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A Review: Different Approaches of Colon Targeted Drug Delivery System

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ABSTRACT

The major goal of any drug delivery system is to supply a therapeutic amount of drug to the target site in the body, in order to achieve desired drug concentration. Colon targeted drug delivery system involves the targeting of drug to colon and is used for the treatment of various diseases related to colon like inflammatory bowel disease, colon cancer, crohn's diseases etc. Targeting to colon directly reduces the need of higher dose, dosing frequency, incidence of side effects and cost effective treatment can also be achieved. Colon was considered as "BLACK BOX" and generally absorption of most drugs occur in upper G.I region. Lack of digestive enzymes and delayed gastric emptying, has given the idea to design colon specific drug delivery system. This review article compares the different approaches to colon targeted drug delivery like pH and time dependent, prodrug, microbial triggered and pulsatile drug delivery system etc. Beside these different new approaches were also used for colon targeting like pressure controlled, osmotic controlled drug delivery systems are highly effective.

Keywords: colon targeted drug delivery, pH sensitive, Pressure controlled, osmotic controlled. Microbial triggered.

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INTRODUCTION

In the past two decades, the pharmaceutical scientists are extensively investigated in the area of colonic region for targeted drug delivery system. During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ[1]. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides[2] and also for the treatment of diseases sensitive to circadian rhythms such as autoimmune rheumatoid arthritis, angina and respiratory diseases like asthma for delivery of steroids, which were absorbable in colon. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon[3]. In 1942, Svartz discovered that sulfasalazine; the sulfanilamide prodrug of 5-aminosalicylicacid (5-ASA) is effective in the treatment of rheumatoid arthritis and anti-inflammatory disease. The exact mode by which the drug target itself to the colon was elucidated much latter in 1970 i.e., enzyme azoreductase inside colon splits azo-bond of sulfasalazine causing the release of the active moiety 5-aminosalicylicacid. Several other azo-bonds containing compounds like olsalazine, bensalazine, and balsalazide were designed and synthesized for the local release 5-aminosalicylic acid. In1986, Saffron and coworkers described the use of azo-bond containing acrylic polymers to the delivery of protein drugs like insulin to the colon[4]. Vaccine delivery can also be achieved as colon is rich in lymphoid tissue and uptake of antigen by mast cells of colonic mucosa triggers immune response which produces rapid local production of antibodies. Region of colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than stomach and Small intestin[5,6]. The colon specific drug delivery system (CDDS) should be capable of protecting the drug via its way to colon i.e. drug release and absorption bypasses the stomach as well as the small intestine, and also bioactive agent can be protected from degradation in either of the dissolution sites but only released and absorbed once the system reaches the colon[5].

Advantages of Colon targeted drug delivery system[7,8,9]

i. Minimization of Adverse effect by targeted delivery in case of ulcerative colitis & crohn's disease
ii. Gastric upset by NSAIDS can be overcome.
iii. Steroidal drugs extensive first pass metabolism can be avoided by designing colon targeted drug delivery system and this prevents the various adverse effect caused by steroidal drug on oral and I.V administration such as methyprednisolone and dexamethasone produces adeno

suppression, Immunosuppression, cushing syndrome, bone resorption.

iv. Minimisation of dose of particular drug because of targeted delivery.

v. Novel site for targeting of anticancerous drug particularly in colorectal cancer.

vi. High retention time leads to increased bioavailability of poorly absorbale drugs

vii. Improved patient compliance

Limitations of colon drug delivery system[10]

i. In colon targeting site of delivery has approx. neutral pH, less number of digestive enzymes, long transit time and designing of proper in-vitro dissolution method making this system difficult as targeted delivery.

ii. The drugs which are poorly soluble find difficulty in absorption from colon , as it contains less amount of fluid as compared to upper gi region, so drug has to be in solution form before it reaches to colon

iii. Colonic microflora sometimes causes degradation of some drugs

iv. Lower surface area and tight junctions in the colon restricts some drug to pass through the mucosal into systemic circulation.

Criteria for selection of Suitable candidate for CDDS

Most suitable candidates for CDDS are those which have poor absorption in stomach and intestine including peptides. Protein and peptide drugs e.g. growth hormones, calcitonin, insulin, interleukin, interferon and erythropoietin. Azo-bonds containing drug such as mesalazine sulfasalazine and olsalazine, Steroids like budesonide, fludrocortisone, prednisolone and dexamethasone requires local drug delivery used to treat irritable bowel disease (IBD) Colonic cancer drugs require local delivery e.g. 5-fluorouracil, doxorubicin, and methotrexate. Small extent of par cellular transport facilate selective absorption of drugs than small intestine e.g. Diclofencac, theophylline, glibenclamide, ibuprofen and metoprolol. To treat infectious diseases such as amoebiasis & helminthiasis requires site specific delivery e.g. metronidazole, mebendazole and albendazole[1,11,12].

Criteria for selection of drug carrier

The selection of carrier for CDDS depends on the nature of the drug, disease and various other physicochemical factors like chemical nature, partition coefficient, functional groups, stability, of drug molecule, etc. which effect the selection of carrier molecule. Besides this, selection also depends on the functional groups of the drug molecule[13]. For example; aniline or nitro groups on a drug molecule may be used in the linking with another benzene group through an azo- bond. The carriers, containing additives like polymers (used as matrices, hydro gels or coating agents) may

influence the release properties and efficacy of the systems[13]. The criteria's of selection is summarized in table 1.

Table 1: Criteria for selection of drugs for CDDS

Criteria	Pharmacological class	Non peptide drugs	Peptide drugs
Drugs used for local action in colon against GIT diseases	Anti- inflammatory drugs	Metoprolol, Nifedipine	Amylin, Oligonucleotide
Drugs used for colon cancer	Antineoplastic drugs	Pseudoephedrine	Glucagon, Epoetin
Drugs poorly absorbed	Antihypertensive & Antianginal drugs	Ibuprofen, Theophylline	Cyclosporine, Desmopressin
Drugs that undergo extensive first pass metabolism	Nitroglycerin & Corticosteroids	Bleomycin, Nicotine	Sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and antiasthamatic drugs	5-Amino-salicylic acid, hydrocortisone Prednisolone,	Somatropin,Urotoilitin

PRIMARY APPROACHES OF COLON DRUG DELIVERY SYSTEM

pH dependent systems

In pH dependent colon drug delivery systems, dosage forms like tablets, capsules, pellets were coated with pH sensitive polymer, selection of the polymer should be done by keeping in mind that polymer should withstand with gastric pH and proximal part of small intestine but should disintegrate at lower regions. Proximal region of small intestine has pH of about 6.5 and about 7.5 in the distal region of small intestine[14], decline in the pH level was observed from caecum to colon, it is about 6.4 in the caecum and as low as 5.7 in the ascending colon[15]. The pH in the transverse colon and descending colon is 6.6 and 7.0 respectively. So by the use of pH sensitive polymer drug release can be somehow achieved in colon, however disintegration of the formulation started as it reaches to ileum because of more lag time at ileocaecal region[16]. Methacrylic esters were most commonly used in colon targeting as they were soluble at pH 6. Eudragit L and S were widely used because eudragit L is soluble at and above pH 6 and eudragit S is soluble at pH 7 and above. Sometimes combination of the above both polymers are done to achieve desirable effect. A comparative study of the generally used enteric-coated polymers such as eudragit, cellulose acetate phthalate with Shellac and Ethyl cellulose as carriers for colon specific drug delivery was conducted to select a suitable carrier. In one study lactose based indomethacin tablets were prepared and coated with any one of the above coating polymers to a varying coating thickness. Dissolution was carried out and dissolution data at a coat concentration of 3% shellac provided the most appropriate polymer coat for colon-specific drug delivery. By making changes in the

thickness of shellac coating drug delivery to terminal ileum, distal or proximal colon can be achieved[17].

Microbial triggered drug delivery system

Colon is rich in microflora and variety of microbes were found in colon, that obtained there basic requirements or fulfill their energy needs from the undigested food present in small intestine such as di- trisaccharides and polysaccharides via fermentation process[18,19]. Colonic microbial flora mainly possesss anaerobic bacteria, e.g. bifidobacteria, bacteroides, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus[20]. Fermentation, to be carried out for their requirements requires specific enzymes and these enzymes were produced by microbes like glucoronidase, arabinosidase, galactosidase, xylosidase, azareducatase, deaminase, nitroreductase, and urea dehydroxylase[21, 34]. Keeping in mind about enzymes that were produced by microbes and are biodegradable, use of biodegradable polymer is carried out in colon targeting that protects our drug from stomach acidic environment and intestine. As it reaches to colon they undergo assimilation by micro-organism, enzymatic degradation or break down of the polymer back bone leading to decrease in their molecular weight and thereby loss of mechanical strength[22,23,24,25,25,26] and polymer can no longer holds the drug[27].

i) Prodrug approach

Prodrug is a pharmacologically inert substance which upon biotransformation releases the active molecule. Prodrug approach employs the release from the formulation by the microflora present in the gut and this can be achieved by linking the active drug with hydrophobic moieties like glucoronic acids, glucose, amino acids, galactose, cellulose, etc. These prodrug molecules get hydrolyzed in the presence of the enzymes released by the microflora[28]. Different prodrugs for colon drug delivery are given in the table 2.

Table 2: Prodrugs evaluated for colon specific drug delivery with there in vitro/in vivo performance

Carrier	Drug investigated	Linkage hydrolyzed	In vitro/in vivo model used	Performance of the Prodrug/conjugates
Suphapyridine (SP) 5-ASA	5-ASA	Azo linkage	Human	Delivers two molecules of 5-ASA as compared to suphasalazine[29]
Amino acid conjugates glycine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized by microflora of large intestine[30]
Tyrosine/methionine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized

				by microflora of large intestine[31]
L – Alanin/D-Alanine	Salicylic acid	Amid linkage	In vitro	Salicylic acid-l-alanine was hydrolysed to salicylic acid by intestinal microorganism but salicylic acid-D-alanine showed negligible hydrolysis thereby showing enantiospecific hydrolysis[32]
Glycine	5-ASA	Amid linkage	In vitro	Prodrug was stable in upper GIT and was hydrolysed by cecal content to release 5-ASA[33]
Glucuronide conjugates glucuronic acid	Naloxone/nalmefene	Glucuronide linkage	Rat	When given to morphine dependent rats, these reversed the GIT side effects caused by morphine without causing CNS withdrawal symptom because of activation in large intestine followed by a resultant diarrheas[34]

ii) Polysaccharide Based Delivery Systems

Naturally occurring polysaccharides, are easily available inexpensive. Chemical, biochemical modification leads to generation of safe, stable, nontoxic, gel forming systems that are biodegradable. Naturally occurring polysaccharides constitutes plant source (guar gum, inulin), animal source (chitosan, chondrotin sulphate), algae (alginates) or microbial (dextran) origin. These polysaccrides undergo degradation by colonic microflora to simple saccharides and hence they regarded as "generally regarded as safe" (GRAS)[35].

Delayed or time controlled release drug delivery system

Time controlled drug delivery system21 includes sustained or delayed release systems. Delayed release or colon targeted drug delivery is achieved by prolonging the lag time. The transit time varies in different parts of G.I tract which is responsible for the delayed release of drug. Main drawbacks of this delivery system were [36].

i. Transit time varies in subject sufferings from irritable bowel syndrome and ulcerative colitis
ii. Peristaltic movement varies from person to person, and this makes difficult to predict colonic delivery time and leads to poor colonic availability of drugs

Enteric coated time-release press coated (ETP) tablets were used for time controlled release are made up of of three components, a drug containing core tablet (rapid release layer), the press coated swellable hydrophobic polymer layer (Hydroxyl propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function)[37]. The tablet does not release the drug in the stomach due to the outer enteric coating layer which gives resistant against acidic environment. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. HPC layer erosion brings the core tablet in contact with fluid present in colon, rapid drug release occurs from the core region.

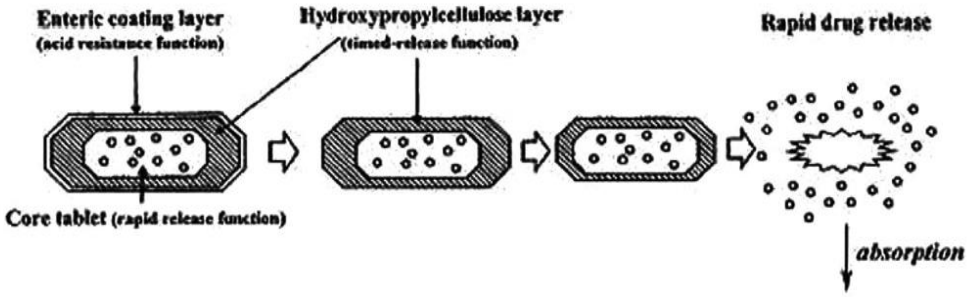

Figure 1: Design of enteric coated timed-release press coated tablet (ETP Tablet)

NOVEL APPROACHES OF COLON TARGETING

Pressure controlled release system

Strong peristaltic waves in the colon occurs only three to four times a day but this result in the more luminal pressure within the colon as compare to pressure in small intestine, which forms the base for design of pressure-controlled systems. Inside, stomach and small intestine, contents are more fluidic in nature because of because of abundant water present in digestive juices, where as in colon, the viscosity get significantly increased due to reabsorption of water from the lumen and formation of feces38. This system consists of drug inside gelatin capsule coated with water insoluble polymer ethyl cellulose on their inner region. The drug is incorporated into the capsule along with suppository base (Dissolves at body temperature). The disintegration capacity of the capsule is the function of thickness of ethyl cellulose, administration of the capsules leads to dissolution of suppository base absorption of water from intestinal contents is resulted in increased viscosity which leads to an increase in the pressure in the capsule causing capsule to expel the drug into the colon[3]. The preferred thickness of the capsule wall is about 35- 60 μm[10].

Pulsatile drug delivery system

i. Pulsincap system

In this system swellable hydrogels are used to seal the drug contents inside capsule and

When it comes in contact with the dissolution fluid, plug gets pushed off from the capsule and the drug will be released. Polymers of different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is the function of length and point of intersection of the plug, in the capsule body[38].

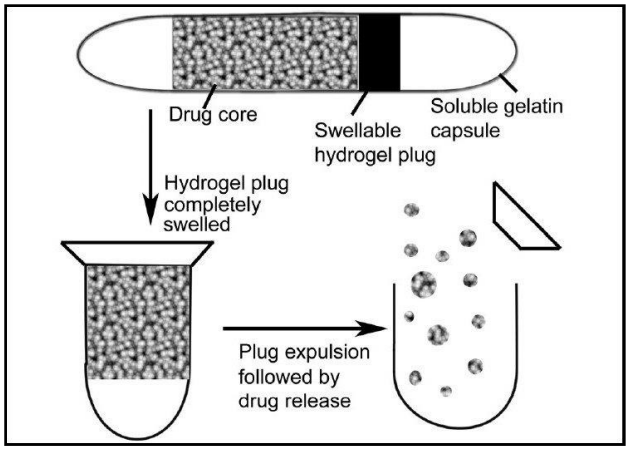

Figure 2: Pulsincap system

ii. Port system

In this system capsule body consists of an insoluble plug which contains osmotically active agent and drug formulation enclosed in a semipermeable membrane. As capsule comes in contact with the dissolution fluid, fluid movements occurs across the semipermeable membrane into the capsule due to which pressure inside the capsule get increased resulting into release of drug due to expelling of the plug[39].

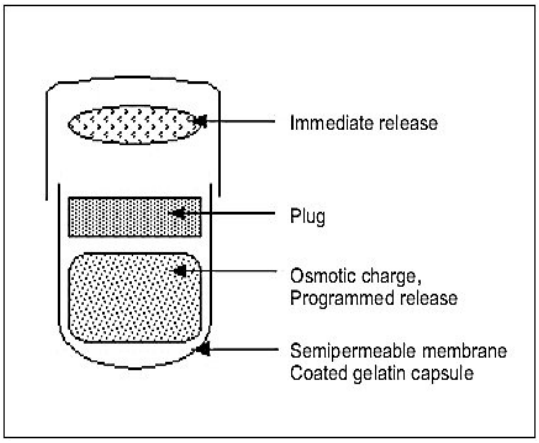

Figure 3: Port system release

Osmotic controlled drug delivery system (ORDS-CT System)

The OROS-CT system is a single osmotic unit or 5-6 push-pull units, each of which is 4 mm in diameter, encapsulated within a hard gelatin capsule[40]. Push pull units are bilayered having outer enteric impermeable membrane and inner semi permeable membrane having orifice from which

drug diffuses out. During their way to through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The outer impermeable enteric membrane dissolved as it reached to small intestine (pH>7). Water enters through the semi permeable membrane resulting into the swelling of push layer which forces the drug into the surrounding environment via orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24 hr[41].

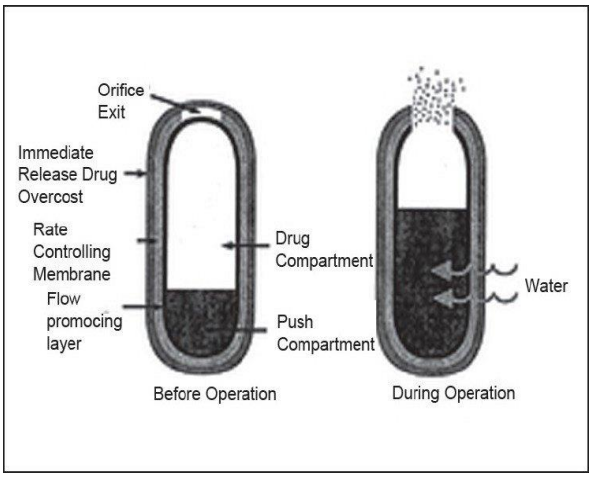

Figure 4: Osmotic controlled drug delivery system

Novel Colon targeted delivery system (CODESTM)

CODESTM is a unique CDDS technology employs combined approach of pH dependent and microbially triggered CDDS. This system utilizes the enzymatic degradation of lactulose polysaccharide by colonic bacteria. The system involves the coating of tablet core that contain lactulose, by acid soluble material, Eudragit E, and then subsequently coated with an enteric material, Eudragit L. The enteric coating provides acid resistant in stomach and as it passes the stomach it get dissolved, Now acid soluble material coating provides resistant to basic pH of the small intestine. When it reaches to colon the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid that will result in lowering of the pH in the surrounding which is sufficient to affect the dissolution of the acid soluble coating and subsequent drug release[42,43].

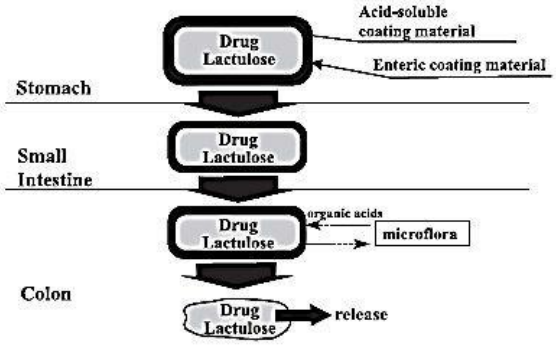

Figure 5: CODESTM delivery

Multi particulate system based drug delivery

Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption. Multiparticulate system involves the drug delivery in the form of pellets, microparticles, granules and nanoparticles and this results in increases bioavailability, decresed systemic toxicity and drug reaches to colon quickly and retained in the colon for prolong period of time .

EVALUATION OF CDDS

CDDS is evaluated by different in vitro and in vivo release studies, for the evaluation of success rate of colon drug delivery systems designed by using different approaches. A successful colon specific drug delivery system is one of that remains intact in the physiological environment of stomach and small intestine, and releases the drug in the colon.

***In-vitro* dissolution test**

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behavior of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are of pH 1.2 (simulated gastric fluid), pH 6.8 to simulate small intestine, pH 7.4 for large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in 6.8 pH phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems[44,45].

***In vitro* Evaluation studies**

CDDS is incubated in a fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals are determined. Release studies were done in buffer media containing enzymes pectinase, dextranase, and cecal contents of rat or guinea pig or rabbit. The time by which extent of drug get released is determined on the basis of degradation of polymer carrier.

***In Vivo* evaluation studies**

For testing a CDDS, animals which resemble the anatomic and physiological conditions as well as the micro flora of human GIT such as dogs, guinea pigs, rats, and pig were used. Guinea pigs are commonly used as experimental model for irritable bowel diseases (IBD). Enzymes like azoreductase and glucouronidase in the GIT of rat and rabbit is fairly comparable to that in the human[46].

CONCLUSION

Colon targeted drug delivery system helps in achieving targeted delivery of drugs to colon, along with this it also offers long transit time, less local irritation and reduce local and systemic side effects. Use of biodegradable polymers makes this CDDS safe and biocompatible, for the in-vitro evaluation of the system the current dissolution techniques are not more suitable. Researches were going on to develop perfect dissolution methods to evaluate the colon targeted drug delivery systems on the basis of drug release studies via utilizing different polymeric approaches.

REFRENCES

1. Sateesh kumar vemula, *et.al.* Different approaches to design and evaluation of colon specific drug delivery systems. Int. J PharmTechnol 2009; 1(1) 1-35.
2. Anil K. Philip, Betty Philip. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Medical Journal 2010; 2 (25): 70-78.
3. D. Sreelatha *et* al. Colon targeted drug delivery–a review on primary and novel approaches J Global Trends in Pharma Sci 2013; 4(3) 1174-1183.
4. Girish N. Patel, Gayatri C. Patel, Ritesh B. Patel. Oral colon-specific drug delivery: an overview. Drug Delivery Technology 2006; 6(7): 62-71.
5. Chourasia MK, Jain S K. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Sci 2003; 6(1)33-66.
6. Basit A, Bloor J. Prespectives on colonic drug delivery, Business briefing. Pharmtech 2003; 185-190.
7. McLeod AD, Friend DR, Thoma NT. Glucocorticoid-dextran conjugates as potential prodrugs for colon specific delivery- hydrolysis in rat gastrointestinal tract contents. J Pharm Sci 1994; 83(9):1284-1288.
8. Vyas S.P and Roop K. Khar. Systems for colon specific drug delivery. In: Controlled drug delivery concepts and advances, 1st ed. Delhi; 2006. p. 218-256.
9. Sonasaniya Balvir, M.R.Patel, K.R.Patel, N.M.Patel. A Review on colon targeted drug delivery system. International Journal of Universal Pharmacy and Bio Sciences 2013; 2(1): 20-34.
10. K.V Vinay kumar *et al*. Colon targeting drug delivery system: A review on recent approaches. International journal of pharma and biosciences 2011; 2(1): 11-19.
11. Antonin *et al*. The absorption of human calcitonin from the transverse colon of man. Int J Pharm 1996; 130 (1): 33-39.

12. Fara JW. Novel Drug Delivery and its Therapeutic Application. In: Presscot LF, Nimmo WS (Ed). Colonic drug absorption and metabolism. Wiley: Chichester, 1989; 103-120.
13. Friend DR, Chang GW. A colon-specific drug delivery system based on drug glycosides and glycosidase of colonic bacteria. J Med Chem 1984; 27: 261-266.
14. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988; 29(8):1035-1041.
15. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carr Sys 2001;18:433-458.
16. Ashord M, Fell JT, Attwood D, Sharma H, Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon. J Control Rel 1993; 26:213- 220.
17. Sinha V R, Rachana Kumaria. Microbially triggered drug delivery to the colon. European Journal of Pharmaceutical Sciences 2003; 18: 3-18.
18. Rubunstein A. Microbially controlled drug delivery to the colon. Biopharm Drug Dispos 1990; 11:465-475.
19. Cummings JH, Englyst HN. Fermentation in the human large intestine and available substrates. Am J Clin Nutri 1987; 45:1243-1255.
20. Vassallo M, Camilleri M, Phillip SF, Brow ML, Chapman NJ, Thomforde GM. Transit through the proximal colon influences stool weight in the a irritable bowel syndrome. Gastroenterology 1992; 102:102-108.
21. Scheline RR. Metabolism of foreign compounds by gastrointestinal microorganisms. Pharmacol Rev 1973; 25:451-523.
22. Peters R, Kinget R. Film-forming polymers for colonic drug deliver: Synthesis and physical and chemical properties of methyl derivatives of Eudragit S. Int J Pharm 1993; 94:125-134.
23. Huang SI, Bansleben DA, Knox JR. Biodegradable polymers: Chymotrypsin degradation of low molecular weight poly (ester-urea) containing phenylalanine. J App Poly Sci 1979; 23:429-437.
24. Swift G. Biodegradable polymers in the environment: are they really biodegradable. Proc ACS Div Poly Mat Sci Eng 1992; 66:403-404.
25. Ratner BD, Gladhill KW, Horbett TA. Analysis of in vitro enzymatic and oxidative degradation of polyurethanes. J Biomed Mat Res 1988; 22:509-527.
26. Hergenrother RW, Wabewr HD, Cooper SL. The effect of chain extenders and stabilizers on the in vivo stability of polyurethanes. J App Biomat 1992; 3:17-22.

27. Park K, Shalaby WSW, Park H (Ed). Biodegradation In: Biodegradable hydrogels for drug delivery, USA: Technomic publishing company, 1993; 13- 34.
28. Ankita Patel, Dhruvita Patel, Trupti Solanki, Dr. P. D. Bharadia, Mr. V. M. Pandya and Mr. D.A. Modi. Novel Approaches for Colon Targeted Drug Delivery System. IJPI's Journal of Pharmaceutics and Cosmetology 2011; 1(5): 86-97.
29. Khan AK, Piris J, Truelone SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977; 2:895-896.
30. Chan RP, Pope DJ, Gilbett AP, Sneta PJ, Baron JH, Bennardjones JF. Studies of two novel sulphasalazine analogs I.P. salazide and balsalazide. Digest Diseases Sci 1983; 28:609-716.
31. Shibasaki J, Inoue Y, Kadoskai YK, Sasaki H, Nakamura J. Hydrolysis of salicyluric acid in rabbit intestinal microorganisms. J Pharmacobio-Dyn 1885; 8:989-995.
32. Nakamura J, Kido M, Nishida K, Sasaki H. Hydrolysis of salicylic acid tyrosine salicylic acid-methionine prodrug in rabbits. Int J Pharm 1992; 87: 59-66.
33. Nakamura J, Tagami C, Nishida K, Saskai H. Unequal hydrolysis of salicylic acid-D-alanine and salicylic acid-L-alanine conjugate in rabbit intestinal microorganisms. Chem Pharm Bull 1992; 40(2):547-549.
34. Simpkins JW, Smulkowski M, Dixon R, Tuttle R. Evidence for the delivery of narcotic antagonists to the colon as their glucuro-nide conjugates. J Pharmacol Exp Thera 1988; 244:195-205.
35. Ashord M, Fell JT, Attwood D, Sharma H, Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon. J Control Rel 1993; 26:213- 220.
36. Fukui E, Miyamura N, Verma K, Kobayashi M. Preparation of enteric coated time released press coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int J Pharm 2000; 204:7-15.
37. Hita V, Singh R, Jain SK. Colonic targeting of metronidazole using azo aromatic polymers, development and characterization. Drug Del 1997; 4: 19- 22.
38. Mundhe Vinayak S, Dodiya Shamsundar S. Review Article: Novel Approach for Colon Targeted Drug Delivery. Indo Am J Pharma Res 2011; 3:158-173.
39. Tarak Jayraj Mehta, Patel AD, Patel MR, Patel NM. Need of colon specific drug delivery: Review on primary and novel approaches. Int. J Pharma ResBDevelopment 2011; 3(1): 134-153.
40. Swanson D, Barclay B, Wong P, Theeuwes F. Nifedipine gastrointestinal therapeutics system. Am J Med 1987; 8(6):3.

41. Philip AK, Pathak K. Osmotic flow through asymmetric membrane: A means for controlled delivery of drugs with varying solubility. AAPS PharmSciTech 2006; 7(3):1-11
42. Masataka K *et al*. Scintigraphic evaluation of a novel colon-targeted delivery system (CODESTM) in healthy volunteers. J Pharm Sci 2004; 93(5):1287-1299.
43. Yang L, James S, Joseph A. Colon specific drug delivery new approaches and in vitro/ in vivo evaluation. Int J Pharm 2002; 235:1 -15.
44. Ahmed IS. Effect of simulated gastrointestinal condition on drug release from pectin/ethyl cellulose as film coating for drug delivery to the colon. Drug Dev Ind Pharm 2005; 31(4-5): 465-470.
45. Cole ET *et al*. Enteric coated HPMC capsules designed to achieve intestinal targeting. Int J Pharm 2002; 231(1):83-95.
46. Mooter VG, Kinget R. Oral colon-specific drug delivery, A review: Drug Delivery 1995; 2:881-931.