dosage form in the stomach, based on the floating principle. 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 h, and an \textit{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 min. The mechanism of release of Clarithromycin from the floating tablets is anomalous diffusion transport and follows zero order kinetics. \textit{In vivo} radiographic studies suggest that the tablet has increased gastric residence time for the effective localized action of the antibiotic (Clarithromycin) in the treatment of H. pylori mediated peptic ulcer.

\textit{Gerard F Notario et al.,} (2003) disclosed a pharmaceutical composition for extended-release of an erythromycin derivative in the gastrointestinal environment. The composition comprises an erythromycin derivative and a pharmaceutically acceptable polymer so that, when ingested orally, the composition induces statistically significantly lower $C_{max}$ in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability and minimum concentration substantially equivalent to that of the immediate release composition of the erythromycin derivative upon multiple dosing. The compositions of the invention have an improved taste profile and reduced gastrointestinal side effects as compared to those for the immediate release composition. The typical composition includes, Clarithromycin – 500 mg, Methocel K100 LV Premium CR Grade – 100 mg to 300 mg, Lactose Monohydrate – 160 mg to 360 mg, Talc – 30 mg and Magnesium Stearate – 10 mg.

\textit{Gerard F Notario et al.,} (2005) disclosed a pharmaceutical composition for extended-release of an erythromycin derivative in the gastrointestinal environment. The composition comprises an erythromycin derivative and a pharmaceutically acceptable polymer so that, when ingested orally, the composition induces statistically significantly lower $C_{max}$ in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability and minimum concentration substantially equivalent to that of the immediate release composition of the erythromycin derivative upon multiple dosing. The compositions of the invention have an improved taste profile and reduced gastrointestinal side effects as compared to those for the immediate release composition. The typical composition includes, Clarithromycin – 500 mg, Methocel K100 LV Premium CR Grade – 100 mg to 300 mg, Lactose Monohydrate – 160 mg to 360 mg, Talc – 30 mg and Magnesium Stearate – 10 mg.
Gopi M. Venkatesh et al., (2005) disclosed a unit dosage form such as a tablet or the like for delivering poorly water soluble macrolide antibiotics such as Clarithromycin into the body in an extended release fashion is designed to release the active ingredient primarily by tablet erosion though the tablet composition does not comprise any dissolution rate controlling agent, a polymer or esters of fatty acids. Such a drug delivery system provides a plasma concentration – time profile suitable for once a day oral administration. The typical composition includes, Clarithromycin – 84.75 parts, Lactose Monohydrate - 10.05 parts, PVP K29/32 – 2 parts prepared in 0.01N HCl in Water, Magnesium Stearate and Talc – 1.5 parts each.

Ashok Rampal et al., (2004) disclosed a controlled release pharmaceutical composition comprising amounts ranging from about 0.1 to about 4.5% w/w of one or more of rate controlling cellulose ether polymers. The typical composition includes, Clarithromycin – 500 mg, Methocel K15M CR – 7 mg, Methocel K4M CR – 28 mg, Lactose – 263 mg, PVP 30 – 12 mg, Sodium Stearyl Fumarate – 17 mg, Magnesium Stearate – 3 mg, Talc – 15 mg and Aerosil 200 – 5 mg.

Vanderbist, Francis et al., (2004) disclosed a pharmaceutical oral sustained release composition of Clarithromycin containing coated pellets comprising each a core containing Clarithromycin and a sustained release coating surrounding the core, in which the sustained release coating comprises at least a water insoluble polymer which is substantially pH independent. Disclosed is a method of treating infection including a sustained release oral form of Clarithromycin constituted by coated pellets and allowing a once a day administration of the drug. The typical composition includes, Clarithromycin – 60 to 72 mg, Microcrystalline Cellulose – 19 to 34 mg, Povidone – 2 mg, Citric Acid Trihydrate – 14 to 19 mg, Stearic Acid – 5 mg, Sucrose Stearate – 4 mg, Hypromellose – 2 mg, Lactose – 19 mg, Polyacrylate dispersion 30% (Dry Residue) – 65.6 mg, Ammonio methacrylate copolymer – 64.83 mg, Ethyl Cellulose – 64.8 mg, Polysorbate 80 – 0.15 mg, Simethicone Emulsion – 1.46 to 1.50 mg, Hypromellose – 7.54 to 10.93 mg, Talc – 14.58 to 22.61 mg, Titanium dioxide – 7.28 to 7.54 mg, Triacetin – 5.03 mg and Triethyl Citrate – 3.52 mg.

Yang et al., (1999) developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, clarithromycin) of Helicobacter pylori–associated peptic ulcers using HPMC and PEO as the
rate-controlling polymeric membrane excipients. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablets remained floating. It was concluded that the developed delivery system had the potential to increase the efficacy of the therapy and improve patient compliance.

*Broad et al.*, (1998) disclosed a controlled release, oral, solid, pharmaceutical composition for a reduced daily dosage regimen is described where the therapeutic ingredient is poorly soluble basic drug. The formulation comprises the use of a water soluble alginate salt, a complex salt of alginic acid and an organic carboxylic acid in admixture with the therapeutic drug. A particular embodiment comprising a once a day dosage form for clarithromycin is also described. The typical composition includes, Clarithromycin – 500 mg, Citric Acid Anhydrous – 128 mg, Sodium Alginate – 80 to 180 mg, Sodium Calcium Alginate – 10 to 22.5 mg, Lactose – 100 mg, Povidone K29/32 – 30 mg, Talc – 30 mg, Stearic Acid – 21 mg and Magnesium Stearate – 10 mg.

*Ashok Rampal et al.*, (2005) disclosed a pharmaceutical composition includes micronized Clarithromycin and exhibits improved dissolution characteristics relative to a pharmaceutical composition that includes unmicronized clarithromycin. The clarithromycin may have a particle size less than approximately 35 microns. One process of preparing an extended release tablet of the clarithromycin includes micronizing the clarithromycin; blending the micronized clarithromycin with one or more rate controlling polymers and pharmaceutically acceptable excipients; granulating the blend; and compressing to form a tablet. To treat a bacterial infection in a mammal in need of treatment, a patient may be administered a pharmaceutical composition that includes micronized clarithromycin. The typical composition includes, Clarithromycin Micronized – 1000 mg, Hydroxypropyl methylcellulose K15M – 10 mg, Hydroxypropyl methylcellulose K4M – 17.5 mg, Polyvinyl pyrrolidone K30 – 25 mg, Lactose – 50 mg, Magnesium Stearate – 12.5 mg, Talc – 10 mg, Sodium Stearyl Fumarate – 20 mg and Colloidal Silicon Dioxide – 5 mg.

*Ashok Rampal et al.*, (2002) disclosed a controlled release pharmaceutical composition suitable for once daily administration of erythromycin or a derivative thereof and the process for its preparation. More preferably it relates to a controlled release pharmaceutical composition of Clarithromycin suitable for once daily administration. The typical composition includes, Clarithromycin – 1000 mg, Sodium Alginate LVCR – 12.5 mg,
Xanthan Gum – 37.5 mg, Crosslinked Polyvinyl pyrrolidone – 125 mg, Magnesium Stearate – 12.5 mg, Talc – 20 mg, Sodium Stearyl Fumarate – 20 mg, Aerosil 200 – 8 mg and Purified Water – Quantity Sufficient.

_Muthaiyyan Esakki Kannan et al., (2004)_ disclosed a controlled release modifying complex for solid oral controlled release pharmaceutical compositions suitable for once-a-day administration. The composition comprises an active pharmaceutical ingredient, release modifying complex and other required pharmaceutically acceptable excipients. The release modifying complex comprises a primary release modifying agent and an auxiliary release modifying agent or varying combinations thereof, wherein said primary, secondary and auxiliary release modifying agents are present in amounts that synergistically effect and extend the release of active pharmaceutical ingredient. The typical composition includes, Clarithromycin – 500 mg, Polyethylene Oxide (Mol.Wt : 200,000) – 150 mg, Polyethylene Oxide (Mol.Wt: 2000,000) – 50 mg, Retrograded Starch – 150 mg, Lactose Monohydrate – 120 mg, Talc – 15 mg, Magnesium Steratae – 15 mg and Purified Water – Quantity Sufficient.

_Rajnikanth et al., (2008)_ have developed a floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with _Helicobacter pylori_ (H.pylori). Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant anti_**H.pylori**_ effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared _H.pylori_ more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of _H.pylori_ was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of _H. pylori_ than the corresponding clarithromycin suspension.

_Boyong Li et al., (2009)_ disclosed a controlled release formulations containing drugs which are preferably considered sparingly soluble to insoluble and which are suitable for
administration to a patient in need of treatment related thereto, and methods of manufacturing the same. The typical composition includes, a bigranular controlled release tablet of which the first extended-release granules of Clarithromycin contains Clarithromycin – 44%, Hydroxypropyl Methylcellulose (Methocel K3 LV) – 56%, Isopropyl Alcohol / Water (9:1) – Quantity Sufficient. Second part of extended-release granules of Clarithromycin contains Clarithromycin – 44%, Hydroxypropyl Methylcellulose (Methocel K3 LV) – 52%, Hydroxypropyl Methylcellulose (Methocel K100M CR) – 4%, Isopropyl Alcohol / Water (9:1) – Quantity Sufficient. The final Clarithromycin extended-release tablets were prepared by blending 23.64% of first part of extended-release granules of Clarithromycin along with 74.86% of second part of extended-release granules of Clarithromycin along with 1.5% of Glyceryl Monostearate.

Hardeep Wadhwa, (2003) disclosed an oral controlled release macrolide pharmaceutical formulation. In a preferred embodiment, the formulation comprises a citrate salt of a preferred macrolide, clarithromycin. Also disclosed are methods for preparing, isolating and characterizing soluble and stable citrate salt of macrolides and use thereof in all solid dosage forms of macrolides. The typical composition includes, Clarithromycin Citrate Salt – 500 mg equivalent, Methocel K15M Premium – 36 to 60 mg, Methocel E4M – 24 to 32 mg, Lactose Monohydrate – 100 mg, Povidone (PVP K-30) – 25 to 40 mg, Magnesium Stearate – 10 mg, Talc – 10 mg, Sodium Starch Glycolate – 20 to 30 mg, Purified Water and Ethyl Alcohol – Quantity Sufficient.

K. Mahalingam et al.,(2009) investigated the formulation development of orally administrable Clarithromycin delayed release tablet. Clarithromycin tablet was designed for the delaying the release to prolong the duration of drug action with the help of various polymers like Microcrystalline Cellulose, HPMC K4M, HPMC K5M, HPMC 6cps, PEG 6000 with different additives are used for the trial and error method. The prepared tablets showed good dissolution profile. The preliminary results from this study suggest that tablets prepared from Microcrystalline Cellulose, HPMC 6cps and PEG 6000 can be used to incorporate antibiotics like Clarithromycin and may be effective when administered orally in the stomach against H.pylori.

Mandaogade Prashant Manohar et al.,(2005) disclosed extended release tablets for oral administration comprising clarithromycin and a pharmaceutically acceptable carrier, wherein
the pharmaceutically acceptable carrier comprises a mixture of lactose and microcrystalline cellulose in a ration ranging from 3:1 to 1:3, and processes for their preparation. The typical composition includes, Clarithromycin – 57.7 to 61.5 mg, Hydroxypropyl methyl cellulose – 4 to 4.2 mg, Lactose – 6.5 to 30.4 mg, Microcrystalline Cellulose – 6.5 to 19.5 mg, Polyvinyl pyrrolidone – 1.35 to 1.4 mg, Sodium Stearyl Fumarate – 2 mg, Talc – 1.65 to 1.8 mg, Magnesium Stearate – 0.35 to 0.5 mg, Colloidal Silicon Dioxide – 0.55 to 0.6 mg and Opadry – 2 mg.

*Kiran Kumar Alladi et al.,* (2011) investigated the development of bioadhesive tablets of Clarithromycin which were designed to prolong the gastric residence time after oral administration. Matrix tablets of Clarithromycin were formulated using four bioadhesive polymers namely Carbopol 974P, HPMC K15M and HPMC K4M carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, bioadhesive force and *In vitro* drug release. Formulation of F9 and F12 which were formulated by using polymers, HPMC K14M, HPMC K15M and Carbopol 974P provided controlled release of Clarithromycin over the period of 12 hrs. The cumulative % of drug release of formulation F9 and F12 were 93.16 and 96.82 respectively. Invitro releases of F1 to F12 were found to be diffusion controlled and followed zero order kinetics. Formulation of F9 and F12 which were formulated by using polymers HPMC. K4M, HPMC K15M and Carbopol 974P were established to be the optimum formulation with optimum bioadhesive force, swelling index & desired invitro drug release. Further investigations are needed to confirm the *In vivo* efficiency, long term stability studies are needed to stabilize the controlled released (F9 and F12) formulations.

*Suriyaprakash TNK et al.*, (2013) investigated the formulation of Clarithromycin tablets from polymeric hydrophilic matrices using Methocel and characterization for its physic-chemical properties and *In vitro* release studies to optimize its release profile with the standard marketed product. Matrix tablets were prepared by wet granulation method using PVP and ethyl cellulose as binding agents. The matrix tablets were evaluated for its thickness, hardness, friability, weight variation, drug content and *In vitro* release studies. The drug delivery was analysed using the paddle method in phosphate buffer pH 6.0 and phosphate buffer pH 6.8 containing 0.5% sodium lauryl sulphate and compared with the USP dissolution limits. The dissolution release profile of formulation F9 was comparable with the market formulation and the difference factor and similarity factor f1 and f2 was found to be
2.44 and 83.18 in dissolution medium without sodium lauryl sulphate and 1.44 and 89.71 in dissolution medium with sodium lauryl sulphate. Stability studies were carried out as per ICH guidelines and tested for its physicochemical properties and In vitro studies. The study shows that the matrix method can be employed for preparing clarithromycin sustained release formulation using combination of hydrophilic polymers like methocels and sodium carboxy methyl cellulose.

Santha Sheela NB et al., (2010) investigated the formulation of floating sustained release tablets of Clarithromycin, by using a combination of hydrophilic polymers (different grades of hydroxypropyl methylcellulose), Kollidon SR and an effervescent substance (sodium bicarbonate). The formulations were evaluated to study the effect of sodium bicarbonate concentration on the floating lag time, total duration of floating, In vitro dissolution release profile and the effect of different fillers and ethyl cellulose concentration on the release profile of drug. It was found that among all the formulations, formulation F4 (HPMC K15M, Avicel 102 pH and sodium bicarbonate) was found to be the optimum formulation as it had good swelling property, floating time and drug release. The drug release of optimized formulation was found to follow Zero order, Higuchi and Korsmeyer-Peppas kinetic models.

Rahul Sutar et al., (2010) investigated to develop and evaluate hydrodynamically balanced matrix tablets of clarithromycin which were prepared by using Hydroxypropyl Methylcellulose K4M (HPMC K4M), Hydroxy Propyl Methyl Cellulose K15M (HPMC K15M) and Chitosan with NaHCO3 as gas forming agent. These matrix tablets were evaluated for their physicochemical properties, buoyancy and tablet density. Effect of hardness on matrix tablet revealed that increase in hardness affects buoyancy lag time due to reduction in porosity of compact mass. The release rate determined in 0.1 N HCL (pH 1.2) showed controlled release of drug following non-Fickian mechanism.

Pranjal Kumar Singh et al., (2012) investigated to develop mucoadhesive tablets of clarithromycin using different bioadhesive polymers. The tablets were prepared using Sodium Carboxy methyl cellulose (SCMC), carbopol 974P and Sodium Alginate as bioadhesive polymers to impart mucoadhesion. Development of mucoadhesive tablets of Clarithromycin which were designed to prolong the gastric residence time after oral administration. Clarithromycin is in a class of medications called macrolide antibiotics. It works by stopping the growth of bacteria. The short biological half-life of drug also favors
development of a sustained release formulation. The present study aims to reduce the dosing frequency. Tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, swelling index, ex vivo mucoadhesive strength, In vitro drug release. The present study concludes that mucoadhesive tablets of clarithromycin can be a good way to swelling and bioadhesion properties a good improve the bio availability of clarithromycin.

Swarnima Pandey et al., (2010) investigated the different polymer blend of sodium alginate, methyl cellulose and hydroxypropyl methylcellulose has been used for preparation of the clarithromycin microcapsules.

Hsiao Yih Ming et al., (2005) investigated a sustained release, solid pharmaceutical preparation for oral use in a daily dosage regimen is provided, which comprises at least one sparingly soluble main drug, such as an erythromycin derivative. The pharmaceutical preparation comprises the main drug(s), a water-soluble alginate salt and an organic carboxylic acid. In particular, a controlled release tablets of clarithromycin is provided. The typical composition includes, Clarithromycin – 500 mg, Citric Acid Monohydrate – 110 to 125 mg, Sodium Alginate – 245 to 250 mg, Lactose Monohydrate – 78 to 88 mg, Povidone K30 – 12 mg, Stearic Acid – 5 mg, Talc – 5 mg and Magnesium Stearate – 10 mg.

Dangi Amish A et al., (2011) developed a gastro retentive controlled release drug delivery system with swelling, floating, and mucoadhesive properties. Ten tablet formulations were designed using hydroxypropylmethylcellulose (HPMC K100M) and xanthan gum as release-retarding polymer(s) and sodium bicarbonate (NaHCO3), Sodium carbonate (NaCO3) and calcium carbonate (CaCO3) as a gas former. Swelling ability, floating behaviour, adhesion period and drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5º C. The tablets were subjected to various physiochemical tests, weight variation, content uniformity, thickness, hardness, floating lag time, adhesion period, total floating time etc. The study data revealed acceptable values of physicochemical properties. Drug release profiles of all formulation followed first order kinetic and diffusion mechanism. Statistical analyses of data revealed that tablets containing HPMC K100M (20% w/w), xanthan gum (5% w/w) and NaHCO3 (12%, w/w) in F8 or CaCO3 (12%, w/w) in F9 were promising systems exhibiting excellent floating properties, extended adhesion periods and sustained drug release characteristics. Both formulations were stored at 40º C/75% RH for 3 months according to
ICH guidelines. Formula F10 showed better physical stability and longer release profile, so F10 was selected for the further *in vivo* study. Abdominal X-ray imaging of formula F10, loaded with barium sulfate, in New Zealand albino rabbit revealed a mean gastric retention period of 9.2 ± 0.51 h.

*Claudio Camponeschi et al.,* (2009) concerns the discovery of a new formulation for oral drug sustained release product, capable to provide a quasi-constant prolonged release of poorly soluble drugs whose solubility depends on the pH. The typical composition includes, Clarithromycin - 500 mg, Mannitol – 100 mg, Citric Acid – 100 mg, Metolose 90 SH 100 SR – 70 mg, Metolose 90SH 4000 SR – 30 mg, PVP K30 – 22.5 mg, PEG 6000 – 11.25 mg, Sodium Dodecyl Sulphate – 0.45 mg, Talc – 8.44 mg and Magnesium Stearate – 4.12 mg.

*Margret Chandira et al.,* (2009) investigated the development of mucoadhesive tablets of Clarithromycin which were designed to prolong the gastric residence time after oral administration. Matrix tablets of Clarithromycin were formulated using four mucoadhesive polymers namely Carbopol 974P, HPMC K15M and HPMC K4M carried out studies for weight variation, thickness, hardness, content uniformity, swelling index, mucoadhesive force and *in vitro* drug release. Formulation of F9 and F12 which were formulated by using polymers, HPMC K14M, HPMC K15M and Carbopol 974P provided controlled release of Clarithromycin over the period of 12 hrs. The cumulative % of drug release of formulation F9 and F12 were 93.16 and 96.82 respectively. The stability studies showed that there was no significant change in adhesive strength, invitro release when stored at room temperature, 40°C, and 2-8°C for a period of 30 days.

*Putta Rajesh Kumar et al.,* (2011) investigated the development of enteric coated esomeprazole core tablet followed by compression coating with clarithromycin coat granules to obtain a single unit core in coat floating tablet. The tablets were prepared by investigating various porous carriers, cellulosic polymers and natural gums. Sodium bicarbonate is used as gas generating agent. The enteric coating of core tablet showed significant protection of esomeprazole from gastric acid by acryl EZE and *in vitro* release of drug in simulated intestinal fluid. The rheological and compressional parameters of the core powder and coat granular beds showed their ease of flow and compaction in to tablet. The tablets showed optimum floating parameters with minimum floating lag time. *In vitro* dissolution in modified dissolution apparatus indicated the clarithromycin release in simulated gastric fluid.
for first 2h and esomeprazole in simulated intestinal fluid for 10h. A zero order drug release was observed for clarithromycin coat and first order drug release for esomeprazole. Porous carriers, HPMC and natural gums as matrix polymers optimization studies indicated their suitability for floating tablet formulations. The dosage forms could be further evaluated for pharmacokinetic studies to study actual drug release In vivo.

*Dehdari S et al.*, (2013) formulated a hydro dynamically balanced delivery system of clarithromycin, which would have the ability to float in the stomach with the desired In vitro release profile. Such a system would be suitable for localized action in the stomach in addition to prolonged systemic absorption for the treatment of *H.pylori*. Wet granulation technique was used to make various tablet formulations. The parameters which were studied included polymer (HPMC K4M) and sodium bicarbonate and fillers like Lactose and microcrystalline cellulose. The formulation with 41.6% clarithromycin, 20%HPMC K4M and 10% sodium bicarbonate gave a floating lag time of less than 3 minutes and a floating time of 12 hours and its release profile followed the Higuchi model.

*Rahul Sutar et al.*, (2010) attempted to develop and evaluate hydrodynamically balanced matrix tablets of clarithromycin which were prepared by using Hydroxypropyl Methylcellulose K4M (HPMC K4M), Hydroxy Propyl Methyl Cellulose K15M (HPMC K15M) and Chitosan with NaHCO3 as gas forming agent. These matrix tablets were evaluated for their physicochemical properties, buoyancy and tablet density. Effect of hardness on matrix tablet revealed that increase in hardness affects buoyancy lag time due to reduction in porosity of compact mass. The release rate determined in 0.1 N HCL (pH 1.2) showed controlled release of drug following non-Fickian mechanism.

*Priyanka Shukla et al.*, (2013) focused on the development of gastroretentive technology which will deliver the antibiotic at predetermined rate to achieve the local concentration enough to act as antibacterial against *H.Pylori*. This technology ensures the maximum utilization of the drug with minimum side effects and maximum patient compliance and also with reduced antibiotic resistance by the bacterium. The tablet contain 15% and 20% having Floating lag time (FLT) 63 seconds and 64 seconds and the drug release was found to be 62.73% and 53.72 respectively. Increasing the polymer ratio the FLT was increase but the drug release was decreased.
Vankdoth Ravi, et al. (2012) Floating matrix tablets of clarithromycin were developed to prolonged gastric residence time and thereby increase drug availability. The tablets were prepared by wet granulation technique, using polymers such as HPMC-K4M, Carbopol 934P and Sodiumalginate, and other standard excipients. Tablets were evaluated for physical characteristics viz, hardness, percentage friability, floating capacity, weight variation and content uniformity. Further, tablets were evaluated for in-vitro release characteristics for 24hr, by linear regression analysis.

Zawar Laxmikant R et al., (2010) prepared the Floating–mucoadhesive tablets of clarithromycin for the treatment of Helicobacter pyloric (H pylori) infection. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, HPMC K15M and carbopol 974P and were evaluated for drug - excipient compatibility, density, buoyancy test, mucoadhesion force, swelling study, drug content and in-vitro release profile. Sodium bicarbonate and citric acid were used for producing effervescent base for buoyancy of tablets. Analysis of drug release from tablet indicates drug release by zero order rate kinetics. No significant change was observed in physical appearance, drug content, floatability or In vitro dissolution pattern after storage at 45 °C / 75% RH for three months.

Patel RP et al., (2010) investigated the formulation, optimization and evaluation of sodium alginate based In situ gel of Clarithromycin and Metronidazole Benzoate. Sodium alginate used as a polymer and CaCO₃ was used as a cross-linking agent. The In situ formulation exhibited well, viscosity, drug content and sustained drug release; this study reports that oral administration of aqueous solutions containing sodium alginate results in formation of In situ gel, such formulations are homogenous liquid when administered orally and become gel at the contact site. The results of a 32 full factorial design revealed that the concentration of sodium alginate and concentration of CaCO₃ significantly affected the dependent variables Q1, Q12 and T80. These In situ gels are, thus, suitable for oral sustained release of Clarithromycin and Metronidazole Benzoate.

Kamalakkannan V et al., (2013) prepared a gastroretentive drug delivery system of clarithromycin. The present study outlines a systematic approach for design and development of hydrodynamically balanced tablets of clarithromycin to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of clarithromycin were prepared employing two different grades of, HPMC K4M, HPMC K10M, HPMC K15M, Chitoson by
effervescent technique. Sodium bicarbonate was incorporated as a gas-generating agent. Drug-excipients compatibility studies were conducted using FTIR spectra. The floating tablets were evaluated for physical characteristics viz. uniformity of weight, hardness, friability, drug content, swelling index, \textit{In vitro} buoyancy. Further, tablets were evaluated for \textit{In vitro} release characteristics. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good \textit{In vitro} buoyancy. The tablet swelled radially and axially during \textit{In vitro} buoyancy studies. HPMC K15M based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited prolonged drug release profiles while floating over the dissolution medium. \textit{In vitro} release mechanism was evaluated by subjecting the dissolution data to various kinetic models and the drug release was found to best fit to Korsmeyer – Peppas equation and followed by Higuchi model and Zero order rate kinetics. Comparison study with marketed product Clarithromycin extended release showed that the optimized formulation F3 has better control over release rate in comparison with the marketed product.

\textit{Chudiwal PD et al.,} (2009) developed an optimized gastro retentive drug delivery system (GRDDS) of clarithromycin floating microspheres by the optimization technique. The clarithromycin microspheres were prepared by non-aqueous solvent evaporation method using different grades of hydroxylpropyl methylcellulose (HPMC) such as HPMC 15M(15cps), HPMC K4M (4000cps), HPMC 100LV (100cps) and ethyl cellulose (EC). The prepared microspheres were characterized by polymer compatibility, percentage yield, buoyancy percentage, drug entrapment efficiency and \textit{In vitro} drug release. An optimized formulation investigated for morphology and particle size analysis by scanning electron microscopy. A32 factorial design was employed in formulating the GRDDS with different viscosity grades of HPMC (X1) and polymer-topolymer ratio Ethyl cellulose: HPMC (X2) as independent variables. Four dependent variables were percentage of yield, drugentrapment efficiency, buoyancy percentage and percentage of cumulative drug release of microspheres after 12h (R12h). Themain effect and interaction terms were quantitatively evaluated using a mathematical model. Regression analysis and numerical optimization were performed to identify the best formulation. The predicted values agreed well with the experimental values, and the results demonstrate the feasibility of the model in the development of GRDDS.

\textit{Amit Bhople et al.,} (2012) prepared and evaluated Mucoadhesive capsule enclosing Microspheres of drugs Clarithromycin and Omeprazole to treat Helicobacter pylori Infection.
Mucoadhesive Microcapsule remains in vicinity of absorption site for prolonged period of time, so residence time of drug at absorption site is increases. No marketed preparation of drug combination Clarithromycin and Omeprazole is available to treat Helicobacter pylori Infection. Preformulation study of drugs was done. Ultraviolet and infrared spectroscopic study of drugs is carried out to check authenticity of drug and interaction between drug and excipient. Evaluation of Microsphere were done including micromeritics studies, percentage recovery of microsphere, drug entrapment study, In vitro drug release, swelling and adhesion property were evaluated separately. Optimization of the batch of microsphere was done. Scanning electron microscopy studies of microspheres were done to study surface topography of the uncoated and coated (optimized) microsphere. Optimization of Microcapsule batch was done. Evaluation of Microcapsule was done. In vitro drug release study (Dissolution study) of optimized batch of Microcapsule was done. Therefore, by the formulation of Mucoadhesive capsule enclosing Microspheres of drugs Clarithromycin and Omeprazole, drugs residence time at absorption site is increases, so drug remains in vicinity of absorption site for prolonged period of time which is most beneficial to treat Helicobacter Pylori infection.

**Balkrushna K Patel et al., (2010)** investigated the preparation of Clarithromycin hydrophilic matrix tablets by direct compression technique followed by In vitro floating characterization statistically. The floating hydrophilic matrix tablets prepared by using different grades of polymer (HPMC) of varying concentrations, different concentration of sodium bicarbonate and varying ratios of MCC. Floating properties such as Floating Lag Time, Total Floating Time, and Swelling index. Tablet hardness had found to be affecting on floating behavior. Hydrophilic matrix floating tablets of Clarithromycin were developed to increase the gastric residence time which leads to increased bioavailability by giving sufficient time to release the drug in GI tract.

**Sanjay S Patel et al., (2006)** investigated floating dosage form containing clarithromycin as drug was designed for the treatment of Helicobacter pylori. Tablets containing hydroxypropylmethylcellulose (HPMC), drug and different additives were compressed using wet granulation and D-optimal design technique. The study shows that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides
optimal floating (floating lag time <30 s; total floating time >10 h). The drug release was sufficiently sustained (more than 8 h) and anomalous diffusion as well as zero-order was confirmed. Optimization of the evaluating parameters with design expert software was employed to get final optimized formulation. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC K15M, 18.09% HPMC K4M, 12.96% sodium bicarbonate which gave floating lag time < 30 s with a total floating time > 10 h, *In vitro* release profile very near to the target *In vitro* release profile and follows anomalous diffusion as well as zero order pattern of release.

### 2.2 PREDNISONE

*Roger Hallgren et al.,* (1998) discloses a pharmaceutical composition for peroral treatment of rheumatoid arthritis and a treatment method therefor are described, wherein said composition comprises 2.5-7 mg of a glucocorticoid as active substance with a regulated sustained release such that at least 90% by weight of the glucocorticoid is release during a period of about 40-80 min, starting about 1-3 hours after the entry of said glucocorticoid into the small intestine of a mammal. The active substance is micronized, followed by wet granulation to form a granulate. Such a granulate has, as such a release rate of 70% during 30 min in water of 37°C. Further, the granulate is laminated with a sustained release inner layer resistant to a pH of 6.8 and a sustained release outer layer resistant to a pH of 1.0. The inner layer is preferably made of Eudragit RL (copolymer of acrylic and methacrylic esters with a low content of quaternary ammonium groups) and the outer layer is preferably made of Eudragit L (anionic polymer synthesised from methacrylic acid and methacrylic acid methyl ester).

*Hazel Judith Bardsley et al.,* (2004) discloses a unit dose formulation comprising 0.25 mg to 2 mg of a Corticosteroid. This small dose can be used to treat rheumatoid arthritis, especially if adapted to release at least 90% by weight of the corticosteroid, 2 to 8 hours after administration.

*Hazel Judith Bardsley et al.,* (2004) discloses a unit dose formulation comprising less than 2.5 mg of Prednisolone or an equivalent, equipotent amount of another Corticosteroid. One embodiment of a method of the invention concerns once daily administration of the unit dose formulation between midnight and 6 a.m. for the treatment of rheumatoid arthritis.
Guy Vergnault et al., (2012) discloses a tablet comprising a core containing an active agent and a coating, the core being disposed within the coating such that the coating has a thickness about a longitudinal axis (X-Y) of about 4.85 to 4.95 mm. The position of the core within the coating dictating that the active agent is released rapidly after a lag time during which time no active agent is released. The composition of one particularly preferred embodiment of the invention is, Core of 5 mg Prednisone tablet containing 8.33% of Prednisone, 64.47% of Lactose Monohydrate, 6.67% of Povidone, 18.33% of Croscarmellose Sodium, 0.5% of Red ferric oxide, 1% of Magnesium Stearate Vegetable Origin. Press Coating (Barrier) includes 50% of Dibasic calcium phosphate dehydrate, 40% of Glycerel behenate, 8.4% of Povidone, 0.1% of Yellow ferric oxide, 1% of Magnesium Stearate Vegetable Origin and 0.5% of Colloidal Silicon Dioxide.The In vitro dissolution profile of the tablet when tested using USP– II (Paddle), 100 rpm, 500 ml, Purified Water. Till 4 hours no drug substance release is observed. However, within 4.5 hours there is approximately 80% release and by 5 hours 100% release of the drug substance observed.

Guy Vergnault et al., (2012) discloses a tablet comprising a core containing an active agent and a coating, the core being disposed within the coating such that the coating has a thickness about a longitudinal axis (X-Y) of about 4.85 to 4.95 mm. The position of the core within the coating dictating that the active agent is released rapidly after a lag time during which time no active agent is released. Content / tablet disclosed is a core tablet with 5 mg / tablet of Prednisone, 39.10 mg / tablet of Lactose, 4 mg / tablet of Povidone K30, 11 mg / tablet of Sodium carboxymethyl cellulose, 0.6 mg / tablet of Magnesium stearate and 0.3 mg / tablet of Silicon dioxide. The prepared core tablet was enclosed within a barrier coat with 50% of Dibasic calcium phosphate, 40% of Glycerel Behenate, 8.4% of Polyvinyl pyrrolidone, 0.1% of Yellow Ferric Oxide, 0.5% of Silicon dioxide and 1% of Magnesium Stearate. The In vitro dissolution profile of the tablet when tested using USP– II (Paddle), 100 rpm, 500 ml, Purified Water. Till 4 hours no drug substance release is observed. However, within 4.5 hours there is approximately 80% release and by 5 hours 100% release of the drug substance observed.

SUMMARY
A comprehensive literature survey was carried out for both Clarithromycin and Prednisone controlled release systems and the important findings are presented in this chapter.
**Clarithromycin**

The following useful information is revealed from the literature review: (i) Most of the research work is on gastro-retentive system based design. The design involves a complex manufacturing process; utilizing costly polymers. For gasification purpose, metallic bi carbonates are added. The success rate from therapeutic stand point is very limited due to factors like short gastric residence time, unpredictable gastric emptying time and also differences in gastric physiology such as gastric pH. (ii) Some of the patents and literatures focussed on the development of controlled release tablets of Clarithromycin by matrix design. The matrix design discussed therein involves use of significant amount of high viscous polymer combinations. In some literatures, the manufacturing process involves two sets of hydro-alcoholic granulation process with two different polymers and finally blending the two granulated blend in a particular ratio to make the controlled release tablets. Based on literature information, high viscosity polymers will be avoided. Rapid swelling and gelling polymers like Carbopol 974P will not be used. pH dependent and pH independent methacrylic acid copolymers will not be used. The present research will focus to design a simple matrix tablet with low viscous polymers and minimum excipients. No organic solvents will be used; instead environment friendly aqueous granulation will be done. Moreover with respect to manufacturing process, top spray fluid bed granulation process will be done. By doing the granulation by top spray fluid bed granulation process, material handling will be less, process time of granulation and drying will be fast as both the process happens simultaneously and the mechanical properties of the granules will be uniform.

**Prednisone**

The following useful information is revealed from the literature review: (i) Marketed / Reference product is a tablet in tablet design. The design involves a complex patented GEOCLOCK™ technology, where an immediate core tablet is embedded within a barriertablet which allows the release of drug from the inner core tablet for a period of 4 hours. The barrier design is made with a combination of Dibasic Calcium Phosphate Dihydrate, Glycerol Behenate and Povidone. The equipment requirement for this design is very complex, costly and high precision tablet in tablet press. The main disadvantage of such high precision complex equipment is in-process rejects & wastages will be very high and output per day will be less compared to the conventional tablet press process. (ii) One prior art patent disclosed the use of pH dependent polymers like Eudragit L and RS grade polymers along with Hypermellose Phthalate. So basically the literature information revealed the use of
either non-conventional excipient combination (like the reference / marketed product) or a combination of pH dependent polymers to control the release of drug. Based on the literature information, drug delivery system design based on “Press coating” and “Tablet in tablet” will be avoided. pH independent / pH dependent methacrylic acid based polymers will not be used. Reservoir type controlled release tablets of Prednisone will be designed by making an immediate release core tablet of Prednisone over which pH independent coating with ethyl cellulose as polymer and Hypromellose as pore former shall be done.

The demerits of the reference / marketed product design is laborious manufacturing process, costly polymers and solvents and all leading to costly end product. Hence, in this investigation controlled release tablets of Clarithromycin and Prednisone will be designed by a simple manufacturing process which will be robust and reproducible at commercial scale. Conventional, low cost standard polymers will be used and Non-aqueous solvents will be avoided to make the manufacturing process cost effective and eco-friendly.
SCOPE & OBJECTIVES
CHAPTER – III

SCOPE & OBJECTIVES

3.1 MOTIVATION
Controlled release dosage form is one of the drug products categorized under the term controlled release dosage forms (FDA, 1997). It refers to products, which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form. Several advantages of controlled release products over immediate release ones have long been recognized (de Haan and Lerk, 1984; Krämer and Blume, 1994; Hoffman, 1998; Das and Das, 2003).

Controlled release solid oral dosage forms can be classified into two broad groups: (i) single unit dosage forms (e.g. tablets) and (ii) multiple unit dosage forms or multiparticulate pellet systems. The systems can be further subdivided into two concepts regarding to the design of dosage forms: (i) matrix systems and (ii) reservoir systems. Of the two concepts, the present area of research of Clarithromycin is on matrix systems and the Prednisone is that of reservoir systems.

Clarithromycin
Matrix or monolithic devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid. The devices can be prepared either by the compression of a polymer/drug mixture or by the dissolution or melting, resulted in the molecularly dispersed drug. The drug transport often results from a combination of several mechanisms included dissolution, diffusion, swelling and erosion. Generally matrix systems can be made by water-soluble matrix formers and water-insoluble matrix formers. The present area of research is on designing the matrix system using water-soluble matrix formers.

Water-soluble or hydrophilic matrices are a well-known type of controlled release oral dosage forms (Melia, 1991; Abrahamsson et al., 1998b; Siepmann and Peppas, 2001). While hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material, several others are also available; including (i) cellulose derivatives: hydroxypropyl cellulose