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Colon targeted drug delivery systems – A Potential Approach

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Day by day there are new developments in field of colon specific drug delivery system. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. New systems and technologies have been developed for colon targeting and to overcome pervious method's limitations. Colon targeting holds a great potential and still need more innovative work. This review article discusses, in brief, introduction of colon along with the novel and emerging technologies for colon targeting of drug molecule.

Keyword: Colon drug delivery, Crohn's disease, Inflammatory Bowel Disease

INTRODUCTION: The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration.[1,2] During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents.[3, 4] There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH-sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems.[5,6] Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery.

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Drugs used in colon cancer[7]

1. 5-fluorouracil
2. 9-aminocamptothecin
3. Capecitabine
4. Cetuximab
5. Trinotecan
6. Levamisole hydrochloride
7. Oxaliplatin
8. Trimetrexate
9. UFT (ftorafur and uracil)
10. Bevacizumab
11. Cisplatin

Advantages of colon targeting drug delivery system:[8,9,10]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bypass initial first pass metabolism.
- Extended daytime or nighttime activity.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.[11]

Limitations of colon targeting drug delivery system:

- Multiple manufacturing steps
- The resident microflora could also affect colonic performance via metabolic degradation of the drug
- Incomplete release of drug
- Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.[12]
- An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis.[13,14]
- Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore prodrugs are new chemical entities and need a lot of evaluation before being used as carriers.[15]

Table 5. Marketed drug products for the treatment of various diseases of colon:[16]

S. No.	MARKETED NAME	COMPANY NAME	DISEASE	DRUG
1	Mesacol tablet	Sun pharma, India	Ulcerative colitis	Mesalamine
2	Mesacol enema	Sun pharma, India	Ulcerative colitis	Mesalamine
3	Asacol	Win-medicare, India	Ulcerative colitis, crohn's disease	Mesalamine
4	SAZO	Wallace, India	Ulcerative colitis, crohn's disease	Sulphasalazine
5	Intazide	Intas, India	Ulcerative colitis	Balsalazide
6	Lomotil	RPG Life, India	Mild ulcerative colitis	Diphenoxylate hcl, atropine sulphate
7	BUSCOPAN	German Remedies, India	Colonic motility disorder	Hyoscine butylbromide
8	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
9	CYCLOMINOL	Neol, India	Irritable colon syndrome	Diclomine
10	Eldicet	Solvay, India	Irritable colon syndrome, Spastic colon	Pinaverium bromide
11	Equirex	Jagsonpal Pharmaceutical, India	Irritable colon syndrome	Clordiazepoxide
12	Normaxin	Systopic labs, India	Irritable colon syndrome	Clidinium bromide
13	Pro-banthine	RPG Life, India	Irritable colon syndrome	Propenthline bromide
14	Entofoam	Cipla, India	Ulcerative colitis	Hydrocortisone acetate

METHODS USED FOR DRUG TARGETTING TO THE COLON:

1. **Formation of prodrugs**: (Example: Azo-Prodrug, Glucuronide conjugate, etc.)
Prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body.[17] Covalent linkage is formed between drug and carrier, which upon oral administration reaches colon without being absorbed from upper part of GIT. In the colon drug release is triggered by high activity of certain enzymes in comparison to stomach and small intestine.

a) **Azo bond conjugate**: Sulfasalazine is mainly used for the treatment of inflammatory bowl diseases. It is 5- Amino Salicylic Acid (5-ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed, where it is reduced by the anaerobic environment into 5-ASA and sulphapyridine as shown in figure 2.[18]

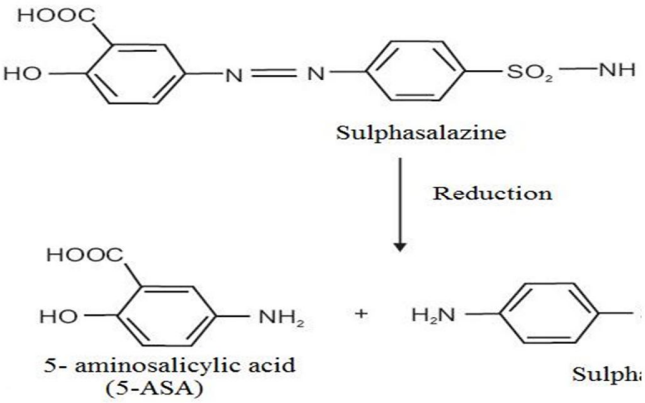


Figure 2. Reduction reaction of sulphasazine in 5-ASA and sulphapyridine

Various studies are conducted on sulphapyridine which lead to the formation of other prodrug like Olsalazine, Balsalazine, 4-amino benzoyl-β-alanine.[19] Intestinal microflora produces glycosidase, one of prominent group of enzyme.
Colon specific formulation of flurbiprofen had been evaluated by using azo-aromatic and pH-sensitive polymer and it was concluded that azo-aromatic polymer (poly-methylmethacrylate-hydroxy rthylmethacrylate : 1:5) and pH sensitive polymer eudragit S can successfully be used for colonic drug delivery.[20] Pulsincap drug delivery of salbutamol sulphate had been investigated. An empty gelatin capsule was coated with ethyl cellulose keeping the cap portion as such. A hydrogel plug made of gelatin was suitably coated with cellulose acetate phthalate in such a way that it was fixed to the body under the cap. Eudragit microspheres containing the salbutamol sulphate were prepared by emulsion solvent evaporation method and were incorporated into this specialized capsule shell. In vitro dissolution results indicated that the onset of drug release was after 7 to 8 hr of the experiment started.[21] Mutual azo prodrug of 5-aminosalicyic acid with histidine, was synthesized by coupling L-histidine with salicylic acid, for targeted drug delivery to the inflamed gut tissue.[22]

b) **Glucuronide conjugate**: Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower gastrointestinal tract secrete glucuronidase that glucouronidate a variety of drugs in the intestine. Since the glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.[23]

c) **Cyclodextrin conjugates**: The hydrophilic and ionisable Cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic Cyclodextrins can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with Cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs.[24] Ibuprofen prodrugs of α- , β-and γ-Cyclodextrins were investigated.[25] Methotrexate prodrugs of α- and γ-Cyclodextrins were also synthesized and result established the primary aim of masking the ulcerogenic potential of free drug, by using 12-fold dose of the normal dose of methotrexate and equivalent doses of the esters.[26]

d) **Dextran conjugates**: Dextran ester prodrugs of metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone was synthesized and proved the efficacy of the prodrugs for delivering drugs to the colon. Methyl prednisolone and dexamethasone were covalently attached to the dextran by the use of a succinate linker.[27]

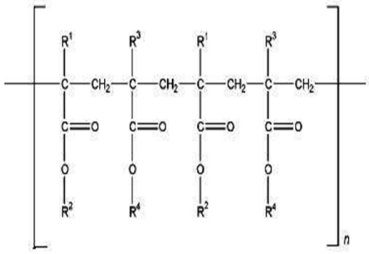
e) **Amino-acid conjugates**: Due to the hydrophilic nature of polar groups like NH2 and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid.[28]

2. Hydrogels:

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic commoners and enzymatically degradable azo aromatic cross-links. In the acidic pH, gels shows less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azoreductase, which ultimately release of drug.[29]

3. Coating with pH dependent polymers:

The pH in the terminal ileum and colon in higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at high pH ranges can be target into the region. A level of pH is higher in the terminal ileum region then in the cecum. Dosage forms are often delayed at the ileocecal junction, careful selection of enteric coat composition and thickness is needed to ensure that disintegration does not occur until the dosage from moves through the ileocecal junction from the terminal ileum into the cecum. Synonyms for eudragit are Eastacryl, Kollicoat MAE, polymeric methacrylates.[30] Delayed release tablets containing mesalazine and coated with eudragit S-100 were studied. These tablets dissolved at a pH level of 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon. The formulation was successful in achieving site specific delivery of mesalazine, failure of the coating to dissolve has been reported.[31] The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets, capsules, pellets, granules, micro-particles and nanoparticles.



For *Eudragit L* and *Eudragit S*:
$R^1, R^3 = CH_3$
$R^2 = H$
$R^4 = CH_3$

For *Eudragit FS*:
$R^1 = H$
$R^2 = H, CH_3$
$R^3 = CH_3$
$R^4 = CH_3$

For *Eudragit RL* and *Eudragit RS*:
$R^1 = H, CH_3$
$R^2 = CH_3, C_2H_5$
$R^3 = CH_3$

Figure 3. Structure of various grade of Eudragit polymers

pH- dependent microbeads of theophylline hydrochloride were developed and evaluated by using alginate and chitosan by ionotropic gelation method followed by enteric coating with eudragit S100.[32] Investigation concentred with the formulation of prednisolone containing 1% eudragit RS PM had been carried out which shows 100% drug release.[33] Tablet containing mesalazine were investigated which was coated with two polymers eudragit L100 and eudragit S100 in combination 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1.[34] Chitosan microspheres contain Ondansetron were prepared by emulsion cross linking method. Work combines eudragit S100 and chitosan polymers. Analysis regression values suggest that the possible drug release was Peppas model. [35]

4. **Timed released systems**: (Example: Pulsatile release, Pulsincap, Delayed release, Sigmoidal release system)
It is based on the concept of preventing the release of drug 3–5 hr after entering into small intestine. In this approach, drug release from the system after a predetermined lag time according to transit time from mouth to colon. The lag time depends upon the gastric motility and size of the dosage form. One of the earliest approaches is the Pulsincap device. This device consists of a non disintegrating half capsule body sealed at the open end with a hydrogel plug, which is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine, the enteric coating dissolves and the hydrogel plug starts to swell. The amount of hydrogel is adjusted so that it pops out only after the stipulated period of time to release the contents.[36] In another approach, organic acids were filled into the body of a hard gelatin capsule as a pH-adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethylcellulose. The capsule was first coated with an acid soluble cationic polymer, then with a hydrophilic polymer hydroxypropyl methylcellulose and finally enterically coated with hydroxy propyl methyl cellulose acetate succinate. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. The enteric layer and the hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released.[37] Pressure-controlled drug delivery systems: This approach relies on the strong peristaltic waves in the colon that lead to a temporarily increased luminal pressure. In the upper GIT, the drug delivery system is not directly subjected to the luminal pressure, since sufficient fluid is present in the stomach and small intestine. Due to raised luminal pressure in the colon, the system raptures and releases the drug.[38] Chronomodulated drug delivery system of salbutamol sulphate had been developed for the treatment of nocturnal asthma. The cores containing salbutamol sulphate were prepared by direct compression method use of microcrystalline cellulose and effervescent agent (sodium bicarbonate) and then coated sequentially with an inner swelling layer containing a hydrocolloid (hydroxypropylmethylcellulose E5) and an outer rupturable layer having eudragit RL/RS (1:1).[39] Drug delivery system was investigated which was built on the principles of the combination of pH and time sensitivity. Press- coated mesalamine tablets with a coat of HPMC E-15 were over-coated with eudragit S100.[40] A novel time and pH dependent system was investigated. The system consists of the core tablet of mesalamine which is compression coated with hydroxypropyl methylcellulose (HPMC K4M). This is then coated with eudragit L100. The result revealed that as the amount of HPMC increases, the lag time and t50 value also increases.[41]

Osmotic pressure controlled systems: The unit reaches intact to the colon where drug release takes place due to osmotic pressure generated by the entry of the solvent. It is also known as OROS.

There are two OROS systems for colon drug delivery:
1. **Osmet pump**: It consists of an enteric coated semi-permeable shell which encloses an osmotic layer along with a central impermeable and collapsible reservoir filled with drug. The interior of this compartment is connected with the external environment through a delivery orifice at one end. After dissolution of the gastric-resistant film, water is allowed to penetrate through the semi-permeable membrane, thus raising the pressure inside the device. Which cause inner reservoir to shrinks and drug formulation to pump out.

2. **OROS CT**: Immediately after ingestion, the hard gelatin capsule shell dissolves. The push and pull unit is prevented from absorbing water in the acidic medium of stomach by enteric coating. The

osmotic pumping action results when the coating dissolves in the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane.[42]

5. **Designing formulations using polysaccharides**: (Example: bacterial Enzymes): Dosage forms enjoy the shielding effect of polysaccharide in upper part of GIT and drug is released in the colon by swelling and biodegradable action of polysaccharidases. Polysaccharides naturally occurring in plant (e.g., pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g., alginates), or microbial (e.g., dextran) origins were studied for colon targeting. These are broken down by the colonic microflora to simple saccharides by saccharolytic species like bacteroides and bifidobacteria. Hydrolysis of the glycosidic linkages on arrival in the colon triggers the release of the entrapped bioactive. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature, and swell under exposure to upper GI conditions, which leads to premature drug release. To overcome this problem, the natural polysaccharides are chemically modified and mixed with hydrophobic water insoluble polymers, whereas in the case of formulations they are usually coated with pH sensitive polymers. A pectin/chitosan-based colonic delivery system has been developed.[43] The use of calcium pectinate as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but retains its integrity in the physiological environment of the small bowel. Other derivatives such as methoxylated and amidated pectins are also developed. The formulation of Guar gum based matrix tablets of metronidazole/tinidazole were developed and the influence of the concomitant administration of these drugs on the usefulness of guar gum as a carrier for colon-specific drug delivery using guar gum matrix tablets of albendazole was studied as a model formulation.[44] The fast disintegrating core tablets of budesonide were coated with khaya gum followed by further coating with eudragit S100 by dip coating technique. Khaya gum did not completely protect the drug release in the upper digestive tract and exhibited different release profile in presence and absence of rat cecal contents and it was concluded that khaya gum alone cannot be used for targeting the drug to the colon.[45] Tablet formulation using pectin as carrier and diltiazem HCl and indomethacin as model drug had been developed. The tablets were coated with inulin followed by shellac. It was revealed that polysaccharides as carriers and inulin and shellac as a coating as a coating material can be used effectively for colon targeting of both water soluble and insoluble drugs.[46]

6. **Redox sensitive polymer coating**:
Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes nonenzymatically by enzymatically generated flavins are being developed for colon targeting.[47] A common colonic bacterium, Bacteroidesfragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model azo compound, 4, 4'-dihydroxyazobenzene were studied. It was found that the azo compounds were reduced at different rates and the rate of reduction could be correlated with the redox potential of the azo compounds.

7. **Bioadhesive systems:**
Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide polypropyline oxide copolymers have been investigated as materials for bioadhesive systems.[48]

RERERENCE:

1. Barbara L, Teresa C, Federica B, Isabella O, Vittorio Z: pH-sensitive polymeric physical-mixture for possible site-specific delivery of ibuprofen. Eur J Pharm Biopharm 2003; 55: 199-202.

2. Lachman L, Lieberman HA, Kanig JL: The theory and practice of industrial pharmacy. 3rd edition. Bombay, Varghese publishing house: Hind Rajasthan building; 1991. p. 293.

3. Antonin KH, Rak R, Beick PR, Schenker U, Hastewell J, Fox R: The absorption of human calcitonin from the transverse colon of man. Int J Pharm. 1996;130: 33-39.

4. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, Yamamoto A, Muranishi S: Chitosan capsules for colon specific drug delivery: Improvement of insulin absorption from the rat colon. J Pharm Sci 1997; 86(9): 1016-1021.

5. Van-den GM, Kinget R: Oral colon-specific drug delivery: a review. Drug Delivery 1995; 2: 81-93.

6. Rama Prasad Y, Krishnaiah Y, Satyanarayana S: In vitro evaluation of guar gumas a carrier for colon-specific drug delivery. J Controlled Release 1998; 51: 281-287.

7. Consumer's guide to cancer drugs. 2nd ed. New York, American cancer society; 2008.

8. Jain NK: Advances in Controlled and novel Drug Delivery. 1st edition. New Delhi, Cbs publisher and distributors; 2008. p. 86-90.

9. Halsas M, Penttinen T, Veski P, Jurjenson H, Marvola M: Time controlled release pseudoephedrine tablets: bioavailability and in vitro/in vivo correlations. Pharmazie 2001; 56: 718 - 723.

10. Kinget R, KalalaW, Vervoort L, van denMooter G: Colonic drug targeting. J Drug Targeting 1998;6(2): 129-149.

11. Rathod S: Colon Targeted Pulsatile Drug Delivery : A Review. Pharm Rev. [serial on the Internet]. 2007; 5(2). Available from: http://www.pharmainfo.net

12. Ratna V. Prabhakaran L, Prushothaman M: Colon targeted drug delivery system - an overview. Pharm Rev. [serial on the Internet]. 2010; 8(2). Available from: http://www.pharmainfo.net

13. Nugent SG, Kumar D, Rampton DS, Evans DF: Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut 2001; 48: 571-7.

14. Jose S, Dhanya K, Cinu TA, Litty J, Chacko AJ: Colon targeted drug delivery: Different approaches. J Young Pharm 2009; 1(1): 13-19.

15. Gaurav T, Ruchi T, Pranay W, Ankita W, Awani KR: Primary and novel approaches for colon targeted drug delivery –A review. International Journal of Drug Delivery 2010; 2(1): 01 – 11.

16. Gulhati CM: Monthly index of medical specialties 2010; 30(2): 22-24.

17. Taber's cyclopedic medical dictionary. 20th ed. F A davis company:Philadelphia. 2001. p.1779

18. Klotz U: Clinical pharmacokinetics of sulfasalazine, its metabolites and other prodrug of 5-aminosalicylic acid. Clinical pharmacokinetics. 1985; 10(4): 285-302.

19. Chan RP, Pope DJ, Gilbert AP, Sacra PJ, Baron JH, Lennard- Jones JC. Studies of two novel sulfasalazine analogue, ipsalazine and balsalazine. Digestive Diseases and Sciences 1983; 28(7): 609-615.

20. Jain SK, Chourasia MK Dengre R: Azo polymers for colon targeted drug delivery. Indian J. Pharm. Sci 2005, 67(1): 43-50.

21. Samanta MK, Suresh NV, Suresh B: Development of Pulsincap drug delivery of salbutamol sulphate for drug targeting. Indian J. Pharm. Sci 2000, 62(2): 102-107.

22. Nagpal D, Gairola RS, Bodhankar SL, Suneela SD: Mutual azo prodrug of 5-aminosalicylic acid for colon targeted drug delivery: synthesis, kinetic studies and pharmacological evaluation. Indian J. Pharm. Sci 2006, 68(2): 171-178.

23. Scheline RP: Drug metabolism by intestinal microorganism. J Pharm Sci 1968; 57: 2021-2037.

24. Tanaka H, Kominato K, Yamamoto R: Synthesis of doxorubicincy clodextrin connjugates. J Antibio 1994; 47: 1025-1029

25. Mhaske DV, Bariwal J, Dev S, Kadam SS, Dhaneshwar SR: Synthesis and pharmacological evaluation of cyclodextrin conjugates prodrugs of Ibuprofen. Indian J Pharm Sci 2005, 67(4): 432-437.

26. Gupta D, Mhaske DV, S.S. Kadam SS, DhaneshwarSR: Synthesis and evaluation of pharmacological activities of cyclodextrin conjugates of methotrexate. Indian J Pharm Sci 2004, 66(1): 26-30.

27. Johansen M, Larsen C: Stability kinetics and of hydrolysis of metronidazole monosuccinate in aqueous solution and in plasma. Int J Pharm 1984; 21: 201-209.

28. Nakamura J, Asai K, Nishida K, Sasaki H: A novel prodrug of salicylic acid, salicylic acid-glutamic acid conjugate utilising hydrolysis in rabbit intestinal microorganism. Chem Pharm Bull 1992; 40: 2164-2168.

29. Brondsted H, Kopecek J: Hydrogels for site specified oral drug delivery: synthesis and characterization. Biomaterials 1991; 12(6): 584 - 592.

30. Rayond C, Rowe RC, Paul JS: Hand book of pharmaceutical excipients, 6th ed., London, Pharmaceutical Press, 2009. p. 525-526.

31. Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-ASA therapy for milding to moderately active ulcerative colitis: A randomized study. New Engl J Med 1987; 317(26): 1625 – 1629.

32. Khan MS, Sridhar BK, Srinatha A: Development and evaluation of pH-dependent microbeads for colon targeting. Indian J Pharm Sci 2010, 72(1): 18-23.

33. Sahib MN, Abdulameer SA, Rasool AAA: Design and in vitro evaluation of prednisolone tablets as a potential colon delivery system. Asian journal of pharmaceutical and clinical research 2009, 2 (4): 84-93

34. Khan MZI, Stedul HP, Kurjakovic N: A pH-dependent colon –targeted oral drug delivery using methacrylic acid copolymers. Ⅱ. Manipulation of drug release using eudragit L100 and eudragit S100 combination. Drug Development and industrial pharmacy 2000;26(5): 549-554.

35. Jose S, Dhanya K, Cinu TA, Aleykutty NA: Multiparticulate system for colon targeted delivery of Ondansetron. Indian J Pharm Sci 2010, 72(1): 58-64.

36. MacNeil ME, Rashid A, Stevens HN: Dispensing device, World Patent ;WO 9009168, 1990.

37. Ishibashi T, Hatano H, Kobayashi M, Mizobe M, Yoshino H: Design and evaluation of a new capsule-type dosage form for colon-targeted delivery of drugs. Int J Pharm 1998; 168(1): 31-40.

38. Brahmankar DM, Jaiswal SB: Biopharmaceutics and pharmacokinetics - a treatise, 2nd ed., Delhi, Vallabh Prakashan, 2009. p. 462-463.

39. Qureshi J, Amir M, Ahuja A, Baboota S, Ali J: Chronomodulated drug delivery system of salbutamol sulphate for the treatment of nocturnal asthma. Indian J Pharm Sci 2008, 70(3): 351-356.

40. Mukesh C. Gohel, Rajesh K. Parikh, Stavan A. Nagori, Mahesh R. Dabhi: Design of a potential colonic drug delivery system of mesalamine. Pharmaceutical development and technology 2008, 13: 447-456.

41. Patel MM, Shah TS, Amin AF: Design, development and optimization of a novel time and pH-dependent colon targeted drug delivery system. Pharmaceutical development and technology 2009; 14:62-69.

42. Theeuwes F, Guittard GV, Wrong PSL (1990) US patent no. 4,904,474

43. Fernandez-Hervas MJ, Fell JT: Pectin/Chitosan mixtures as coating for colon specific drug delivery: an in vitro evaluation. Int J Pharm 1990; 169(1): 115-9.

44. Krishnaiah YS, Seethadevi A, Nageswara RL, Bhaskar RP, Karthikeyan RS, Satyanarayana V: Guar gum as acarrier for colon specific delivery; influence of Metronidazole and Tinidazole in In Vitro release of Albendazole from Guar gum matrix tablets. Int J Pharm Pharm Sci 2001;4(3): 235 - 243.

45. Prabhakara Prabhu, Nissara Ahmed, Harish N M, Mohd. Gulzar Ahmed, R. Narayana Charyulu, D. Satyanarayana, Marina Koland: Investigation of colon specificity of novel polymer khaya gum. Indian J Pharma Educ Res 2010;44(1): 56-65.

46. V. Ravi, T.M. Promod Kumar, Siddaramaiah: Novel colon targeted drug delivery system using natural polymers. Indian J Pharm Sci 2008, 70(1): 111-113.

47. Gingell R, Walker R: Mechanism of azo reduction by non-specificity of Streptococcus faecalisazoreductase. Xenobiotica 1975; 5: 563-571.

48. Lenaerts, V. and Gurny, R: Bioadhesive drug delivery systems. CRC Press, Boca Raton, 1990.