2. REVIEW OF LITERATURE

Ahmadi F. et. al., (2011) developed oral matrix system using dextran of different molecular weight for delivery of budesonide to the colon. Different batches of tablets were prepared using three different drug to polymer ratios by direct compression method. Various studies like weight variation hardness content uniformity and drug release studies with different pH medium like 1.2 pH, 7.4 pH and 6.8 pH buffers containing 4% rat caecal content were performed. The in vivo studies were performed on rats using acetic acid induced colitis model. The studies showed that only 10% of the drug was released in 1.2 pH and 7.4 pH buffer while maximum amount of drug release taken place in 6.8 pH buffer containing rat caecal contents. The selected formulation showed more effectiveness as compared to non targeted formulation against acetic acid induced colitis. This concluded that the matrix tablet of drug with dextran can be used for the treatment of ulcerative colitis.(18)

Varshosaz J. et. al., (2011) formulated the conjugate system of budesonide with dextran of different molecular weights using glutarate as spacer. The conjugate was further subjected to various studies like degree of substitution, solubility, stability, drug release studies in presence and absence of rat colonic content and in vivo studies using acetic acid induced colitis model. The results showed that degree of substitution is dependent on the molecular weight of polymer. The solubility of drug was dependent on degree of substitution. All the conjugates were stable at different pH. In vitro drug release studies showed that very less amount of drug was released in stomach and small intestine. The presence of colonic content increased the drug release. The Dextran 70000 conjugate showed more effective healing against induced colitis as compared to mesalamine and budesonide suspension.(19)

Das S. & Ng KY. (2010) formulated multi-particulate calcium-pectinate (Ca-pectinate) bead formulations for colon-targeted delivery of resveratrol. The Ca-pectinate beads were made acid resistant adding polyethyleneimine (PEI) in the cross-linking solution were not sufficient to endure the upper GI environment and premature release of resveratrol occurred before their arrival to the colon, the beads were hardened by. The effects of PEI concentration, cross-linking time, and pectin to resveratrol ratio were investigated on bead’s characteristics, encapsulation efficiency, swelling-erosion, and resveratrol retention pattern of formulated beads. Formulated beads were spherical with approximately 1 mm diameter. The drug release from formulation was
dependent on the concentration of PEI in cross-linking solution and a minimum cross-linking time. As the concentration of PEI increases in the cross-linking solution, the beads become harder. The present study revealed that optimized Ca-pectinate beads hardened with PEI can be used for colon-specific delivery.\(^{(20)}\)

**Elias EJ. et. al., (2010)** investigated the matrix tablet of curcumin using guar gum as polymer in different ratios. The prepared tablets were subjected to further studies like hardness, drug content, friability and \textit{in vitro} release studies with different pH mediums and colonic fluids. The matrix tablet containing 40% guar gum showed 91% drug release after 24 hours in presence of rat ceacal content which showed susceptibility to colonic bacteria. The results concluded that guar gum can be used as polymer for targeting curcumin to the colon.\(^{(21)}\)

**Kotagale N. et. al., (2010)** studied the polymer-coated polysaccharide tablets of azathioprine for colon targeting. The tablets formulations were prepared by direct compression method using different ratios of avicel (MCC), inulin and triacetin and then coated with Eudragit-S, Eudragit-L and cellulose acetate phthalate. The formulations were then subjected to friability, thickness, hardness, weight variation, content uniformity and \textit{in vitro} drug release. Hardness and percentage friability were in the range of 7.23-7.43 kg/cm\(^2\) and 0.21-0.41\%, respectively, and showed 99-100\% uniformity in drug content. The formulation containing Eudragit-S, Eudragit-L and cellulose acetate phthalate (ES, EL and CAP) (1:1:1) showed only 9.75\% drug release in first 5 h (lag phase) and satisfactory release in lowered pH conditions. Drug release increased with the plasticizer (triacetin) concentration. Increase in the concentration of inulin and citric acid above 5\% w/w increases the drug release. The addition of inulin in the formulation with coating level 28\% w/w demonstrated increased drug release in presence of rat ceacal content. Thus inulin containing ES, EL and CAP (1:1:1) polymer-coated formulation system can be used for the targeted delivery of azathioprine to the colon.\(^{(22)}\)

**Saboktakin MR. et. al., (2010)** developed hydrogel of Ac-poly(amidoamine)-chitosan for colon targeting of 5-aminosalicylic acid. The different formulations were subjected to various studies like particle size, encapsulation efficiency, swellability, and \textit{in vitro} drug release to exploit pH sensitive and biodegradability properties of hydrogel. The hydrogels were in the nanorange and sufficient encapsulation efficiency. The \textit{in vitro} release studies showed that the formulation release the drug in the colon due to biodegradation due to colonic bacteria.\(^{(23)}\)
Sen G. *et al.*, (2010) evaluated the effect of microwave initiated synthesized polyacrylamide grafted guar gum on the controlled release of 5-amino salicylic acid from matrix. Various studies like percentage grafting and *In vitro* drug release in different pH mediums were carried out. The studies showed that the percentage grafting is dependent on the time of exposure to microwave irradiation; Further, the drug release study showed that the system can be used as a carrier for pH triggered colon targeted drug delivery. (24)

Umadevi SK. *et al.*, (2010) developed various formulations of chitosan microspheres encapsulating aceclofenac for colon targeting using various ratios of chitosan, span 85 and glutaraldehyde. The microspheres were subjected to various evaluations like SEM, FTIR and DSC studies which showed that the microspheres have smooth surface and there is no interaction between polymer and drug. Average particle size was in the range of 41-80 mm. The swelling index and entrapment efficiency were in the range of 0.37-0.82 and 51-75% respectively. The optimized batch showed drug release of 83.6% at 8 h and 104% at 24 h in SCF containing rat caecal content. When coated with Eudragit, chitosan microspheres showed no release of the aceclofenac in the physiological environment of the stomach and small intestine and released 95.9±0.34% in the colon. The *in vivo* studies suggested that aceclofenac microspheres showed prolonged effect of aceclofenac in rats and produce a significant anti-inflammatory effect. (25)

Amrutkar JR. and Gattani SG., (2009) prepared matrix tablets of Indomethacin by wet granulation method using cross-linked chitosan (ChI) and chondroitin sulfate (ChS) polysaccharides as binder and carrier. The ChI and ChS PEC was characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder X-ray diffraction studies (XRD). The matrix tablets were tested *in vitro* for their suitability as colon-specific drug delivery systems. FTIR studies showed the formation of PEC due to electrostatic interaction between the protonated amine (NH(3)(+)) group of ChI with the free carboxylate (COO(-)) group and sulfate (SO(4)(2-)) group of ChS. DSC and XRD indicated that the PEC has different thermal characteristics from ChI or ChS. The release rate from the tablet is dependent upon the concentration of polysaccharide and cross-linking time. The study confirmed that selective delivery of indomethacin to the colon can be achieved using cross-linked ChI and ChS polysaccharides. (26)

Bigucci F. *et al.*, (2009) studied pectin hydrogels microspheres formed by complexation with chitosan for the colon-specific delivery system of vancomycin hydrochloride. The hydrogels
were prepared at different weight ratios (4:1, 7:1, 10:1; pectin/chitosan), loaded with vancomycin hydrochloride (2:1, 4:1; polymer/drug weight ratio) and collected by spray-drying. The microspheres were subjected to characterization studies like morphology, swelling behavior, mucoadhesive properties and drug loading efficiency. The in vitro drug release studies were carried out at pH 2.0, 5.5 and 7.4 with and without pectinolytic enzyme. The studies showed that water uptake and drug availability increases with increase in pH and decrease by raising the pectin/chitosan weight ratio. The drug release increased in the presence of pectinase due to breakdown of glycoside bonds within pectin. The results showed that pectin/chitosan microspheres can be used as potential carrier for colon targeting. (27)

Canevari M. et. al., (2009) synthesized three different conjugates of Poly (ethylene glycol) with mesalazine for colon specific drug delivery. The conjugate prepared by using diamino poly (ethylene glycol) showed highest drug loading and was investigated for in vitro and in vivo studies. The release profile showed minimum release of mesalazine in the stomach and upper intestine and good release in the colon. The in vivo results against induced colitis showed that conjugate is more effective than the control. (28)

Ji CM. et. al., (2009) studied the film coating of guar gum for colon-specific delivery of 5-fluorouracil. The pellets of drug were coated with guar gum and pH-sensitive polymer Eudragit FS sequentially in a fluid-bed coater. Eudragit FS coating prevent the drug release in the stomach and dissolves in small intestine. The guar gum coating provides protection of the pellets in the intestine until it reaches colon and degraded by microbial enzymes at the proximal colon. The results indicate that guar gum is a feasible coating material to achieve timed and enzyme-triggered fluorouracil release. (29)

Kaur K. et. al., (2009) studied prednisolone beads coated sequentially firstly with hydrophobic layer of Eudragit RS/RL, then with the chitosan, organic acid and Eudragit RS/RL and the outermost enteric coating layer. The dissolution studies showed no release of drug in gastric and intestinal while a continuous release was observed in the colonic fluid. The results of plasma pharmacokinetic studies showed that there is significant delay in absorption profile as compared to simple enteric coated formulation which showed effective colon specific drug delivery. (30)

Maculotti K. et. al., (2009) studied chondroitin sulphate/chitosan microspheres (CS/CH) for oral delivery of ovalbumin, a protein. The microspheres were prepared by a new emulsion-complex coacervation technique was used for the formulation. In vitro dissolution testing was performed
under conditions simulating the intestinal fluids with and without chondroitinase ABC enzyme. Results showed that drug release from microspheres is approximately 30% in 24 h in the different aqueous media tested, which increased to 100% in the presence of chondroitinase. (31)

Patel JK. et al., (2009) studied controlled release matrix formulation for mesalamine using compritol 888 ATO (glyceryl behenate) as an inert matrix-forming agent to control the release of mesalamine, and pectin, a polysaccharide, as bacterial dependent polymer for colon targeting. The matrix tablets for these formulations were prepared by direct compression and their in vitro release tests were carried out. The formulation was optimized by 3(2) full factorial design by studying dependent variable like release rate on the basis of independent variable like amount of glycercy behenate (X(1)) and pectin (X(2)). Drug release from the matrix tablets formulations lasted for over 24 h and the release is because of formed pores and channels in the matrices. These may provide the release pathway for the inner embedded drugs. The co-mixing of polysaccharide pectin, into the waxy matrices played a meaningful role in targeting the tablets to colon. The mechanism of drug release drug release was diffusion-controlled. The results of the full factorial design indicated that an optimum amount of compritol ATO 888 and a high amount of pectin favors the colon targeting and controlled release of mesalamine from dosage form. (32)

Vaidya A. et al., (2009) developed multiparticulate system for colon targeting of metronidazole using pectin microspheres. These microspheres were coated with Eudragit(R) S-100 using oil-in-oil solvent evaporation method. The SEM was used to characterize the surface of these microspheres and a distinct coating over microspheres could be seen. The in vitro drug release studies exhibited no drug release at gastric pH, however continuous release of drug was observed from the formulation at colonic pH. Further, the release of drug from formulation was found to be higher in the presence of rat caecal contents, indicating the effect of colonic enzymes on the pectin microspheres. The in vivo studies were also performed by assessing the drug concentration in various parts of the GIT at different time intervals which exhibited the potentiality of formulation for colon targeting. Hence, it can be concluded that Eudragit coated pectin microspheres can be used for the colon specific delivery of drug. (33)

Maestrelli F. et al., (2008 a) studies influence of type of pectin (amidated or non-amidated) and microsphere preparation conditions (CaCl₂ concentration and cross-linking time) on the release of theophylline from enteric-coated calcium pectinate microspheres. The studies showed that entrapment efficiency increases with increase in concentration of CaCl₂ The release profile
showed no degradation of microspheres by pectinolytic enzymes. Notwithstanding this unforeseen result, coated MS prepared at 2.5% w/v CaCl₂ concentration were able to adequately modulate drug release through a mixed approach of pH and transit time control, avoiding drug release in the gastric ambient, and reaching the colonic targeting where 100% release was achieved within less than 24h. (34)

Maestrelli F. et al., (2008 b) exploited the effect of cyclodextrin to enhance drug solubility and permeation in microspheres prepared from Ca-pectinate and chitosan for colon targeting. Release studies revealed that due to reservoir effect drug alone was released faster than in the presence of cyclodextrin from MS without chitosan. But due to affinity for cyclodextrin by both polymer and drug the release rate is slow for MS containing chitosan. Permeation studies showed that cyclodextrin and chitosan were having synergistic effect in enhancing drug permeation. (35)

Nunthanid J. et al., (2008) developed colonic drug delivery system with the combination of time-, pH-, and enzyme-controlled system using Spray-dried chitosan acetate and hydroxypropyl methylcellulose. The tablets having HPMC:CSA at 60:40 and 50:50% weight ratio showed no release for 5-6h and pass as such through stomach and small intestine which was due to the swelling with gradual dissolving of CSA and HPMC in 0.1N HCl and the less solubility of CSA at higher pH. After reaching the colon, the drug release was over 90% within 14h. (36)

Philip AK. et al., (2008) investigated the prodrug of flurbiprofen with L-glycine to overcome gastric side-effects and for the colon-specific delivery of the drug. Coupling method was used for the synthesis of amide prodrug (FLU-GLY). The synthesized prodrug was characterized by elemental analysis, Fourier transform (FT)-IR, FT-NMR, mass (FAB) spectroscopy, and determinations of R(f), R(t) and R(M) values, respectively. Aqueous solubility and lipophilicity (logP) value were determined at pH 1.2, 4.0, 6.8 and 7.4. In-vitro reversion of FLU-GLY to flurbiprofen was measured at different pH and in a simulated colonic environment. Acute toxicity and ulceration potential were evaluated in-vivo in albino rats. Pre-formulation studies showed increased hydrophilicity but a non-significant increase in lipophilicity of the prodrug. In-vitro reversion studies suggested that cleavage of prodrug takes place in colonic pH, when the colonic microfloral enzymes (amidase) hydrolyzed the FLU-GLY amide linkage. In-vivo evaluation indicated that the prodrug was much less toxic and had less ulcerogenic activity than the parent drug. This concluded that colonic delivery can be used for reducing the dose administered and undesirable side-effects. (37)
Ravi V. et al., (2008) studied the use of natural polysaccharides like Chitosan and guar gum as carrier for targeting dilitazem to the colon. The matrix tablet was prepared with blend of polymer-drug and coated with inulin and shellac. They were then subjected to evaluation for average weight, hardness and coat thickness. *In vitro* dissolution studies were carried out in pH 1.2 HCl buffer for 2 h, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid. *In vitro* studies showed that the tablets coated with inulin and shellac have minimum drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Among the polymers used, chitosan was found to be the suitable polymer for colon targeting. The study revealed that polysaccharides as carriers and inulin and shellac as coating materials can be used effectively for colon targeting of drugs for treating local as well as systemic disorders. (38)

Mladenovska K. et al., (2007) studied Chitosan-Ca-alginate microparticles of 5-aminosalicylic acid for colon-specific delivery. The microparticles were prepared using spray drying method followed by ionotropic gelation/polyelectrolyte complexation. *In vitro* drug release studies confirmed that the drug was released in a controlled manner. Biodistribution studies of [(131)I]-5-ASA loaded chitosan-Ca-alginate microparticles showed the dominant localization of 5-ASA in the colon with lesser systemic bioavailability. (39)

Wei H. et al., (2007) evaluated film coating of pectin combined with ethylcellulose in different ratios for the development of colon-targeted drug delivery systems using 5-fluorouracil pellets. Studies revealed that the formulation with pectin to ethylcellulose in 1:2 (w/w) and film coat TWG-13% and TWG-20%, showed drug release of 9.8 +/- 0.7% and 4.1 +/- 0.4%, respectively, in the first 5 h of the dissolution study in the simulated gastric and small intestinal conditions.

With 4% w/v rat caecal content in dissolution medium, the film coat with the formulations of TWG-13% and TWG-20% released 96 +/- 1.3% and 85.0 +/- 0.3%, respectively, of 5-fluorouracil at the end of 24 h of the dissolution study, whereas in the control study the formulations released 51.4 +/- 1.0% and 34 +/- 0.5%, respectively, of 5-fluorouracil in absence of rat caecal contents at the end of 24 h. The results of the study show that the formulation of TWG-20% (pectin to ethylcellulose 1:2, w/w) is most likely to provide targeting of 5-fluorouracil for local action in the colon. (40)

Orlu M. et al., (2006) prepared tablets of microsponges containing FLB and Eudragit RS 100 coated with pectin: hydroxypropylmethyl cellulose (HPMC) mixture. The microsponges were
spherical in shape, between 30.7 and 94.5 microm in diameter and showed high porosity values (61-72%). *In vitro* studies exhibited that compression coated colon specific tablet formulations started to release the drug at the 8th hour corresponding to the proximal colon arrival time due to the addition of enzyme, following a modified release pattern while the drug release from the colon specific formulations prepared by pore plugging the microsponges showed an increase at the 8th hour which was the time point that the enzyme addition made. This study presents a new approach based on microsponges for colon specific drug delivery. *(41)*

**Smoum R. et. al., (2006)** studied colon specific drug delivery of salmon calcitonin, a protein drug using Chitosan-pentaglycin-phenylboronic acid conjugate with pentaglycin acts as spacer. The formulation was then subjected to enzyme inhibition assay for trypsin and elastase in presence of chitosanase. The results showed that in presence of chitosanase the inhibitory effect is more prominent as against without chitosanase. Further the degradation of salmon calcitonin by trypsin reduced due to the conjugate. *(42)*

**Sinha VR. et. al., (2004)** investigated colonic delivery formulation of 5-fluorouracil with a considerably reduced coat weight and gum concentration Rapidly disintegrating core tablets containing 50 mg of 5-fluorouracil were compression coated with 175 and 150 mg of granules containing a mixture of xanthan gum (XG) and guar gum (GG) in varying proportions. It was observed that reduction of coat weight did not affect the initial drug release rate in simulated upper gastrointestinal tract (GIT) conditions. 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% caecal content and 80.34+/-3.89% in presence of 4% caecal content after 19 h of incubation. *(43)*

**Sinha VR. et. al., (2002)** investigated polysaccharides or synthetic polymer such as xanthan gum, guar gum, chitosan and Eudragit E as binder for colon targeting of tablet of indomethacin. The tablets were then coated with Eudragit-L 100 to give protection in the stomach. The dissolution studies showed that the drug release rate is dependent on the concentration of Polysaccharide/polymer used as binder. The dissolution studies showed that Chitosan is more effective than guar gum for targeting water insoluble drugs to the colon. In addition to it is also concluded that formulation having both chitosan and Eudragit E retarded the drug release till microbial degradation occur in the colon. *(44)*
Hirsch S. et al., (1999) investigated Lauroyl dextran and crosslinked galactomannan for drug delivery of theophylline to the colon. Lauroyl dextran with degrees of substitution between 0.12 and 0.40, showed swelling between 195 and 50% in aqueous medium, crosslinked galactomannan showed swelling between 309 and 520%. Theophylline tablets were coated with 4% aqueous dispersions of crosslinked galactomannan or 4% dispersions of Lauroyl dextran in a 1:1 mixture of 1-propanol and water with 10% glycerol as a plasticizer. The in vitro dissolution studies were carried out in buffer pH 5.5. After 4 h, galactomannanase or dextranase were added to dissolution medium for simulation of colon conditions. The results showed similar dissolution rates for both Lauroyl dextran and crosslinked galactomannan during the first 4 h and a relatively quick disintegration after enzyme addition which showed microbial degradation of polymeric coating.\(^{(45)}\)

McLeod AD. et al., (1994) studied dextran conjugates for colon targeting with two glucocorticoid, dexamethasone and methylprednisolone. The results showed that dextran conjugates release less drug in upper GI tract contents but were rapidly degraded in caecal and colonic contents. So glucocorticoid dextran conjugates may be used for the treatment of colitis.\(^{(46)}\)