2. LITERATURE REVIEW

Mukesh R. Patel et al\(^1\) (2011) investigated that the enteric coating of Eudragit S 100 to the matrix tablet containing Eudragit RLPO and Eudragit RSPO can be used successfully to achieve gastric resistance and timed release of Tegaserod Maleate. The enteric coating level emerged as the critical factor in determining the duration of the lag phase, whereas the release rate mainly depended on the ratio of Eudragit RLPO and Eudragit RSPO in matrix tablet.

Prabhu et al\(^2\) (2008) investigated the controlled release and transport of leuprolide acetate polypeptide in the colon using novel combinations of rate-controlling polymers. Studies demonstrated Carbopol-containing combination formulations had maximum swelling and the slowest disintegration properties. A decrease in dissolution rate is observed from all combination formulations when compared with their individual counterparts. Carbopol combinations showed the slowest overall release. Drug transport studies using the everted sac technique demonstrated good correlation to the swelling, disintegration, and dissolution studies. Thus, novel polymer combinations can be used to deliver polypeptide drug to the colon effectively compared with individual polymers.

Salunkhe et al\(^3\) (2008) developed colon targeted drug delivery system by using dextrin (polysaccharide) as a carrier for ibuprofen. Matrix tablets containing various excipients and dextrin are prepared by wet granulation technique using different binder systems. Drug release profile is evaluated in simulated gastric, intestinal fluid and simulated colonic fluid. The results of in-vitro study indicate that matrix tablets containing dextrin as carrier and ethyl cellulose as binder are most suitable to deliver the drug specifically in colonic region as compare to matrix tablets of dextrin with other binder systems.

Omar et al\(^4\) (2007) developed a colon-specific drug delivery technology CODES associated with pH- or time-dependent systems. The core tablets contained the drug either in free form or as microspheres with 2 different polymer:drug:lactulose ratios 1:1:0.5 and 2:1:0.5. The release profiles of the coated CODES systems are compared with uncoated compressed tablets. The results of the study indicated that MB-HCl CODES colon-specific drug delivery can act as a successful trigger for drug targeting in the colon. Furthermore, a sustained release of the drug can be achieved from modified CODES containing the drug in the form of microspheres.
Mundargi et al\textsuperscript{5} (2007) developed colon targeted drug delivery systems for metronidazole (MTZ). Tablets are prepared using various polysaccharides or indigenously developed graft copolymer of methacrylic acid with guar gum (GG) as a carrier. To improve the colon specificity, some selected tablet formulations are enteric coated with Eudragit-L 100 to give protection in an acidic environment. Drug release studies are performed in simulated gastric fluid (SGF) for 2 hr followed by simulated intestinal fluid (SIF) at pH 7.4. Preparations with xanthan gum as a matrix showed the time-dependent release behavior. In-vitro release is performed in the dissolution media with rat caecal contents. Results indicated an enhanced release when compared to formulations studied in dissolution media without rat caecal contents, because of microbial degradation or polymer solubilization.

Zhang et al\textsuperscript{6} (2007) studied In-vitro enzymatic degradation of carboxymethyl konjac glucomannan (CMKGM) to evaluate the feasibility of CMKGM used as carrier materials to prepare colon-specific drug delivery systems. The solutions with rat gastrointestinal tract (GIT) contents or with commercial enzymes are chosen to stimulate in vivo GIT environment, respectively. Study demonstrated that CMKGM are degraded mainly in the simulated cecal and colonic media, but not in the simulated gastric and enteric media. Degradation of KGM and CMKGM by enzymes obeyed Michaelis-Menton kinetics. CMKGM with lower DS are more susceptible substrates. CMKGM are more susceptible substrates in solution with pH 6.0-6.8.

Liu et al\textsuperscript{7} (2007) studied a microbially triggered colon-targeted osmotic pump (MTCT-OP). The gelable property at acid condition and colon-specific biodegradation of chitosan are used to: (1) produce the osmotic pressure, (2) form the drug suspension and (3) form the in situ delivery pores for colon-specific drug release, respectively. Budesonide release from the developed formulation is inversely proportional to the osmotic pressure of the release medium, confirming that osmotic pumping is the major mechanism of drug release. These results showed that MTCT-OP based on osmotic technology and microbially triggered mechanism had a high potential for colon-specific drug delivery.

Asghar et al\textsuperscript{8} (2006) carried out drug modifications through covalent linkages with carrier or prodrug for colonic delivery. Report suggests that drug carrier systems larger than 200 mm possess very low gastric transit time due to physiological condition of the bowel in colitis. And for this reason and considering the selective uptake of micron or sub-micron particles by cancerous and inflamed cells/ tissues a multiparticulate approach based on pellets, granules and
microsphere or nanoparticle type formulation is expected to have better pharmacological effect in the colon.

Paharia et al\textsuperscript{9} (2006) prepared Eudragit-coated pectin microspheres for colon targeting of 5-FU by emulsion dehydration method using different ratios of FU and pectin, stirring speeds and emulsifier concentration.

Tuğcu-Demiröz et al\textsuperscript{10} (2006) developed colon-specific delivery systems of ondansetron using natural polymers such as guar gum and sodium alginate. Matrix tablets are prepared by a direct compression method. A high amount of polymers provided slow drug release whereas the release of ondansetron from the tablets prepared with low amount of polymers is found to be fast. Ondansetron-alginate and/or guar gum matrix tablet formulations can deliver the drug to the small and large intestine thus these matrix may be a promising system for the reduction of visceral sensitivity and inhibition of motor activity in irritable bowel syndrome (IBS).

Akhgari et al\textsuperscript{11} (2005) evaluated the effect of two factors (ratio of Eudragit S100 and Eudragit L100 and the coating level) on indomethacin release from pellets in order to optimize coating formulations for colonic delivery. The results of this study revealed that factorial design is a suitable tool for optimization of coating formulations to achieve colon delivery. It is shown that coating formulation consisted of Eudragit S100: Eudragit L100 in 4:1 ratio at 20\% coating level has potential for colonic delivery of indomethacin loaded pellets. The optimized formulation produced dissolution profiles that are close to predicted values.

Al-Saidan et al\textsuperscript{12} (2005) developed and evaluated guar gum-based matrix tablets of rofecoxib for their intended use in the chemoprevention of colorectal cancer. Matrix tablets containing 40\% (RXL-40), 50\% (RXL-50), 60\% (RXL-60) or 70\% (RXL-70) of guar gum are prepared by wet granulation technique, and are subjected to In-vitro drug release studies. The guar gum matrix tablets RXL-70 are subjected to in vivo evaluation in human volunteers to find their ability of targeting rofecoxib to colon. The delayed t-max, prolonged absorption time, decreased Cmax and decreased ka indicated that rofecoxib is not released significantly in stomach and small intestine, but is delivered to colon resulting in a slow absorption of the drug and making it available for local action in human colon.

Burke et al\textsuperscript{13} (2005) developed a colon specific drug delivery to facilitate targetted release of therapeutic proteins as well as small molecule drugs. The enzyme-modified hydrogel retains the drug until it reaches the colonic environment where bacteria secrete enzymes (namely beta-
mannanase) to degrade the gel and release the drug molecule. Laser scanning confocal microscopy combined with fluorescence recovery after photobleaching is used to quantify the diffusion of the drug conjugate. The diffusion coefficient of solutes in the lightly crosslinked galactomannan hydrogel is approximately equal to the diffusion coefficient in the guar solution for simple diffusional drug loading. After drug loading, alpha-galactosidase treatment generates additional physical crosslinks in the hydrogel matrix as well as between the drug-oligomer conjugate and the hydrogel, which reduces diffusion of the drug-oligomer conjugate significantly.

Bourgeois et al (2005) provided a "proof of concept" of colon delivery of beta-lactamases by pectin beads aiming to degrade residual beta-lactam antibiotics, in order to prevent the emergence of resistant bacterial strains. Pectin beads are prepared according to ionotropic gelation method using CaCl2 as a gelling agent. In-vitro studies showed that beta-lactamases are released from pectin beads in colonic medium due to the action of pectinolytic enzymes. The study demonstrated that a multiparticulate system with suitable characteristics for site-specific colonic delivery can be prepared. This system could be used to target beta-lactamases to the colon in order to hydrolyse antibiotic residues during treatment and prevent their impact on colonic microflora.

Momin et al (2004) developed colon targeted drug delivery systems for sennosides using guar gum as a carrier. Matrix tablets containing various proportions of guar gum are prepared by wet granulation technique using starch paste as a binder. The tablets are evaluated for content uniformity and In-vitro drug release study as per BP method. T (50) % value from the dissolution studies is taken for selecting the best formulation. The results of study indicates that matrix tablets containing 50% guar gum and coated with 10% hydroxy propyl methylcellulose phthalate are most suitable for drugs like sennosides which are mainly active in the lower GIT.

Cheng et al (2004) investigated Time- and pH-dependent colon-specific drug delivery systems (CDDS) for orally administered diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA), respectively. DS tablets and 5-ASA pellets are coated by ethylcellulose (EC) and methacrylic acid copolymers (Eudragit L100 and S100), respectively. Result shows that two types of CDDS, 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.
Nykänen et al\textsuperscript{17} (2004) investigated the optimal amounts and locations of citric acid in formulations intended as drugs targeted at the colon. Ibuprofen is used as the model drug. Drug release rates are studied in phosphate buffer at pH 6.8 and 7.4. In vivo tests confirmed that between 10 and 15\% citric acid in the tablet matrix delayed the commencement of drug absorption most. This kind of formulations could be suitable for preparation of colon-specific dosage forms. It is probably unnecessary to include citric acid in granule cores. No logical correlation between In-vitro and in vivo results is obtained.

Chourasia et al\textsuperscript{18} (2004) developed microspheres consisting of cross-linked of guar gum for colon-targeted delivery of metronidazole. An emulsification method involving the dispersion of aqueous solution of guar gum in castor oil is used to prepare spherical microspheres. In-vitro release rate studies are also carried out in simulated colonic fluid (SCF) in the presence of rat cecal contents, which showed improved drug release. In-vitro release studies exhibited 31.23+/−1.49\% drug release in 24 h in dissolution medium without rat cecal matter. However, the incorporation of 4\% w/v cecal matter obtained after 6 days of enzymes induction increased the drug release to 96.24+/−4.77\%.

Tuğcu-Demiröz et al\textsuperscript{19} (2004) developed colon-specific delivery systems for mesalazine (5-ASA) using guar gum as a carrier. Two different types of guar gum are used in the experiments. Tablets are tested and In-vitro release studies are performed by a flow-through cell apparatus with and without galactomannanase enzyme. High viscosity guar gum, in the form of a matrix tablet is capable of protecting the drug from being released in the upper region of gastrointestinal (GI) system, i.e. stomach and small intestine. X-ray imaging technique is used to monitor the tablets throughout the GI system on 8 healthy volunteers. Barium sulphate is used as a marker in the tablets for in vivo studies. These results showed that, the matrix tablets reached the colon; not being subjected to disintegration in the upper region of the GI system in all the subjects.

Xing et al\textsuperscript{20} (2003) investigated a novel formulation for colon-specific drug delivery using calcium alginate gel beads-entrapped liposome and bee venom peptide as a model drug. The release rate of bee venom from the coated calcium alginate gel beads-entrapped liposome is dependent on the concentration of calcium and sodium alginate, the amount of bee venom in the liposome, as well as the coating. Furthermore, a human gamma-scintigraphy technique is used in vivo to determine drug delivery more precisely. The colonic arrival time of the tablets is found to
be 4-5 h. The results clearly demonstrated that the coated calcium alginate gel beads-entrapped liposome is a potential system for colon-specific drug delivery.

Luppi et al.\textsuperscript{21} (2003) entrapped Vancomycin in carriers composed by a swellable, mucoadhesive and biodegradable albumin core, coated with fatty acids able to improve a colon-specific release. Bovine serum albumin nanospheres (core) are prepared from protein solutions using a coacervation method followed by thermal cross-linking at different temperature, or from protein solutions at different pH using a coacervation method followed by thermal cross-linking at 75°C. The results indicated that nanospheres present an adequate loading capacity, a great swelling tendency and good mucoadhesion ability. Moreover, albumin cores showed a pH-dependent release according to the structure of thermally denaturated protein while microcapsules showed a pH-dependent release according to the different fatty acids solubility in acidic and alkaline media.

Krishnaiah et al.\textsuperscript{22} (2003) studied the in vivo performance of guar gum-based colon-targeted tablets of ornidazole (dose 250 mg) in comparison with an immediate release tablet of ornidazole (250 mg) in human volunteers. Six healthy volunteers participated in the study, and a cross over design is followed. The delayed Tmax, decreased Cmax, and decreased ka of ornidazole from guar gum-based colon-targeted ornidazole tablets, in comparison with the immediate tablets, indicated that the drug is not released in stomach and small intestine, but targeted to colon. Slow absorption of ornidazole from the less absorptive colon might result in the availability of drug for local action in the colon.

Krishnaiah et al.\textsuperscript{23} (2003) developed colon-targeted drug delivery systems for ornidazole using guar gum as a carrier. The core formulation containing ornidazole is directly compressed. Compression-coated tablets of ornidazole containing various proportions of guar gum in the coat are prepared. All the formulations are evaluated for to In-vitro drug release studies. The results of the study show that compression-coated ornidazole tablets with either 65\% (OLV-65) or 75\% (OLV-75) of guar gum coat are most likely to provide targeting of ornidazole for local action in the colon owing to its minimal release of the drug in the first 5 hr.

Chang et al.\textsuperscript{24}(2002) prepared a novel pH-sensitive nanogel based on pectin cross-linked with glutaraldehyde (PT-GA) is designed and synthesized for drug delivery. The In-vitro drug-release behavior of the drug-loaded nanogel particles in three kinds of media, i.e., simulated gastric fluid, simulated intestine fluid and simulated colon fluid, is studied. PT-GA nanogel exhibits a
faster release at a high pH, and the release could be further accelerated in the presence of pectinolytic enzyme, indicating that the nanogel may be used for colon-specific drug delivery.

Sinha et al\(^\text{25}\) (2002) developed a single unit, site-specific drug formulation allowing targeted drug release in the colon. Tablets are prepared using xanthan gum, guar gum, chitosan and Eudragit E using Indomethacin is used as a model drug. The prepared tablets are enteric coated with Eudragit-L 100. The coated tablets are tested in-vitro for their suitability as colon specific drug delivery systems. The study shows that chitosan could be successfully used as a binder, for colon targeting of water insoluble drugs in preference to guar gum when used in the same concentration. Site specific drug release would be at a retarded rate due to microbial degradation or polymer solubilization takes place in the colon.

Cole et al\(^\text{26}\) (2002) investigated enteric coating of HPMC capsules containing paracetamol. Two enteric polymers, Eudragit L 30 D-55 and Eudragit FS 30 D are studied, which are designed to achieve enteric properties and colonic release, respectively. Dissolution studies demonstrated that capsules coated with Eudragit L 30 D-55 are gastro resistant for 2 h at pH 1.2 and capsules coated with Eudragit FS 30 D are resistant for a further 1 h at pH 6.8. For HPMC units coated with Eudragit L 30 D-55, complete disintegration occurred predominately in the small bowel in an average time of 2.4 h post dose. For HPMC capsules coated with Eudragit FS 30 D, complete disintegration did not occur until the distal small intestine and proximal colon in an average time of 6.9 h post dose.

Park et al\(^\text{27}\) (2002) designed a multilayer coated system that is resistant to gastric and small intestinal conditions but can be easily degraded by colonic bacterial enzymes to achieve effective colon delivery of prednisolone. Coated tablets containing chitosan and cellulose acetate phthalate (CAP) as coating materials. Release aspects of prednisolone in simulated gastrointestinal fluid and rat colonic extracts (CERM) are investigated. Also, colonic bacterial degradation study of chitosan is performed in CERM. The rapid increase of prednisolone in CERM is revealed as due to the degradation of the chitosan membrane by bacterial enzymes.

Pang et al\(^\text{28}\) (2000) used a commercial empty enteric capsule and a coated capsule for the measurement of colon transit time. In-vitro stability study is performed by immersing these capsules in a colourless buffer of variable pH which mimicked the conditions in the stomach and the small bowel. Capsule disruption is determined. Colon transit scintigraphy with 99mTc-DTPA charcoal is performed in five normal volunteers using these two capsules. The In-vitro stability
of these two types of capsule is similar and the colon transit scintigraphy findings are almost identical. Most capsules dissolved in the ascending colon and very few in the terminal ileum. It is concluded that enteric capsule is a suitable alternative to coated capsule for measurement of colon transit.

Sémé et al\textsuperscript{29}(2000) developed theophylline pellets coated with Eudragit NE30D aqueous dispersions, containing various pectin HM/Eudragit RL30D ionic complexes, using an Uni-Glatt fluidized-bed apparatus. The theophylline release from the coated pellets, after an initial latency phase, occurred linearly as a function of time. The theophylline release rate is dependent on the pectin HM content of the complexes incorporated in the coatings. The lowest theophylline release from the coated pellets is obtained when the pectin HM content of the complexes is 20.0\% w/w (related to Eudragit RL), i.e. when the complexation between pectin HM and Eudragit RL is optimal. The theophylline release from the coated pellets is slower in presence of the pectinolytic enzymes when the pectin content of complexes is higher than 20\% w/w.

Krishnaiah et al\textsuperscript{30} (1999) developed colon-specific delivery systems for 5-aminosalicylic acid (5-ASA) using guar gum as a carrier. In-vitro drug release studies are carried out in simulated gastric and intestinal fluids and in pH 6.8 buffer containing rat cecal contents. The application of 175 mg of coating formulation containing 150 mg of guar gum over 5-ASA core tablets resulted in the release of less than 2\% drug in simulated gastric and intestinal fluids and about 93\% of 5-ASA in pH 6.8 buffer containing rat cecal contents. The study confirmed that selective delivery of 5-ASA to the colon can be achieved using guar gum as a carrier in the form of a compression coating over the drug core.

Nykänen et al\textsuperscript{31} (1999) investigated whether drug release rates from enteric matrix granules could be influenced by using organic acids as excipients. Ibuprofen is used as a model drug and Eudragit S and Aqoat AS-HF as enteric polymers. Drug absorption is studied in bioavailability tests in healthy volunteers. In-vitro /in vivo correlation are also investigated. It is concluded that although inclusion of an organic acid in a formulation retarded In-vitro release of the model drug, no corresponding effect is evident in in vivo studies. Bioavailability tests are therefore important early on during development of new dosage forms or formulations. Although no correlation between In-vitro and in vivo results is generally evident correlation could be demonstrated for individual formulations following mathematical transformation of data.