CHAPTER 3: REVIEW OF LITERATURE

Shendge and Sayyad, 2013 prepared compression coated tablets of budesonide with ethyl cellulose /Eudragit RLPO and tested for colonic delivery. Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineral corticoid activity. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in ulcerative colitis, crohn's disease and inflammatory bowel disease. In this study, each 150 mg core tablet of budesonide was compression coated with 60% ethyl cellulose and 40% Eudragit RLPO, 70% ethyl cellulose and 30% Eudragit RLPO and 80% ethyl cellulose and 20% Eudragit RLPO at a coat weight of 200 mg, 250 mg and 300 mg respectively. Drug release studies were carried out in pH 6.8 phosphate buffer IP solution. The Eudragit RLPO/Ethyl cellulose envelope was found to be a good delivery system for budesonide to be delivered to the colon.

Huang et al., 2013 design a zero-order release of compression-coated tablets using hydroxypropylcellulose (HPC) as the coating layer and glipizide which was solubilized by manufacturing the inclusion complex of β-cyclodextrin as a model drug. The effects of the weight ratio of drug and the viscosity of HPC on the release profile were investigated by "f2" factor with GlucotrolXL®. The uptake and erosion study, the correlation coefficient (R) and the exponent (n) were used as indicators to justify drug release mechanism. Bioavailability in vivo was determined by administering the compression-coated tablets to rabbits in contrast with GlucotrolXL®. It was found that the formulation presented a well zero-order behavior at the weight ratio of drug 11:14 (core:layer) and the combination of HPC-L (8.0 mPas) and HPC-M (350 mPas) (8:9), with the f2 of 66.90. The mechanism for zero-order release of these compression-coated tablets was solvent penetration into the dosage form and drug dissolution from the erosion of the gelled HPC matrix. The parameter AUC0-∞ of the compression coated tablets and the market tablets
where 37,255.93±1474.08 h ng/ml and 43265.40±1015.28 h ng/ml, while the relative bioavailability was 87.66±1.56%. These studies demonstrate that the designed compression-coated tablets may be a promising strategy for peroral controlled release delivery system of water-insoluble drugs.

Jani et al., 2013 developed an oral press-coated tablet by means of direct compression to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. The aim of the present study is to develop colon targeted drug delivery systems for simvastatin by using HPMC K100M and ethylcellulose (EC) as coating material. By applying $3^2$ full factorial design, compression coated tablets of simvastatin containing different proportions of EC and HPMC K100M was prepared. All the formulations were evaluated for the hardness, friability, thickness, weight variation, drug content uniformity, and in-vitro drug release studies for 12 h. Press coated tablets of simvastatin released different amount of the simvastatin, within the 12 h dissolution study, in the physiological environment of the stomach and small intestine, depending on the proportion of EC: HPMC K100M used in the formulation. The compression coated formulations have been formulated to release minimum amount of simvastatin within 5 h dissolution study in the physiological environment of the stomach and small intestine. The results of the dissolution study showed that compression coated tablet F6 with EC: HPMC K100M (100: 125) is most likely to provide targeting of simvastatin for local action in the colon owing to its minimal release of the drug in first 5 h.

Shah et al., 2013 design and optimize compression coated tablet to provide an immediate release of hydrochlorothiazide in stomach and extended release of metoprolol succinate in intestine. Compression coated tablet was prepared by direct compression method which consisted of metoprolol succinate extended release core tablet and hydrochlorothiazide immediate release coat layer. Barrier coating of Hydroxy Propyl Methyl Cellulose (HPMC) E15LV was applied onto the core tablets to prevent burst release of metoprolol succinate in acidic medium. A $3^2$ full factorial design was employed for optimization of the amount of polymers required to achieve extended release of drug. The percentage drug release at given time Q3, Q6, Q10, Q22; were selected as dependent variables. Core and compression coated tablets were evaluated for
pharmaco-technical parameters. *In vitro* drug release of optimized batch was found to comply with Pharmacopoeial specifications. Desired release of metoprolol succinate was obtained by suitable combination of HPMC having high gelling capacity and polyethylene oxide having quick gelling capacity. The mechanism of release of metoprolol succinate from all batches was anomalous diffusion.

Nahid et al., 2013 investigated press coated tablet for pulsatile drug delivery of Ketoprofen for chronotherapy of rheumatoid arthritis. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of rheumatoid arthritis. The press coated tablets containing Ketoprofen in the inner core were formulated by direct compression method with an outer coating of different amounts of HPMC K4M. The release profile of press coated tablet exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 32 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 7.1.4 software. The optimized batch F6 gave a lag time of 6 hr and drug release of 95.74% which consisted of 40% HPMC K4M and 2% SSG.

Bajpai et al., 2012 developed pulsatile release tablet of losartan potassium for chronotherapy in hypertension. The prepared system consisted of a core tablet coated with versatile and safe hydrophilic cellulosic ethers such as, hydroxypropyl methylcellulose, hydroxypropyl cellulose and sodium carboxy methylcellulose to produce burst release after predetermined lag time. Various formulation factors were studied through series of test and *in vitro* dissolution study. It was found that core tablets containing superdisintegrant failed to produce burst drug release pattern while effervescent agent was able to do so. Results also reveal that coating composition and coating level affects lag time. Formulation containing effervescent agent in core and coated with 200 mg hydroxypropyl cellulose provide lag time of 4.5 h with 73% drug release in 6 h that followed a sigmoidal release pattern. These values were close to the desired objective of producing lag time of 5-6 h followed by fast drug release. This approach can thus provide a useful means for timed release of losartan and is helpful for patients with morning surge.
Ahmad et al., 2012 developed a novel colon targeted Assam Bora rice starch compression coated tablet for site specific delivery of 5-FU to the colon without the drug being released in stomach or small intestine. Core tablet of 5-FU was prepared using microcrystalline cellulose (MCC) and spray dried lactose by direct compression method. The in vitro drug release study in different physiological environment confirmed insignificant release of 5-FU in physiological condition of stomach and small intestine further fast and major drug release in caecal content. In vivo drug absorption of optimized formulation was performed in order to establish its targeting potential in colon. It is concluded from the present study that Assam Bora rice starch can be used as a drug carrier for an effective colon targeted delivery system for drugs effective against the large intestine resident disease condition.

Jadhav et al., 2012 investigated the in-vitro performance of compress coated tablet of Budesonide. A novel colon targeted tablet formulation was developed by press coating of Budesonide with guar gum and Eudragit S-100 as barrier layer. The entire device was enteric coated so that variability in gastric emptying time can be overcome and a colon specific release can be achieved. Different ratios of polymers were selected to achieve suitable lag time for the treatment of Crohn's disease and ulcerative colitis. In-vitro release studies for prepared tablets were carried out for 2 h in 1.2 pH phosphate buffer, 3 h in pH 6.8 phosphate buffer and 6 h in simulated colonic fluid. In vitro studies revealed that the tablet coated with guar gum and Eudragit S-100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. colon specific release has been achieved from tablet of F5 formulation (0:100) which not given release in stomach and small intestine and about 98.87% drug release in the colon.

Kapse and Mandore, 2011 developed an oral press-coated tablet by means of direct compression to achieve the timecontrolled disintegrating or rupturing function with a distinct predetermined lag time and produce sustained drug delivery. This press-coated tablet containing Diltiazem hydrochloride (DIL) as a model drug in the inner core was formulated with an outer shell by different weight ratios of low viscosity grade
hydrophilic polymer of Hydroxypropylmethylcellulose (HPMC) 3-cps, 5-cps, 6-cps powder respectively and weight ratio of that used 1:2.86, 1:3, 1:4, 1:5 for each press-coated polymer to core tablet. The release profile of the press-coated tablet exhibited a time period without drug release (time lag) in pH 1.2 followed by a rapid and complete release phase, the lag phase was markedly dependent on the weight ratios of Core. This ratio of core to press coated polymer press coated tablets displayed acid resistance in the stomach. *In vitro* dissolution test in pH 6.8 the release of press-coated tablet shows sustained drug release and to avoid gastrointestinal disturbances. 1:3 weight ratio shows better sustained release action then other.

Negar et al., 2011 used the principles of compression coat to minimizing the drug release in upper gastro intestinal tract and targeting to colon. Compression coated tablets of Ibuprofen were prepared by direct compression method using chitosan (300, 250, 200 & 175 mg). Tablets were evaluated for their physicochemical properties and *in vitro* drug release studies. *In vitro* drug release studies were performed with and without rat caecal contents. In the rat caecal contents tablets showed enhanced drug release due to degradation of chitosan coat by colonic colonic enzymes. The *in vitro release* studies in pH-6.8 phosphate buffer containing 2% w/v of rat caecal contents showed the cumulative percentage release of Ibuprofen after 26h as 31.94% ±0.59, 67.89% ± 0.45 and 55.87 % ± 0.45 and 82.52 % ± 0.92 respectively. Coat thickness and amount of chitosan controls the release rate. Formulations are best fitted with Korsmeyer-Peppas kinetics and mechanism of drug release was non-Fickian. FTIR studies reveals there is no drug-polysaccharide interaction. F1 formulation was a promising system for drug targeting to colon.

Kalyani and Rama, 2011 prepared compression coated tablets by direct compression method using guar gum alone (or) combination of guargum/metalose 90 SH polymers. Tablets are evaluated for their physicochemical properties and *in vitro* drug release studies. All the properties of core and coat formulations are within house specifications. *In vitro* drug release studies are performed without rat caecal contents (as a control) and with rat caecal contents. In the rat caecal contents formulations shows enhanced drug release due to degradation of guar gum coat by colonic galactomannanase enzyme. Coat thickness and amount of guargum/metalose 90 SH parameters controls the release rate.
Compared to individual guar gum combination of guar gum with metalosee 90 SH (F9) provides minimize the drug release in upper GIT and maximizing the release of drug in colon. All the formulations ar best fitted with zero order kinetics and mechanism of drug release was non-Fickian (super case -II). FTIR studies reveals there is no drug-excipient interaction. Optimized F9 formulation was a promising system targeting to colon for treatment of various colonic diseases like Inflammatory Bowel disease.

Tarak et al., 2011 developed colon-specific drug delivery systems based on polysaccharide chitosan, were evaluated using in-vitro method. Metronidazole is choice of drug for intestinal amoebiasis. These drugs are to be delivered to the colon for their effective action against E. histolytica wherein the trophozoites reside in the lumen of the caecum and large intestine and adhere to the colonic mucus and epithelial layers. But the pharmacokinetic profile of metronidazole indicates that the drug is completely and promptly absorbed after oral administration reaching a concentration in plasma of about 10 mg/ml approximately 1 hr after a single 500 mg dose. The administration of this drug in conventional tablet dosage form provides minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis, but with unwanted systemic effects.4,5The factors Amount of chitosan (X1), amount of carbopol 934P (X2) showed significant effect on the release of metronidazole from the colon specific tablet formulation. Optimizing was performed using a 32 full factorial design to yield tablet that released a >80% in 12 hour.batch(0,0) as per the contour plot s shows the optimize batch. Present study summarized that chitosan and carbopol can be used successfully to deliver the drug in to colon.

Sridhar et al., 2011 developed a polysaccharide based compression coated tablets of secnidazole for colon delivery. Core tablet containing secnidazole was compression coated with various proportions of guar gum, xanthan gum and chitosan, either alone or in combinations. Drug release studies were performed in simulated gastric fluid (SGF) for 2 h followed by simulated intestinal fluid (SIF, pH 7.4) up to 24 h. Secnidazole release from the prepared formulations was dependent on the type and concentration of polymer used in the formulation. Tablets coating containing either guar gum or xanthan gum showed ~30-40% drug release in 8 h. In vitro dissolution studies of selected
formulations performed in the dissolution media with rat caecal contents showed 54.48±0.24 - 60.42±0.16% of drug release. Formulations with single polymer in coating layer were unsuitable for targeting secnidazole release to colon region. Combination of chitosan with guar gum or xanthan gum exhibited control over secnidazole release.

Chickpetty and Raga, 2010 used compression coating as one of the strategies for delivering drugs to the colon. The present research work is aimed to develop colon targeted compression-coated delivery systems for diclofenac sodium by using different proportion of guar gum (GG) and locust bean gum (LBG) mixture in the ratio 1:1 in combination with hydroxy propylmethyl cellulose (HPMC) as a coating materials. Effect of proportion of GG-LBG mixture: HPMC ratio on percent of drug release in upper part of gastrointestinal tract and in the colon was studied on developed formulations. It was found that compression-coated formulation released 0 to 6.70 % of diclofenac sodium in the physiological environment of stomach and small intestine. The compression-coated formulation containing GG-LBG mixture: HPMC in the ratios 9:1, 8:2, 7:3, 6:4 and 5:5 released 35.84%, 47.62%, 78.61%, 94.82% and 98.03% of diclofenac sodium respectively in simulated colonic fluid indicating the susceptibility of gum mixture to the rat caecal contents. The results revealed that the tablets compression-coated with GG-LBG mixture and HPMC in the ratio 6:4 is most likely to provide targeting of diclofenac sodium for local action in the colon owing to their minimal drug release in physiological environment of stomach, and small intestine and more than 90% of drug release in the colon. The IR study indicates that the drug is intact in the formulation and no possibility of interaction between the diclofenac sodium and guar gum or locust bean gum or other formulation excipients.

Josephine et al., 2010 formulated colon specific drug delivery system based on a natural polysaccharide; locust bean gum (550, 450, 350 & 250mg) and evaluated by in vitro and in vivo methods. The in vitro studies in pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents showed the cumulative percentage release of Mesalazine after 26h as 33.75% ±0.1988, 46.25% ± 0.9640 and 95.75 % ± 0.1013 respectively. These studies on the polysaccharide indicated that locust bean gum as a coating material, proved capable of protecting the core tablet containing Mesalazine under conditions mimicking mouth to
colon transit. This study clearly established that locust bean gum in the form of compression coat is a potential carrier for drug targeting to the colon.

Chikkanna and Mayasandra, 2010 studied the effect of formulation variables on the release properties of timed-release press-coated tablets using the Taguchi method of experimental design. Formulations were prepared based on Taguchi orthogonal array design with different types of hydrophilic polymers (X1), varying hydrophilic polymer/ethyl cellulose ratio (X2), and addition of magnesium stearate (X3) as independent variables. The design was quantitatively evaluated by best fit mathematical model. The results from the statistical analysis revealed that factor X1, X3 and interaction factors between X1X2 and X1X3 were found to be significant on the response lag time (Y1), whereas only factor X1 was found to be significant on the response percent drug release at 8 hrs (Y2). A numerical optimization technique by desirability function was used to optimize the response variables, each having a different target. Based on the results of optimization study, HPC was identified as the most suitable hydrophilic polymer and incorporation of hydrophobic agent magnesium stearate, could significantly improve the lag time of the timed-release press-coated tablet.

Prabhakara et al., 2010 investigated the colon specificity of novel natural polymer khaya gum and compare with guar gum. Release profile of tablets was carried out in presence and absence of rat cecal contents. The fast disintegrating core tablets of budesonide, were initially prepared by direct compression technique. Later, these tablets were coated with khaya gum or guar gum. After suitable pre compression and post compression evaluation, these tablets were further coated using Eudragit L-100 by dip coating technique. X-ray images were taken to investigate the movement, location and the integrity of the tablets in different parts of gastro intestinal tract in rabbits. The release profiles revealed that khaya gum or guar gum, when used as compression coating, protected the drug from being released in the upper parts of the gastro intestinal tract to some extent but the enteric coated formulations completely protected the drug from being released in the upper parts of the gastro intestinal tract, and released the drug in the colon by bacterial degradation of gums. It was found that both the polysaccharide polymers exhibited different release profiles in presence and absence of rat cecal contents. However, further enteric coat
helped in targeting the drug to colon very effectively. Better dissolution models revealed the colon specificity of polysaccharides and alone can not be used either for targeting the drug to the colon or for sustaining or controlling the release of drug.

Ilango et al., 2010 Colon targeted tablet formulation was developed using okra polysaccharide (*Abelmuschus esculentus*) as a microbially triggered material and also as the carrier. Okra polysaccharide was isolated from *Abelmuschus esculentus* and used for tablet formulation with Ibuprofen as model drug. The matrix tablets with four different proportions of the okra (20%, 30%, 40% & 50%) with 1% ethylcellulose in all the four formulations and the formulations were coded as WO1, WO2, WO3, & WO4. In all the formulations constant 100 mg Ibuprofen were incorporated. The formulations were evaluated for their hardness, weight variation, friability, and drug content and were characterized by FTIR. Matrix tablets were subjected to *in vitro* drug release studies. The release studies were carried out for 2 hours in pH 1.2, 3 hours in pH 7.4 phosphate buffer and for 10 hours in pH 6.8 PBS. The % Release of these formulations i.e. WO1, WO2, WO3 & WO4 were found to be 20.75, 18.48, 13.37 & 11.99 respectively at 5th hour. The fifth matrix tablet (WO5) with 10% ethyl cellulose, 40% okra polysaccharide and 100 mg ibuprofen was formulated. The % cumulative release of this formulation (WO5) was found to be 4.59 at 5th hour. Among the above, WO3 was chosen as the optimized formulation for further studies. The *in vitro* dissolution studies were carried out with pH 1.2, pH 7.4 and the study continued in pH 6.8 PBS with rat cecal matter at 6th hour in simulated colonic fluid in order to mimic conditions from mouth to colon. The post five hour studies were carried out without rat cecal also as a control. The observation made was that the maximum release was 98.09% at 10th hour with rat cecal matter and a mere 32.70 % and 46.98% without rat cecal matter at 8th and 10th hour respectively. These findings were confirmed by *in vivo* investigation using X-ray images of rabbits ingested with okra matrix tablets (WO5) containing barium sulphate as contrast medium instead of Ibuprofen. The tablet began to disintegrate at 8th hour of tablet ingestion. These observations drive us to conclude that the okra polysaccharide under investigation has the potential to carry the drug almost intact to the intended site i.e. Colon where it undergoes degradation due to the presence of anaerobic microbes there. Thereby both the aims contemplated are achieved.
Prajapati et al., 2010 evaluated statical influence of different concentration of HPMC K4M and ethyl cellulose on Propranolol hydrochloride release compression coated tablet using $3^2$ full factorial design. Tablets were prepared by direct compression technique. Time controlled pulsatile Propranolol hydrochloride tablets containing 40 mg of Propranolol hydrochloride were developed using different ratio of hydroxypropyl methylcellulose and ethyl cellulose that retard the drug release in the physiological environment of stomach and 2-3 hr in intestine. Formulation was optimized on basis of acceptable tablet properties and *in vitro* drug release. To analyse the release mechanism of optimize batch zero order, first order, Higuchi, Hixson Crowell, Korsmeyer–Peppas kinetic model were used. The kinetics release of optimize batch F3 was best explained by zero order model, Hixson Crowell, and Korsmeyer–Peppas kinetic model.

Swati et al., 2010 investigated the in-vitro performance of compress coated tablet of Atenolol. A novel colon targeted tablet formulation was developed by press coating rapidly disintegrating tablet of Atenolol with guar gum and Eudragit L-100 as barrier layer. The entire device was enteric coated so that variability in gastric emptying time can be overcome and a colon specific release can be achieved. Different ratios of polymers were selected to achieve suitable lag time for the treatment of angina pectoris. In-vitro release studies for prepared tablets were carried out for 2 h in 0.1 N HCL, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid. *In vitro* studies revealed that the tablet coated with guar gum and Eudragit L-100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Programmable pulsatile, colon-specific release has been achieved from tablet of F4 formulation (50:50) which meet demand of chronotherapeutic drug delivery.

Nunthanid et al., 2009 used spray-dried chitosan acetate (CSA) and ethylcellulose (EC) as new compression coats for 5- aminosalicylic acid tablets. Constrained axial or radial swelling of pure CSA and EC/CSA tablets in 0.1 N HCl (stage I), Tris–HCl, pH 6.8 (stage II), and acetate buffer, pH 5.0 (stage III), was investigated. Factors affecting *in vitro* drug release, i.e., % weight ratios of coating polymers, dip speeds of dissolution apparatus or pH of medium or colonic enzyme (b-glucosidase) in stage III, and use of a
super disintegrant in core tablets, were evaluated. Swollen CSA gel dissolved at lower pH and became less soluble at higher pH. The mechanism of swelling was Fickian diffusion fitting well into both Higuchi’s and Korsmeyer–Peppas models. EC:CSA, at 87.5:12.5% weight ratio, provided lag time rendering the tablets to reach stage III (simulated colonic fluid of patients), and the drug was released over 90% within 12 h. The system was a dual time- and pH-control due to the insolubility of EC suppressing water diffusion and the swelling of CSA in the stages I and II. The erosion of CSA gel in the stage III induced the disintegration of the coat resulting in rapid drug release. The lower dip speed and higher pH medium delayed the drug release, while a super disintegrant in the cores enhanced the drug release and no enzyme effect was observed.

Janugade et al., 2009 prepared oral press-coated tablet by using direct compression and wet granulation methods to achieve the predetermined lag time. This press-coated tablet containing montelukast sodium in the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer ethylcellulose and hydrophilic polymer low-substituted hydroxypropylcellulose. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. It was observed that lag time decreases with increasing concentration of low-substituted hydroxypropylcellulose. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time.

Mayur et al., 2009 developed a time and pH-dependent system for colon specific drug delivery of mesalamine. The colon specific drug delivery system (CDDS) is designed such that the inner most part consists of a core tablet of mesalamine which is then compression coated with a pH-independent hydrophilic polymer (Hydropropylmethyl cellulose). This is then coated with a pH-dependent methacrylic acid copolymer (Eudragit® S100). The concentration (coating level) of Eudragit® S100 was optimized to provide an enteric coat that allows the tablet to pass intact through the stomach and is targeted to the colon. The coating thickness and grades of HPMC were optimized to set a desired lag time in the intestine. From the in vitro evaluation it can revealed that the developed CDDS can exhibit site-specific drug targeting to the colon.
Bhosale et al., 2009 achieved successful delivery specifically to the colon using guar gum and HPMC K4M as a compression coat over a core tablet of ibuprofen. In this study, Guar gum along with Hydroxypropylmethyl Cellulose (HPMC) was used as a compression-coating polymer. The drug delivery system was based on the gastrointestinal transit time concept, assuming colon arrival time to be 6 h. Rapidly disintegrating core tablets containing 100 mg ibuprofen were compression coated with guar gum and HPMC. A 32 full factorial design was applied for optimization of the formulation. Both variables, coat weight of the tablet (X1) and the proportion of guar gum in polymer blend (X2) and, had an influence on the percent drug release after 6 h of dissolution of tablet in the presence of rat cecal content. The results revealed that for protecting the rapidly disintegrating core of ibuprofen in the physiological conditions of stomach and upper intestine, the core tablet should be coated with 60% of guar gum in coat formulation and at 225 mg coat weight. The proportion of guar gum exhibited predominant action as compared to coat weight. The guar gum–HPMC coating was found to be a promising drug delivery system for colon targeting.

Soad et al., 2009 formulated budesonide (BUD) compression-coated tablets for colonic specific delivery. Pectin and guar gum were used as enzyme-dependent polymers. For comparison purposes, both pH- and time-dependent polymers were also tried. In vitro release studies were carried out at different pH (1.2, 6.8, and 7.4). Therapeutic efficacy of the prepared tablets compared to commercially available capsules and enema were evaluated in trinitrobenzenesulfonic acid-induced rabbit colitis model. In pH-dependent polymers, Eudragit (EUD) S100/EUD L100 (1:1) released 45.58% in the target area (colon). For time-dependent polymers, decreasing cellulose acetate butyrate (CAB) ratio increased the release in both pH 6.8 and 7.4 till it reached 40.58% and 93.65%, respectively, for 25% CAB. In enzyme-dependent polymers, increasing pectin ratio to 75% retarded the release (4.59% in pH 6.8 and 54.45% in pH 7.4) which was significantly enhanced to 99.31% using pectinolytic enzyme. Formula F14 coated with 75% pectin significantly reduced the inflammatory cells in the connective tissue core of the colon of the treated group and significantly decreased myeloperoxidase activity (3.90
U/g tissue weight). This study proved that BUD compression-coated with 75% pectin may be beneficial in the treatment of inflammatory bowel disease.

Ashish et al., 2009 developed press coated tablet for pulsatile drug delivery of ketoprofen using hydrophilic and hydrophobic polymers. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of rheumatoid arthritis. The press coated tablets containing ketoprofen in the inner core was formulated with an outer shell by different weight ratio of hydrophobic polymer (micronized ethyl cellulose powder) and hydrophilic polymers (glycinemax husk or sodium alginate). The release profile of press coated tablet exhibited a lag time followed by burst release, in which outer shell ruptured into two halves. Authors also investigated factors influencing on lag time such as particle size and viscosity of ethyl cellulose, outer coating weight and paddle rpm. The surface morphology of the tablet was examined by a scanning electron microscopy. Differential scanning calorimeter and Fourier transformed infrared spectroscopy study showed compatibility between ketoprofen and coating material.

Timucin et al., 2007 prepared compression coated tablets of nisin were prepared containing pectin/HPMC for colonic delivery for treating colonic infectious diseases such as by Clostridium difficile. In this study, each 100 mg core tablet of nisin was compression coated with 100% pectin, 90% pectin–10% HPMC, 85% pectin–15% HPMC, 80% pectin–20% HPMC, 75% pectin–25% HPMC, 100% HPMC at a coat weight of 400 mg. The concentration and the biological activity of nisin were quantified using Well Diffusion Agar Assay. Drug release studies were carried out in pH 3.3 buffer solution. System degradation/erosion experiments were carried out in pH 1.2, 3.3, and 6.8 buffers using a pectinolytic enzyme. It was found that pectin alone was not sufficient to protect the nisin containing core tablets. At the end of the 6 h 40% degradation was observed for 100% pectin tablets. HPMC addition required to control the solubility of pectin, a 5% increase in HPMC ratio in pectin/HPMC mixture provided a 2-h lag time for nisin release. Eighty percent pectin–20% HPMC appeared to be an optimum combination for further evaluation. Tablets maintained their integrity during the 6-h dissolution test, approximating the colon arrival times.
Nasra et al., 2007 developed compression coated tablets of metronidazole to reach the colon intact has been investigated in vitro, using pectin as a carrier. Rapidly disintegrating metronidazole core tablets were prepared and compression coated with pectin. The effect of the coat:core ratio as well as the incorporation of different percentages of chitosan in the pectin coat on drug release was investigated. In vitro release studies indicated that compression coated formulations were able to protect the tablet cores from premature drug release, but at high pectin coat: core ratios 4: 1 (F13) and 5: 1 (F14). Inclusion of chitosan 3% and 5% w/w (F12) in the pectin coat offered better protection at a lower coat: core ratio (3: 1). When the dissolution study was continued in pH 6.8 PBS containing 1.5% w/v rat caecal contents, compression coated tablet formulations F13, F14 and F12 released about 70.25% ± 9.9%, 51.3% ± 5.45% and 20% ± 5.01% drug respectively at the end of 24 hours.

Carla et al., 2007 produced a quick/slow biphasic delivery system for ibuprofen. A dual component tablet made of a sustained release tableted core and an immediate release tableted coat was prepared by direct compression. Both the core and the coat contained a model drug (ibuprofen). The sustained release effect was achieved with a polymer (hydroxypropyl methylcellulose (HPMC or ethylcellulose) to modulate the release of the drug. The in vitro drug release profile from these tablets showed the desired biphasic release behavior: the ibuprofen contained in the fast releasing component was dissolved within 2 minutes, whereas the drug in the core tablet was released at different times (≈16 or > 24 hours), depending on the composition of the matrix tablet. Based on the release kinetic parameters calculated, it can be concluded that the HPMC core was suitable for providing a constant and controlled release (zero order) for a long period of time.

Howard et al., 2007 investigate the in-vitro and in-vivo performance of a press-coated tablet (PCT) intended for time delayed drug release, consisting of a rapidly disintegrating theophylline core tablet, press-coated with barrier granules containing glycercyl behenate (GB) and low-substituted hydroxypropylcellulose (L-HPC). The PCTs showed pulsatile release with a lag time dependent upon the GB and L-HPC composition of the barrier layer. In-vivo γ-scintigraphic studies were carried out for PCTs containing GB:L-HPC at 65:35 w/w and 75:25 w/w in the barrier layer in four beagle dogs, in either the fed or...
fasted state. The in-vivo lag time in both the fed and fasted states did not differ significantly ($p > 0.05$) from the in-vitro lag time. Additionally, no significant difference ($p < 0.05$) between invivo fed and fasted disintegration times was observed, demonstrating that in-vivo performance of the PCT was not influenced by the presence or absence of food in the gastrointestinal tract. A distinct lag time was obtained prior to the appearance of drug in plasma and correlated ($R^2 = 0.98$) with disintegration time observed from scintigraphic images. However, following disintegration, no difference in pharmacokinetic parameters ($\text{AUC}_{0-6 \text{ dis}}$, $K_{el}$, $C_{max}$) was observed. The current study highlighted the potential use of these formulations for chronopharmaceutical drug delivery.

Vijaya et al., 2007 used the inexpensive, nontoxic naturally available flax seed polymer and chitosan combination as colonspecific drug carriers and to study the influence of chitosan on the release characteristics of the formulation. Core tablets of mesalazine were prepared by wet granulation with starch paste and were compression coated with coating formulations containing different weight ratios of flax seed polymer and chitosan 2:3, 3:2 and 4:1. The tablets were subjected to invitro drug release studies in simulated colonic fluids (4% w/v of rat cecal contents). The invitro studies in pH 6.8 phosphate buffer containing 4% w/v rat cecal contents showed that the cumulative percentage of mesalazine after 26 h were 52.16±0.06, 64.10±0.08 and 98.00±0.19 (mean ±s.d) respectively for tablets containing different weight ratios of flax seed polymer and chitosan 2:3, 3:2 and 4:1. The invivo studies conducted in six healthy male human volunteers for the various formulations revealed that the drug released was initiated only after 5h transit time of small intestine and the bioavailability (AUC 0-t*) of the drug was found to be 196.97±3.02, 245.8±5.10 and 910.51±9.61 (mean ± s.d) respectively for tablets containing different weight ratios of flax seed polymer and chitosan 2:3, 3:2 and 4:1. The results of study indicates that compression coated tablets containing 4:1 ratio of flax seed polymer and chitosan held a better dissolution profile higher bioavailability and hence a potential carrier for drug targeting to colon.
Shivakumar et al., 2006 formulated oral controlled onset system of meloxicam that match chronobiology. The multiparticulate system comprising of drug loaded non pareil seed coated with Eudragit S-100 by powder layering technique in a conventional coating pan. *In vitro* dissolution studies of the coated pellets shows that pellet with lower coat weight (>10%) controlled the drug release below 6 pH but fail to controlled the release at higher pH 7 followed by rapid release. Since meloxicam is a drug which exhibits a pH dependent solubility, a coating weight of 12% weight gain was sufficient to minimized the effectively target the drug to the colon.

Ying and Liangyuan, 2005 developed rheophylline pulsatile release tablets consisting of a fast-swelling core with a water-insoluble ethylcellulose. Effects of coating material, the amount of the plasticizer, subcoating, the type of the disintegrant, and coating level on the release profiles were investigated. Results showed that ethylcellulose was the best candidate polymer for pulsatile release tablets. Rupture time increased with increasing the amount of the plasticizer, but 15% plasticizer provided the best release profiles. The lag time of tablets containing different disintegrants increased in the following order: croscarmellose (Ac-Di-Sol®) < sodium starch glycolate (Explotab®) < low-substituted hydroxypropyl cellulose (L-HPC) < crospovidone (Kollidon® CL) and the rupture time increased with higher coating level.

Yuan et al., 2005 chemically modified HPMC (Hydroxypropyl methylcellulose) using maleic anhydrides, to obtain pH-sensitive HPMCAM (Hydroxypropyl methylcellulose acetate maleate) polymers for use as novel duodenum-specific coating agents. The pharmaceutical properties of HPMCAM, such as film forming, acid values, pH-sensitive values, water vapor permeability, tensile strength and Tg, were investigated, and found to show good film forming properties. The pH sensitive values were 3.0 to 3.7. Core tablets containing berberine chloride (BER·HCL) were press coated with pH-sensitive HPMCAM (Hydroxypropyl methylcellulose acetate maleate). *In vitro* results demonstrate that HPMCAM could completely suppress drug release within 2h in a simulated gastric fluid (pH 1.2) and rapidly release the drug in a simulated pathological duodenal fluid (pH
3.4). These results indicate that HPMCAM might be a useful material for a duodenum-specific drug delivery system.

VR Sinha et al., 2005 evaluate a formulation with a considerably reduced coat weight and gum concentration for colonic drug delivery in vivo using gamma scintigraphy. In vitro studies have found this formulation to be useful for delivery of 5-fluorouracil to the colon. Rapidly disintegrating core tablets containing 99mTc-DTPA were prepared and compression coating with 150 mg of granules containing a mixture of xanthan (XG), guar gum (GG) and starch. The ratios of the two gums XG:GG in the coat was kept 10:20. In vitro dissolution studies on XG:GG::10:20 tablets containing 99mTc-DTPA were carried out in simulated upper GIT conditions and also in presence of colonic contents. Cumulative percent release of technetium in the upper GIT conditions and transit time amounted to 4%. The total amount of technetium released in the 24 h of the dissolution study was 53±3.23%. Upon introduction of cecal content into the dissolution medium (4%), the release of technetium from the compression-coated tablet increased to 78.34±5.34%. Gamma scintigraphy studies carried out in six healthy human volunteers showed that the tablet remained intact during its transit through the upper GIT. The anatomical site of disintegration was found to be the ascending colon/hepatic flexure and the disintegration of the tablet started between 4 and 6 h post-dose in all the volunteers with a further spread of tracer into the ascending, transverse, descending and sigmoidal colon.

Raimar et al., 2005 performed clinical studies and shown that circadian patterns influence the pharmacokinetics of certain drugs used in the treatment of different diseases. For such drugs, the bioavailability is influenced by the time of administration. The objective of this study was to investigate differences in the pharmacokinetic patterns between a pulsatile drug delivery system using a pulsatile capsule, an immediate release tablet and a controlled release tablet. Metoprolol was chosen as a model drug and the dosage forms were administered to four dogs and the plasma levels were measured using LC-MS/MS. Pharmacokinetic parameters were determined for each dosage form. Fluctuations in the plasma time curves over the observation period indicated that physiological factors like motility have an influence on the drug absorption. The comparison of the plasma time
curves of the dosage forms showed that each dosage form caused significant differences in the drug plasma levels. The pulsatile drug delivery capsule caused two defined Cmax values for each dose between 1–1.75 and 2.5–3.5 h. Implications for the use of a pulsatile drug delivery device for chronopharmacotherapy are discussed. Pulsatile drug delivery offers a promising way for chronopharmacotherapy if the time of administration and pulse time are adjusted to the circadian pattern.

Gang et al., 2004 investigated Time- and pH-dependent colon-specific drug delivery systems (CDDDS) for orally administered diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA), respectively. DS tablets and 5-ASA pellets were coated by ethylcellulose (EC) and methacrylic acid copolymers (Eudragit® L100 and S100), respectively. The in vitro release behavior of the DS coated tablets and 5-ASA coated pellets were examined in dogs. Two types of CDDDS, prepared herein by means of the regular coating technique, are able to achieve site-specific drug delivery targeting at colon following oral administration, and provide a promising strategy to control drug release targeting the desired lower gastrointestinal region.

Puttipipatkhachorn et al., 2004 formulated a tablet system consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing buflomedil HCl as model drug were prepared by direct compression of different ratios of spray-dried lactose and microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing a superdisintegrant (croscarmellose sodium) and an outer rupturable layer of ethylcellulose. The effect of core composition, level of swelling layer and rupturable coating, and magnesium stearate in rupturable layer was investigated. The lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the cores and increased with increasing levels of both swelling layer and rupturable ethylcellulose coating. Addition of magnesium stearate to the ethylcellulose coating lowered the mechanical strength of the film and improved the robustness of the system.

Shan et al., 2004a designed dry-coated tablet with optimal lag time to simulate the dosing time of drug administration according to the physiological needs. The formulations
Ph.D Thesis
Review of Literature

containing different weight ratios of coarse/fine particles of EC powders or 167.5 µm EC powder/excipients in the upper layer of the outer shell to influence the release behavior of diclofenac sodium from dry-coated tablet were also explored. The results indicate that diclofenac sodium released from all the dry-coated tablets exhibited an initial lag period, followed by a stage of rapid drug release. Its lag time might be freely modulated, depending on the amount of EC powder added. Once different excipients were respectively incorporated into the upper layer of the outer shell, different release mechanisms were observed as follows: time-controlled explosion for Explotab, disruption for Avicel and spray-dried lactose, erosion for dibasic calcium phosphate anhydrate, and sigmoidal profile for hydroxypropyl methylcellulose.

Shan et al., 2004b formulated press-coated tablet containing sodium diclofenac in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of micronized ethylcellulose (EC) powder and hydrophilic excipients such as spray-dried lactose (SDL) or hydroxypropyl methylcellulose (HPMC). The release profile of the press-coated tablet exhibited a time period without drug release (time lag) followed by a rapid and complete release phase, in which the outer shell ruptured or broke into 2 halves. The lag phase was markedly dependent on the weight ratios of EC/SDL or EC/HPMC in the outer shell.

Yuichi et al., 2004 invented a novel one-step dry-coated tablets (OSDRC) manufacturing method to develop delayed-release tablets. The manufacturing method for OSDRC is different from conventional methods in that dry-coated tablets can be made with only one process. One of the major advantages of OSDRC is that we can expect to produce tablets, which always contain the core exactly in the center of the whole tablet. This characteristic means that the thickness of outer layer is constantly uniform, which is difficult to achieve with the conventional dry-coated tablets. The effects of different outer layer thicknesses and various compression pressures were examined using HPMC to evaluate OSDRC applicability to delayed-release tablets. They proved that the lag-time can be adjusted only by changing the thickness of the outer layer without any arrangement of its ingredients, which is quite different from the conventional approach. Further, the lag-time of each OSDRC prepared in the 100–200 MPa compression
pressure range was almost the same, indicating the lag-time of OSDRC under these compression pressures does not vary. The release rate of the drug (acetaminophen) from the OSDRC with 0.5 and 1.0 mm outer layer thicknesses was almost constant independent of compression pressure. In conclusion, OSDRC could be a platform for delayed-release tablets, which do not utilize the conventional method used for dry-coated tablets.

VR Sinha et al., 2004 designed a compression coated tablet 5-fluorouracil for colonic drug delivery with a considerably reduced coat weight and gum concentration for the treatment of colorectal cancer. Rapidly disintegrating core tablets containing 50 mg of 5-fluorouracil were prepared and compression coating with 175 mg of granules containing a mixture of xanthan gum (XG) and guar gum (GG) in varying proportions was done. With this coat weight, a highly retarded drug release was observed. At the end of 24 h of dissolution the amount of drug released increased to 25 ± 1.22%, 36.6 ± 1.89% and 42.6 ± 2.22%, respectively in XG:GG 20:20, 20:10 and 10:20 tablets. Studies of XG:GG (10:20) tablets in presence of colonic contents showed an increased cumulative percent drug release of 67.2 ± 5.23% in presence of 2% cecal content and 80.34 ± 3.89% in presence of 4% cecal content after 19 h of incubation.

Krishnaiah et al., 2003 compared the guar gum-based colon-targeted tablets of 5-fluorouracil against an immediate release tablet by in vitro dissolution and in vivo pharmacokinetic studies in human volunteers. Twelve healthy volunteers participated in the study. 5-Fluorouracil was administered at a dose of 50 mg both in immediate release tablet and colon-targeted tablet. On oral administration of colon-targeted tablets, 5-fluorouracil started appearing in the plasma at 6 h, and reached the peak concentration ($C_{\text{max}}$ of 216±15 ng/ml) at 7.6±0.1 h ($T_{\text{max}}$), whereas the immediate release tablets produced peak plasma concentration ($C_{\text{max}}$ of 278±21 ng/ml) at 0.6±0.01 h ($T_{\text{max}}$). The AUC for 5-fluorouracil from colon-targeted tablet and immediate release tablet were found to be 617±39 and 205±21 ng/ml/h, respectively. Colon-targeted tablets showed delayed $t_{\text{max}}$, delayed absorption time ($t_a$), decreased $C_{\text{max}}$ and decreased absorption rate constant when compared to the immediate release tablets. The results of the study indicated that the guar gum-based colon-targeted formulation did not release the drug in
stomach and small intestine, but delivered it to the colon resulting in a slow absorption of the drug and making it available for local action in colon.

Krishnaiah et al., 2003 performed the pharmacokinetic evaluation of guar gum-based colon-targeted tablets of mebendazole against an immediate release tablet was carried out in human volunteers. Six healthy volunteers participated in the study and a crossover design was followed. Mebendazole was administered at a dose of 50 mg both in immediate release tablet and colon-targeted tablets. On oral administration of colon-targeted tablets, mebendazole started appearing in the plasma at 5 h, and reached the peak concentration \( (C_{\text{max}} \text{ of } 25.7\pm2.6 \text{ ng/ml}) \) at \( 9.4 \pm 1.7 \text{ h (} T_{\text{max}} \text{) whereas, the immediate release tablets produced peak plasma concentration (} C_{\text{max}} \text{ of } 37.2 \pm 6.8 \text{ ng/ml}) \) at \( 3.4\pm0.9 \text{ h (} T_{\text{max}} \text{). Colon-targeted tablets showed delayed } t_{\text{max}} \text{ and absorption time, and decreased } C_{\text{max}} \text{ and absorption rate constant when compared to the immediate release tablets. The results of the study indicated that the guar gum-based colon-targeted tablets of mebendazole did not release the drug in stomach and small intestine, but delivered the drug to the colon resulting in a slow absorption of the drug and making the drug available for local action in the colon.}

Kenneth and Michael, 2003 developed a novel adhesive coating that allows even small quantities of immediate-release (IR) powders to be press-coated onto controlled-release (CR), coated dosage forms without damaging the CR coating. The process was exemplified using a pseudoephedrine osmotic tablet (asymmetric membrane technology, AMT) where a powder weighing less than 25% of the core was pressed onto the osmotic tablet providing a final combination tablet with low friability. The dosage form with the adhesive plus the press-coated powder showed comparable sustained drug release rates to the untreated dosage form after an initial 2-h lag. The adhesive layer consisted of an approximately 100-mm coating of Eudragit RL, polyethylene glycol (PEG) and triethyl citrate (TEC) at a ratio of 5:3:1.2. This coating provides a practical balance between handleability before press-coating and good adhesion.

Bodmeier et al., 2003 investigated the swelling characteristics of various swellable polymers in swelling layers that induce the rupturing of an outer polymer coating in
pulsatile drug delivery systems (DDS). An apparatus was designed to measure simultaneously the swelling and water uptake of swellable polymers. The swelling of several excipients decreased in the following order: croscarmellose sodium > low-substituted hydroxypropyl cellulose > sodium starch glycolate > crospovidone > hydroxypropyl methylcellulose. The swelling behavior and the rupture of the outer polymeric coating of a pulsatile DDS were evaluated.

Vivek and Rachna, 2003 made comparison of the usual enteric coating polymers viz. Eudragit, a cellulose acetate phthalate with shellac and ethyl cellulose, as carriers for colon specific drug delivery. Lactose based indomethacin tablets were prepared. These were coated with one of the coating polymers to a varying coat thickness. The coated formulations were evaluated for dissolution rates under simulated stomach and small intestine conditions. From the dissolution data obtained, it was found that the dissolution rate varied with the type and concentration of the polymer applied. Comparative dissolution data revealed that, of all the various polymers and coat thicknesses used, a 3% (m/m) coat of shellac was most suitable for colonic drug delivery. It retarded drug release by 3–4 h (the usual small intestinal transit time) in simulated small intestinal fluid, where after a rapid drug release was observed.

Toyohio et al., 2003 made time-release formulation to avoid drug–drug interaction between Diltiazem and midazolam. They made core tablet of Diltiazem and compress coated it with PEG-6000 and PEO with midazolam in compress coating layer. They studied in vitro and in vivo study. They found that metabolism between Diltiazem and midazolam can be reduced by time interval between absorption of both drugs.

Durig et al., 2002 evaluated a new grade of ethylcellulose, Aqualon® T10 (T10 EC), for compression coating of time-controlled dosage forms. Core tablets are made by theoylline as drug and other excipients like diluent, disintegrant. Core tablets are compression coated with different grade of ethyl cellulose. Based on the results, they found that the new grade of ethylcellulose, Aqualon T10 Pharm EC improved compactibility, exhibits excellent flowability, and provides superior lag time control by virtue of its molecular structure (high ethoxyl content and low molecular weight).
Hyun et al., 2002 formulated coated system that is resistant to gastric and small intestinal conditions but can be easily degraded by colonic bacterial enzymes was designed to achieve effective colon delivery of prednisolone. Various coated tablets containing prednisolone were fabricated using chitosan and cellulose acetate phthalate (CAP) as coating materials. Release aspects of prednisolone in simulated gastrointestinal fluid and rat colonic extracts were investigated. From these results, a three layer (CAP/Chitosan/CAP) coated system exhibited gastric and small intestinal resistance to the release of prednisolone in vitro most effectively. The rapid increase of prednisolone in rat colonic extracts was revealed as due to the degradation of the chitosan membrane by bacterial enzymes. The designed system could be used potentially for colon delivery of prednisolone by regulating drug release in stomach and the small intestine.

Krishnaiah et al., 2002a developed colon targeted drug delivery systems for metronidazole using guar gum as a carrier. Matrix, multilayer and compression coated tablets of metronidazole containing various proportions of guar gum were prepared. All the formulations were evaluated for the hardness, drug content uniformity, and were subjected to in vitro drug release studies. The amount of metronidazole released from tablets at different time intervals was estimated by high performance liquid chromatography method. Matrix tablets and multilayer tablets of metronidazole released 43–52% and 25–44% of the metronidazole, respectively, in the physiological environment of stomach and small intestine depending on the proportion of guar gum used in the formulation. Both the formulations failed to control the drug release within 5 h of the dissolution study in the physiological environment of stomach and small intestine. The compression coated formulations released less than 1% of metronidazole in the physiological environment of stomach and small intestine. When the dissolution study was continued in simulated colonic fluids, the compression coated tablet with 275 mg of guar gum coat released another 61% of metronidazole after degradation by colonic bacteria at the end of 24 h of the dissolution study. The compression coated tablets with 350 and 435 mg of guar gum coat released about 45 and 20% of metronidazole, respectively, in simulated colonic fluids indicating the susceptibility of the guar gum formulations to the rat caecal contents. The results of the study show that compression
coated metronidazole tablets with either 275 or 350 mg of guar gum coat is most likely to provide targeting of metronidazole for local action in the colon owing to its minimal release of the drug in the first 5 h. The metronidazole compression coated tablets showed no change either in physical appearance, drug content or in dissolution pattern after storage at 40 °C/75% RH for 6 months.

Krishnaiah et al., 2002b developed novel tablet formulations for site-specific delivery of 5-fluorouracil to the colon without the drug being released in the stomach or small intestine using guar gum as a carrier. Fast-disintegrating 5-fluorouracil core tablets were compression coated with 60% (FHV-60), 70% (FHV-70) and 80% (FHV-80) of guar gum, and were subjected to in vitro drug release studies. Guar gum compression-coated tablets released only 2.5–4% of the 5-fluorouracil in simulated GI fluids. When the dissolution study was continued in simulated colonic fluids (4% w/v rat caecal content medium) the compression-coated FHV-60, FHV-70 and FHV-80 tablets released another 70, 55 and 41% of the 5-fluorouracil respectively. The results of the study show that compression-coated tablets containing 80% (FHV-80) of guar gum are most likely to provide targeting of 5-fluorouracil for local action in the colon, since they released only 2.38% of the drug in the physiological environment of the stomach and small intestine.

Murat and Timucin, 2002 prepared pectin–HPMC compression coated core tablets of 5-aminosalicylic acid (5-ASA) for colonic delivery. Each 100 mg core tablet contained 5-ASA and was compression coated at 20 kN or 30 kN using 100% pectin, 80% pectin–20% HPMC, or 60% pectin–40% HPMC, at two different coat weights as 400 or 500 mg. Drug dissolution/system erosion/degradation studies were carried out in pH 1.2 and 6.8 buffers using a pectinolytic enzyme. The system was designed based on the gastrointestinal transit time concept, under the assumption of colon arrival times of 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the solubility of pectin. The optimum HPMC concentration was 20% and such system would protect the cores up to 6 h that corresponded to 25–35% erosion and after that under the influence of pectinase the system would degrade faster and delivering 5-ASA to the colon. The pectin–HPMC
envelope was found to be a promising drug delivery system for those drugs to be delivered to the colon.

Eiji et al., 2001 evaluate the effect of magnesium stearate (MgSt) or calcium stearate (CaSt) on the dissolution profiles of diltiazem hydrochloride in the core of press-coated (PC) tablets with an outer shell composed of hydroxypropylmethylcellulose acetate succinate (HPMCAS). In JP first fluid (pH 1.2), the lag time increased with decreasing porosity and was greatest by the addition of MgSt to HPMCAS. While, in JP second fluid (pH 6.8), it increased with decreasing porosity by the addition of CaSt, but hardly changed by the addition of MgSt. Thus, using tablets prepared with the same composition as the outer shell, the changes in IR spectra and uptake amount of the dissolution media after immersion in first fluid and second fluid were determined. The results suggested that some physicochemical interaction occur between MgSt and HPMCAS in tablets with HPMCAS and MgSt and the uptake increased markedly in each dissolution medium. These phenomena seem to cause a prolongation of lag time in first fluid but a shortening of it in second fluid in PC tablets with HPMCAS and MgSt. In contrast, CaSt and HPMCAS did not show such interactions and increased the hydrophobic properties of the outer shell. Consequently, the lag time was only slightly prolonged in first fluid, however, markedly prolonged in second fluid due to suppression of second fluid penetration into micro pores in the outer shell and HPMCAS gelvformation on the surface in PC tablets with HPMCAS and CaSt.

Madhusudan et al., 2001 made novel compression coated tablet dosage form using theohylline drug. Special punch for compression coating tablet made. Cup shape compression coating layer made and put drug tablet in it and add other half of coating material. The compression coated tablet process provides a means of compression coating by simple modifications to a three layer. The core is not required to be compactable nor is adhesion between core and coating a prerequisite.

Yassin et al., 2001 prepared three colon drug delivery systems of metronidazole (MD) for effective treatment of a number of colon diseases such as pseudomembranous colitis, clostridium difficil diarrhea, ulcerative colitis, and Crohn's disease to selectively deliver
MD to the colon, which can enhance its therapeutic efficacy and reduce its adverse effects. Two of them were prepared by coating MD tablets with either Eudragit S100 or Eudragit RS 100 using film coating technique. The third was prepared by coating MD tablets with pectin USP using compression coating technique. Different coat thicknesses were prepared from each polymer. In-vitro drug release evaluation was achieved by studying the dissolution profile of MD from the coated tablets in conditions mimicking mouth-to-colon transit using USP dissolution tester. The susceptibility of pectin coats to degradation by colon bacterial enzymes was tested by monitoring MD release in phosphate buffer saline containing rat caecal contents. Both Eudragit S 100 and Eudragit RS 100 failed to give complete protection to MD tablets. Partial protection was achieved for both polymers only at high coat thicknesses. Pectin coated tablets with coat weight 350 mg/tablet gave almost complete protection indicated by negligible release after 5 hours dissolution testing. Thinner coats of pectin showed partial protection and direct proportionality between the coat thickness and release rate. 100% release of MD was observed after 9 hours incubation with rat caecal contents indicating susceptibility of pectin to degradation by colon bacterial enzymes. The in-vitro results indicate the superiority of pectin system over both the Eudragit systems in delivering drugs selectively to the colon.

Douglas and Karen, 1999 found that the drug release rates were significantly influenced by the ethylcellulose polymer level, its particle size and to a lesser degree, its viscosity grade. A micronized version of ETHOCEL ethylcellulose, ETHOCEL FP, has been shown to be much more effective than its granular counterpart in the controlled release applications. A recent study has addressed the effect of the particle size of the polymeric film former on the functionality of a compression coating in a model controlled release tablet. Compression coated tablet of Tramadol HCl were prepared using ETHOCEL Standard 10FP Premium, ETHOCEL Standard 100FP Premium, ETHOCEL Standard 10 Premium as a coating polymer. The average particle sizes of the 3 grades of ethylcellulose were 5 microns (10FP), 40 microns (100FP) and 250 microns (10G). It was found that as the particle size of the polymer decreased, the release rate slowed (% dissolved/time) and the lag times increased. This suggests that the smaller particle size polymer flows and consolidates more efficiently during the compression process,
resulting in a coating with a lower degree of porosity. When developing a controlled release dosage form with compression coatings, it has been well demonstrated that the physicochemical properties of added film formers can be chosen to yield the desired release profile.

Krishnaiah et al., 1998 studied suitability of polysaccharide, guar gum, to develop colon-specific drug delivery systems of indomethacin by compression coating technique. In vitro release studies in pH 6.8 phosphate buffered saline (PBS) containing 4% w/v rat caecal contents haven demonstrated the susceptibility of guar gum to the colonic bacterial enzyme action with consequent drug release. Gamma-scintigraphic studies in human volunteers with technetium-99m-DTPA as a tracer in sodium chloride core tablets compression coated with guar gum have shown that the gum coat protect the drug (tracer in the present study) from being released in the stomach and small intestine. On entering the ascending colon, the tablets commenced to release the tracer indicating the breakdown of the gum coat by the enzymatic action of colonic bacteria. The study clearly established that guar gum, in the form of compression coat, is a potential carrier for drug targeting to colon.

Brian et al., 1998 used Nuclear magnetic resonance (NMR) imaging in the optimization of a compression-coated regulated release system. Core containing ranitidine hydrochloride was compression coated with a granulated mixture of Eudragit RSPO (520 g), Eudragit S-100 (138 g), triethyl citrate (35 g) and magnesium stearate (7 g). nother portion of the cores was coated with a dry blend of ethyl cellulose (74.5%, w/w), Emdex (24.5%, w/w) and magnesium stearate (1%, w/w). Nuclear magnetic resonance (NMR) imaging is routinely used to detect the protons of mobile water molecules within samples. In this investigation, this non-destructive, non-invasive technique was used to determine the cause for faster than predicted drug release from a dissolution-based regulated-release tablet. The NMR images of tablets, from two different formulations, taken at various intervals of time while immersed in static USP dissolution medium showed that the tablet with faster than predicted drug release had a porous coating. The porous coat of ethyl cellulose exposed more of the core surface area to the dissolution medium than desired and this caused an increase in the rate of dissolution of the core. The data presented in
this paper demonstrate the usefulness of NMR imaging in solid dosage form development.

Iskandar and Louis, 1997 used cross-linked amylose (CLA), a hydrophilic polymer, to design dry-coated tablets for time-independent. To make the cores, CLA was mixed with the model drug in different proportions and then compressed. The cores were coated manually, consisting of either pure CLA or a mixture of CLA with a small proportion of solute. Diltiazem HCl and acetaminophen were the model drugs used. CLA dry-coated tablets behave as reservoir systems where the outer gel layer acts as a solution-diffusion membrane, through which transport occurs by a process of dissolution of the permeating drug in the polymer at one interface and diffusion down a gradient in thermodynamic activity. After the drug has established a uniform concentration gradient within the outer membrane (lag time), drug release is linear for the range of constant thermodynamic activity in the core. For the same core composition, decreasing the coating thickness or incorporating small amounts of NaCl in the shell shorten the release lag time and increase the release rate. By varying the drug to CLA ratio in the core we are able to optimize the release profiles. Zero-order release profiles with or without a time delay were developed. Tablets for complex delivery (staircase profile) were also devised.

Mitsuyuki et al., 1996 developed delayed-release tablets containing diltiazem hydrochloride (DIL) using hydroxyethylcellulose (HEC) of three viscosity grades to treating time-related symptoms which need time-controlled or site-specific delivery in the gastrointestinal tract. The tablets consisted of a core containing 30 mg of DIL and an outer shell formed by compressing HEC. DIL in the core was rapidly released from the tablets after a lag time and lag time was more prolonged with an increase in viscosity of HEC. The rate of water-uptake was greater in the CM-L4 type HEC tablet of a low viscosity grade (14 cps) than those in CM-L3 and CM-L2 type HEC (27 and 95 cps, respectively) tablets. There was little difference in lag time to the start of release of DIL from CM-type HEC tablets between JP XII 1st (pH 1.2) and 2nd (pH 6.8) fluids. A human volunteer study was performed using the delayed-release tablets prepared with CM-type HEC of two or three viscosity grades. The $t_{\text{max}}$ and MRT values of HEC tablets were significantly increased with an increase in viscosity of HEC and showed only small
variations between subjects, respectively. On the other hand, although the AUC values were almost the same, the $C_{\text{max}}$ values decreased with prolongation of lag time. These results indicate that the lag time can be optionally controlled by selecting HEC with a proper viscosity and/or by changing the amount of HEC forming the outer shell.

Conte et al., 1993 developed formulation of non-steroidal anti-inflammatory drugs (NSAIDs) and a mucosal protective agent in one tablet. The active substances are formulated in a press-coated tablet in which the inner core contains sodium diclofenac and the outer shell sucralfate. The outer shell composition includes rapidly disintegrating agents for the prompt release of the mucosal protective agent. Diclofenac release from the core starts only when the outer layer has completely disintegrated. *In vitro* release of the anti-inflammatory drug is not influenced by the sucralfate delivery impulse. Preliminary *in vivo* studies confirm that the presence of sucralfate does not prevent diclofenac absorption from the GI tract.

Maggi et al., 1993 utilized press coating technique to reduce most common risk connected with non-steroidal anti-inflammatory drugs (NSAIDs) oral administration is presented by their local irritation effects on the mucosa of the gastro-intestinal tract. To prevent NSAID-induced mucosal lesions and ulcer formation or exacerbation a new dosage form was designed for the administration in sequential pulses of a mucosal protective agent firstly and then NSAID. The active substances are formulated in a press-coated tablet in which the inner core contains sodium diclofenac and the outer shell sucralfate. The shell composition includes rapidly disintegrating agents for the prompt release of the mucosal protective agent sucralfate. Diclofenac release from the core starts only when the outer layer has completely disintegrated. *In vitro* release of the anti-inflammatory drug is not influenced by the sucralfate delivery impulse. Preliminary *in vivo* studies confirm that the presence of sucralfate does not prevent diclofenac absorption from the GI tract.