eudragit RLPO</td>
<td>Microspheres</td>
<td>(Singh and Chaudhary 2011)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Polyvinyl pyrrolidone, ethyl cellulose</td>
<td>Microspheres</td>
<td>(Zhao et al. 2010)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Eudragit L-100, PEG</td>
<td>Microspheres</td>
<td>(Ramachandran et al. 2010)</td>
</tr>
<tr>
<td>Rosiglitazone maleate</td>
<td>HPMC, EC</td>
<td>Microspheres</td>
<td>(Rao et al. 2009)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Eudragit S 100</td>
<td>Microspheres</td>
<td>(Junyaprasert and Pornsuwannapa 2008)</td>
</tr>
<tr>
<td>Aspirin, Salicylic acid, Ethoxybenzamide, Indomethacin and Riboflavin</td>
<td>Enteric acrylic polymers</td>
<td>Microspheres</td>
<td>(Sato et al. 2004)</td>
</tr>
<tr>
<td>Riboflavin, Aspirin</td>
<td>Dichloromethane and Ethanol.</td>
<td>Microspheres</td>
<td>(Sato et al. 2003)</td>
</tr>
<tr>
<td>Acetohydroxamic acid</td>
<td>Polycarbonates</td>
<td>Microspheres</td>
<td>(Umamaheshwari et al. 2003)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Polycarbonate resin</td>
<td>Microspheres</td>
<td>(Joseph et al. 2002)</td>
</tr>
</tbody>
</table>

2. MUCOADHESIVE DDS

A. TABLET FORMULATIONS

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Constituent(s)</th>
<th>Dosage form(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebivolol</td>
<td>Sodium alginate, sodium CMC, Carbopol 974P, EC</td>
<td>Tablet</td>
<td>(Shirsand et al. 2013)</td>
</tr>
<tr>
<td>Drug(s)</td>
<td>Constituent(s)</td>
<td>Dosage form(s)</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Carbopol, chitosan</td>
<td>Tablet</td>
<td>(Yedurkar et al. 2012)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>HPMC, chitosan and sodium carboxy methyl cellulose</td>
<td>Tablet</td>
<td>(Bayrak et al. 2011)</td>
</tr>
<tr>
<td>Captopril</td>
<td>HPMC E5, HPMC E50, sodium salt of carboxy methyl cellulose (NaCMC)</td>
<td>Tablet</td>
<td>(Mandal et al. 2011)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>HPMC, HPC, chitosan, carbopol, sodium carboxymethylcellulose</td>
<td>Tablet</td>
<td>(Sonani et al. 2010)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>HPMC K4M, Carbopol 934</td>
<td>Tablet</td>
<td>(Shayeda et al. 2009)</td>
</tr>
<tr>
<td>Propranolol Hydrochloride</td>
<td>Locust bean gum and chitosan</td>
<td>Tablet</td>
<td>(Vijayaraghavan et al. 2008)</td>
</tr>
<tr>
<td>Lercanidipine hydrochloride</td>
<td>PEO, HPMC</td>
<td>Tablet</td>
<td>(Charde et al. 2008)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>HPMC K4M, HPMC K15M, CP 934</td>
<td>Tablet</td>
<td>(Yamsani et al. 2007)</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>CP 940P, HPMC</td>
<td>Tablet</td>
<td>(Carlo Ceschel et al. 2006)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>CP, Na CMC</td>
<td>Tablet</td>
<td>(Singh et al. 2006)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Psyllium husk, HPMC, Crosspovidone</td>
<td>Tablet</td>
<td>(Chavanpatil et al. 2006)</td>
</tr>
<tr>
<td>Low molecular weight Heparin (LMWH)</td>
<td>Polycarbophil, HEC</td>
<td>Mini-tablet</td>
<td>(Schmitz et al. 2005)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>HPMC, CP 940, HP β-CD</td>
<td>Tablet</td>
<td>(Jug and Becirevic-Lacan 2004)</td>
</tr>
<tr>
<td></td>
<td>Thiolated chitosan derivatives</td>
<td>Tablet</td>
<td>(Roldo et al. 2004)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Sod. CMC, HPMC, EC</td>
<td>Tablet</td>
<td>(Chowdary et al. 2003)</td>
</tr>
</tbody>
</table>

B. MICROSPHERES FORMULATIONS

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Constituent(s)</th>
<th>Dosage form(s)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethylchitosan chloride</td>
<td>Eudragit L100</td>
<td>Microspheres</td>
<td>(Marais et al. 2013)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Carbopol, polycarbophil, chitosan</td>
<td>Microspheres</td>
<td>(Nagda et al. 2011)</td>
</tr>
</tbody>
</table>
Drug(s) | Constituent(s) | Dosage form(s) | Reference(s)
--- | --- | --- | ---
Tramadol HCl | HPMC E15 | Microspheres | (Belgamwar et al. 2011)
Venlafaxine | Linseed mucilage | Microspheres | (Nerkar and Gattani 2011)
Amoxicillin | Ethyl cellulose, Carbopol-934P | Microspheres | (Patel and Chavda 2009)
Cyclosporine-A | Chitosan | Microspheres | (Malaekeh-Nikouei et al. 2008)

[CA: Citric acid; CMC: Carboxymethylcellulose; CP: Carbopol; DOS: Sodium dioctylsulphosuccinate; EC: Ethylcellulose; HP-β-CD: Hydroxypropyl- β-Cyclodextrin; HPC: Hydroxypropylcellulose; HPMC: Hydroxypropylmethylcellulose; MC: Methylcellulose; Paa: Polyacrylic acid; PEG: Polyethylene glycol; PMA: Polymethylacrylic acid; PMMA: Polymethyl methacrylate; PVP: Polyvinylpyrrolidone; SLS: Sodium lauryl sulphate]

3.2. AN UPDATED REVIEW ON SYSTEMATIC DESIGN AND OPTIMIZATION OF ORAL DRUG DELIVERY SYSTEM

A product development scientist has to handle a heterogeneous group of formulations. These dosage forms may vary markedly from oral to topical, transdermal, parenteral, ophthalmic, pulmonary, nasal, rectal formulations with diverse rates of release and site specificity.

An exhaustive literature inquest carried out by me in pharmaceutical journals and texts till date, reveals that the DoE optimization techniques have been employed for almost all of these dosage forms, ranging from the simple conventional ones to that of the most intricate novel DDS. The updated literature reports unequivocally point out the increasing application of DoE (Design of Experiment) techniques, with a significant shift in the focus of the formulator from optimization of the conventional formulations to that of the modern drug delivery devices (Singh 2006).

Recently this approach together with the federal philosophy of quality by design (Qbd) has been assigned a new acronym by us as “Fbd” (Singh et al. 2011)

However, the work on DoE optimization of various DDS started relatively lately. Albeit the initial studies on drug delivery optimization were reported in early eighties, the major work has only been undertaken in the last decade. Since oral route is the most preferred and complied route of drug administration, most DDS explored for the purpose are the oral CR matrices, micro- and macroparticulate systems, floating systems, solid dispersions, osmotic pumps, etc. Besides, considerable work has also been carried out on transdermal therapeutic systems (patches, gels, ionophoresis and electroporation) and mucoadhesive dosage forms (gels, patches and tablets). Verily, DoE optimization techniques have
become an integral and regular phenomenon globally in rational drug delivery and dosage form design in pharmaceutical drug industry (Singh 2005)

Amongst the conventional dosage forms, tablets have predominantly been investigated, whereas, amongst various DDS, macroparticulates and CR matrices have majorly been studied followed by microparticulates, fast release (FR) dosage forms, transdermal drug delivery systems (TDDS) and vesicular systems. Here in below we reproduce the extensive search carried out by us on the use of optimization techniques in developing diverse types of solid oral CR DDS, GRDDDS.

3.2.1. ORAL CONTROLLED RELEASE MATRICES

The FbD optimization on oral CR matrix delivery devices started since early eighties (Harris et al., 1989). Such devices encompass, the inert matrices like hydrophilic (Joly and Brossard 1987; Gohel and Patel 1997), hydrocolloid (Waaler et al. 1992), silicone elastomer (Li and Peck 1991) and the lipid matrices (Singh et al. 1998).

Table 12: FbD formulation optimization reports on compressed oral sustained release matrices formulated using natural or semisynthetic polymers

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Factor(s)/Polymer(s)</th>
<th>Design</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>CP 971P and HPMC</td>
<td>CCD</td>
<td>(Singh et al., 2012)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>CP 974P and HPMC K15M</td>
<td>CCD</td>
<td>(Kapil et al., 2012)</td>
</tr>
<tr>
<td>Pravastatin Sodium</td>
<td>HPMC K4M and CP 934P</td>
<td>FD</td>
<td>(Maurya et al., 2012)</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>CP 940, Eudragit</td>
<td>BBD</td>
<td>(Elbary et al., 2011)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Polycarbophil, pluronic F68</td>
<td>FD</td>
<td>(Bhosale et al., 2011)</td>
</tr>
<tr>
<td>Tramadol HCl</td>
<td>HPMC, CP 971P</td>
<td>CCD</td>
<td>(Singh et al., 2010)</td>
</tr>
<tr>
<td>Hydralazine HCl</td>
<td>HPMC, carbomer</td>
<td>CCD</td>
<td>(Singh et al., 2009)</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>HPMC K15M, PVP K30</td>
<td>CCD</td>
<td>(Mandal et al., 2007)</td>
</tr>
<tr>
<td>Losartan potassium</td>
<td>HPMC K15M, HPMC K100M, Na CMC</td>
<td>BBD</td>
<td>(Chopra et al., 2007)</td>
</tr>
<tr>
<td>Salt of a weakly alkaline drug</td>
<td>HPMC, amount of water, tablet hardness</td>
<td>FD</td>
<td>(Huang et al., 2003)</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>HPMC of various viscosity grades, adhesive type, lubricant, preparation method</td>
<td>RSM</td>
<td>(Li et al., 2003)</td>
</tr>
</tbody>
</table>

(EC: Ethylcellulose; HCl: hydrochloride; HPMC: Hydroxypropylmethylcellulose; Na CMC: Sodium carboxymethylcellulose; BBD: Box-Behnken design; CCD; FD: Factorial design)
The other response variables that have been optimized include, disintegration time, BA, bioequivalence, etc (Dincer and Ozdurmus 1977) Tables 12 & 13 depicts the use of statistical experimental design in optimization of oral sustained release (SR) matrices, categorized on the basis of various types of polymers (natural, semisynthetic, synthetic) and the type of dosage form (matrices, dispersions, coated tablets). FbD optimization reports on SR matrices formulated using synthetic polymers like acrylates, polymethacrylates, silicone elastomers, polyethylene glycols, etc. are shown in Table 13 (Singh, Kumar and Ahuja 2005).

Table 13: FbD formulation optimization reports on oral sustained release matrices formulated using synthetic polymers

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Factor(s) investigated /Polymer(s)</th>
<th>Design</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol sulphate</td>
<td>Methocel® K100M, xanthan gum, Carbopol® 974P</td>
<td>RSM</td>
<td>Chaibva and Walker (2011)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>HPMC K15M, Etvlcellulose</td>
<td>RSM</td>
<td>Madgulkar et al., (2009)</td>
</tr>
<tr>
<td>Serratiopeptidase</td>
<td>Eudragit S 100</td>
<td>FFD</td>
<td>Rawat and Saraf (2009)</td>
</tr>
<tr>
<td>Protein</td>
<td>Chitosan, Tri poly phosphate</td>
<td>FD</td>
<td>Asghar and Chandran (2006)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Eudragit L 100, compression force</td>
<td>CCD</td>
<td>Ibric et al. (2003)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>PEG 6000, lactose, stearic acid</td>
<td>RSM</td>
<td>Grassi et al. (2003)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Eudragit RS PO, compression force</td>
<td>CCD</td>
<td>Ibric et al. (2002)</td>
</tr>
</tbody>
</table>

(CP: Carbopol; D-OD: D-Optimal design; EC: Ethylcellulose; HPMC: Hydroxypropylmethylcellulose; MCC: Microcrystalline cellulose; MS: Magnesium stearate; PEG: Polyethylene glycol; BBD: Box Behnken design; CCD: Factorial design; FFD: Fractional factorial design)

3.2.2. GASTRORETENTIVE SYSTEMS

GR delivery systems have evolved with the overall objective of localized delivery to the GIT, using the concept of floating-buoyancy or bioadhesions (Hou et al.,
The most commonly studied variables in the optimization of floating-bioadhesive CR systems include the polymer-to-drug ratio, different polymer grades, and ratio of polymers and ratio of diluents. If these variables are not addressed during the system design, the duration of buoyancy, dissolution time, BS, compression force, and tablet density will be greatly affected, which in turn affect the drug’s overall performance (Kannan et al. 2003).

Mucoadhesive gels and tablets have also been optimized separately for bioadhesion strength and drug release profile. Limited reports on optimization of hydrodynamically balanced DDS are available in literature. The input variables vary from 2 to 4 and the response variables from 1 to 5. The commonly employed designs are CCD, SMD and FD. Table 14 enlists various optimization reports on floating DDS (Singh 2005).

Table 14: FbD formulation optimization reports on floating drug delivery systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer(s)/Factor(s)</th>
<th>Design</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Ethylcellulose</td>
<td>FFD</td>
<td>(Vinodbhai et al., 2011)</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Psyllium husk (X1), HPMC K4M</td>
<td>FFD</td>
<td>(Kharia et al. 2010)</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Eudragit S100, Eudragit L100-55</td>
<td>CCD</td>
<td>(Gupta and Pathak 2008)</td>
</tr>
<tr>
<td>Ranitidine HCl</td>
<td>Compritol, Gelucire 50/13 and 43/01</td>
<td>FD</td>
<td>(Patel et al. 2007)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>HPMC K4M</td>
<td>FD</td>
<td>(Narendra et al., 2006)</td>
</tr>
<tr>
<td>Ceftriaxone axetil</td>
<td>HPMC k4M, HPMC k100LV</td>
<td>FD</td>
<td>(Patel and Patel 2006)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Citric acid, stearic acid</td>
<td>FD</td>
<td>(Dave, Amin and Patel 2004)</td>
</tr>
<tr>
<td>Calcium</td>
<td>HPMC of various grades, HPMC:CP ratio, MS</td>
<td>Taguchi</td>
<td>(Li et al. 2002)</td>
</tr>
</tbody>
</table>

(CP: Carbopol; EC: Ethylcellulose; HPMC: Hydroxypropyl methylcellulose; MS: Magnesium stearate; CCD: Central Composite Design; FD: Factorial design)

Literature review shows that controlling/sustaining/prolonging/targeting of drug/dosage form comes in existence in early eighties and since then it becomes one of the specific area of research; it reflects that it is a promising area to work on, for getting much better, practically possible dosage form.
To achieve different aims of modified release, various technologies have been investigated, e.g. sustained, delayed, pulsatile, targeted, and programmed release delivery systems. In all the delivery types, the main mechanisms associated with drug transport in these systems include diffusion, swelling, erosion, ion exchange, and osmotic effect which have been investigated in several studies.

Out of different types used for making controlled release, hydrophilic matrix type delivery systems are popular because of their ease of manufacture. It excludes complex production procedure such as coating and pelletization, and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation, while multi-particulate system further decreases the irritation by distributing the drug concentration in subdivided unit.

During development of new delivery systems, systematic FbD methodology with RSM efficiently surmounts the hiccup of balancing floatation and bioadhesion employing optimized polymer. It is well-documented to develop “the best possible” formulation under a given set of conditions circumventing unnecessary experimentation and thus, save, time, money and effort. The site of absorption of glipizide lies in the stomach. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency and decrease dose requirements.
3.3 REFERENCES


15. Belgamwar VS, Patel HS, Joshi AS, Agrawal A, Surana SJ, Tekade AR. Design and development of nasal mucoadhesive microspheres containing


48. Deshpande A, Shah NH, Rhodes CT, Malick W. Evaluation of Films Used


76. Hyon S, Ikada Y, inventor; Polylactic Acid Type Microspheres Containing Physiologically Active Substance and Process for Preparing the Same. U S Pat, 5100669, 1992.


91. John WI, Ramasamy C, Anisree GS Formulation Of Controlled Release


120. Mutalik S, Udupa N, Kumar S, Agarwal S, Subramanian G, Ranjith AK.


198. Vijayaraghavan C, Vasanthakumar S, Ramakrishnan A. In vitro and in vivo
literature review


