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NOVEL COLON SPECIFIC DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Now a days, various routes of administration have been explored for the effective delivery of the drug to the target site. The oral route is considered to be most convenient for the administration of drugs to patients. But it has a serious drawback in conditions where localized delivery of the drug in the colon is required. Colon target aimed mainly because of less enzymatic activity, longer transit time so it is suitable to deliver the protien and peptide drugs. It also have drawbacks like less water content, presence of fecal content. Different approaches are designed based on prodrug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure etc to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes for colon targeting. The efficiency of drug delivery system is evaluated using different in vitro and in vivo release studies.This review updated the research on different approaches for formulation and evaluation of colon-specific drug delivery systems (CDDS).

INTRODUCTION: Among the various routes of administration, the oral route is considered to be most convenient for the administration of drugs to patients. On oral administration of conventional dosage forms drug normally dissolves in the gastro-intestinal fluids and is absorbed from regions of the gastro-intestinal tract, which depends upon the physicochemical properties of the drug. It has a serious drawback in conditions where localized delivery of the drug in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT.

Dosage forms that deliver drugs in the colon rather than upper GIT has number of advantages. Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon where by high local concentration can be achieved while minimizing side effects. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine.

Additionally, the colon has a long retention time and appears highly responsible to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices. These

delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules, where they are needed most and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the Gastrointestinal tract, namely stomach and small intestine. Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation.

For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may need to be delivered in a presolubilized form or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon.

Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident microflora could also affect colonic performance via degradation of the drug.

History: 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., colon specific azoreductase splits sulfasalazine causing the release of the active moiety 5- aminosalicylicacid. After the several other azo-bonds containing compounds designed to locally release 5-aminosalicylicacid were synthesized bensalazine, balsalazide and olsalazine. In1986, Saffron and coworkers described the use of azo containing acrylic polymers to the delivery of protein drugs like insulin to the colon [1].

The patents which are taken on colon drug delivery system from the date year 1994 to 2007 (**table 1**).

TABLE 1: LIST OF PATENTS ON COLON TARGETED DRUG DELIVERY APPROACHES

Patent No	Title	Patenting Date
5302397	Polymer-based drug delivery system	12/04/94
5407682	Process for the preparation of azo-and/or disulfide polymer matrix drug delivery system for the site specific delivery of an active agent in the colon	18/4/1995
5525634	Colonic drug delivery system	11/06/96
5536507	Colonic drug delivery system	16/07/1996
5626877	Polymer-based drug delivery system	06/05/97
5866619	Colonic drug delivery system	02/02/99
6200602	Composition for enhanced uptake of polar drugs from the colon	13/3/2001
6228396	Colonic drug delivery composition	08/05/01
6322819	Oral pulsed dose drug delivery system	27/11/2001
6319518	Colon selective drug delivery composition	20/11/2001
6231888	Local delivery of non steroidal anti inflammatory drugs (NSAIDS) to the colon as a treatment for colonic polyps	15/5/2001
6413494	Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides	2/7/2002
6368629	Colon-specific drug release system	09/04/02
6605300	Oral pulsed dose drug delivery system	12/08/03
6506407	Colon-specific drug release system	14/1/2003
20050118268	Timed pulsatile drug delivery systems	02/06/05
20070243253	Colonic drug delivery formulation	18/10/2007
20070178108	Colon Specific Gene and Protein and Cancer	02/08/07

Anatomy and physiology of colon: Irrespective of therapy desired for local (colonic) or systemic delivery of drug, the development and aim of the drug delivery to colon remains same [2], that is;

- The drug must not absorb from other regions of the gastro intestinal tract (GIT).
- It should only suffer negligible degradation in the small intestine lumen.
- The release of the drug in the colon should be at quantitatively controlled rate and the released drug in the colon should be absorbed from the lumen of the large intestine without any appreciable degradation.

In order to meet these properties, a thorough knowledge of the anatomy and physiology of GIT is required. The GI tract is divided into stomach, small intestine and large intestine. In GIT, the large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal.

The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus [3]. The human intestine and colon were shown in **Figure 1 and Figure 2** respectively.

The colon is a cylindrical tube, made up of four-layers, serosa, muscularis externa, sub mucosa, and mucosa. The colon does not have villi, but due to presence of plicae semilunares (cresentic folds) the intestinal surface of the colon is increased to approximately 1300 cm^2.

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen [4]. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria.

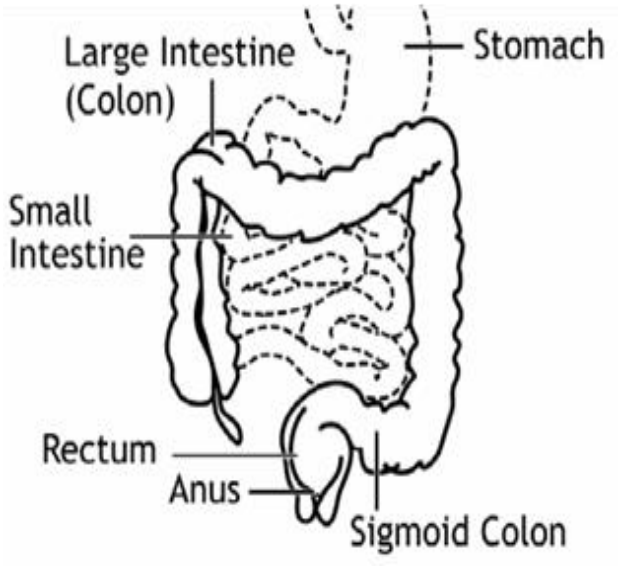

FIG. 1: STRUCTURE OF HUMAN INTESTINE

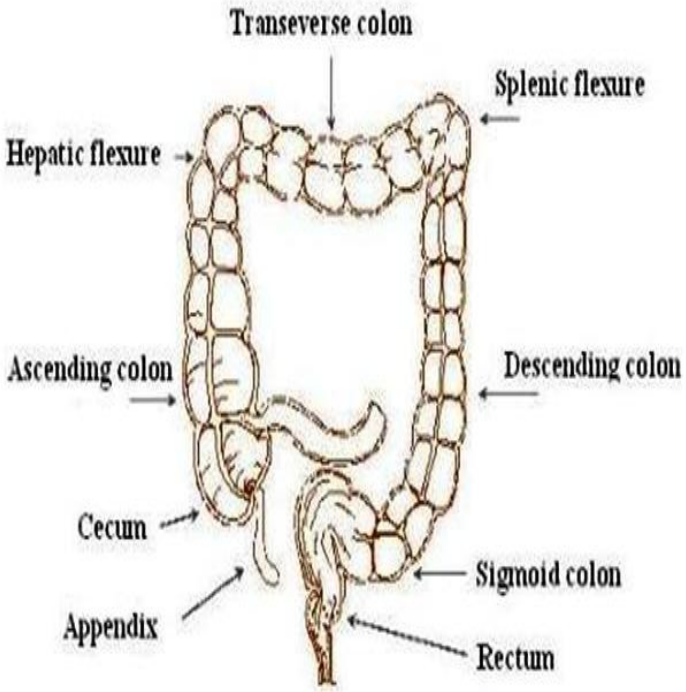

FIG. 2: STRUCTURE OF COLON

TABLE 2: PROPERTIES OF GASTRO INTESTINAL TRACT

Region of GIT	Property	Measured value
Total GIT	Surface area	$2\text{-}10^6$ cm^2
Small intestine	Length	
-Duodenum		20-30 cm
-Jejunum		150-250 cm
-Ileum		200-350 cm
Large intestine	Length	
-Cecum		6-7 cm
-Ascending colon		20 cm
-Descending colon		45 cm
-Transverse colon		30 cm
-Sigmoid colon		40 cm
-Rectum		12 cm
-Anal canal		3 cm
	Internal diameter	
Small intestine		3-4 cm
Large intestine		6 cm
	pH	
Stomach		Fasted 1.5-2.0, fed 3.0-5.0
Duodenum		5-7
Jejunum		6-7
Ileum		7
Colon		5.5-7
Rectum		7
Colon	Redox potential	
-Right		- 415
-Mid		- 400
-Left		- 380

Factors affecting Colon Absorption [5]:

1. Physical properties of drug such as pKa and degree of ionization.
2. Colonic residence time as commanded by GIT motility.
3. Degradation by bacterial enzymes and metabolic products.
4. Local physiological action of drug.
5. Selective and non-selective binding to mucus.
6. Disease state.

Transit through GIT [6]: The drug delivery systems first enter into stomach and small intestine via mouth and then reach colon. The nature and pH of gastric secretion and gastric mucus influence the drug release and absorption. In order to successfully reach colon in an intact form, the drug delivery systems should bypass the barriers in the stomach and small intestine.

Gastrointestinal transit varies from 1 hr to 3 hrs depending upon the condition (fasting or non-fasting). Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hrs to reach the ileocecal junction and the time period is consistent. During this period the dosage form is exposed to enzymes present in small intestine.

Compared to the other region of GIT, movement of material through the colon is slow. Total time for transit tends to be highly variable and influenced by number of factors such as diet particularly dietary fiber content, mobility, stress, disease condition and drugs. The colonic transit time of a capsule in adult is 20-35 hrs. Improved residence time with subsequent longer transit time and the contact of dosage form with micro flora in colon govern the release and absorption of drug from dosage form.

Colonic Microflora [7]: The human alimentary canal is highly populated with bacteria and other microflora at both ends, the oral cavity and the colon/rectum. In between these two sites, the GIT is very sparsely populated with microorganisms. Microorganisms of the oral cavity do not normally affect oral drug delivery systems and as such will not be considered here further. However, gut microflora of the colon have a number of implications in health and the treatment of disease such as IBD. This sectionpresents some background information on gut micro flora as it relates to colonic-based delivery system. Concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalyzing a wide range of metabolic events.

Many colon-specific drug delivery systems rely on enzymes unique to gut micro flora to release active agents in the colon. However, only two or three enzyme systems have been exploited in this area: azoreductases and glycosidases (including glucuronidase). A large number of polysaccharides are actively hydrolyzed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. In addition, ethereal sulfate prodrugs or carboxylated prodrugs may be metabolized in the colon to the parent drug leading to local delivery in the colon. There is certainly room for innovative approaches to carry and release drugs in the colon based on the metabolic capabilities of the colon microflora.

Azoreductases produced by colon play a central role in a number of delivery systems, most notably in catalyzing the release of 5-ASA from a variety of prodrugs. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for beta-glycosidases activity are lactobacilli, bacteroides and bifidobacteria. As with azo-reductase activity, the level of bacterial glycosidase activity in the gastrointestinal tract is associated with the concentration of bacteria in a givenregion.

Stomach and Intestinal pH: Generally, the release and absorption of orally administered drugs are influenced by the GI pH. The gradient in the GIT is not in an increasing order. In stomach the pH is 1.5-2 and 2-6 in fasted and fed conditions respectively [6]. The acidic pH is responsible for the degradation of various pH sensitive drugs and enteric coating may prevent it. In small intestine, the pH increases slightly from 6.6-7.5 and decreases to 6.4 in colon.

Radio-telemetry shows the highest pH level (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drop to 6.4+0.6. The pH in the mid colon is 6.6+0.8 and in the left colon 7.0+0.7. Since there is minimal variation in the pH from ileum to colon, apparently pH dependent polymer drug delivery may not be much selective. However, possible exploitation of pH variation in GIT leads to successful development of various colonspecific drug delivery systems.

General considerations for design of Colonic Formulations: Formulations for colonic delivery are, in general, delayedreleased dosage forms which may be designed either to provide a 'burst release' or a sustained/prolonged /targeted.

1. Pathology of disease, especially the affected parts of the lower GIT.
2. Physico-chemical and bio-pharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery.
3. The preferred release data of the drug.

Very common physiological factor which is considered in the design of delayed release colonic formulations is pH gradient of the gastrointestinal tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH is 6.6±0.4) to the end of the ileum (pH is 7.5±0.5), a decrease in the cecum (pH is 6.4±0.6) and then a slow rise from the right to the left colon with a final value of 7.0±0.7. Some reports suggested that alterations in gastrointestinal pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations [8].

Drugs suitable for CDDS: Based on literature review, the following different categories of drugs are suitable for colon drug delivery.

- Drugs used to treat irritable bowel disease (IBD) require local delivery at drug to colon e.g., sulfasalazine, olsalazine, mesalazine, steroids like fludrocortisone, budesonide, prednisolone and dexamethasone.
- Drugs to treat colonic cancer require local delivery e.g. 5-fluorouracil, doxorubicin, and methotrexate.
- Protein and peptide drugs - eliminating drug degradation e.g. growth hormones, calcitonin, insulin, interleukin, interferon and erythropoietin.
- To treat infectious diseases (amoebiasis & helminthiasis) - requires site specific delivery e.g. metronidazole, mebendazole and albendazole,
- To treat rheumatoid arthritis (NSAIDS), nocturnal asthma, angina require delay in absorption due to circadian rhythms
- Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport e.g., glibenclamide, diclofencac, theophylline, ibuprofen, meto-prolol, and oxyprenolol.

Limitations and challenges in Colon Targeted Drug Delivery:

1. One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system *in-vitro*. This is due to the rationale after a colon specific drug delivery system is quite diverse.

2. As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.

3. Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.

4. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.

5. The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation [8, 9].

The literature also suggested that the cytochrome P-450 (3A) class of drug metabolizing enzymes have lower activity in the colonic mucosa. A longer residence time of 3 to 5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

Advantages: Colon-specific drug delivery system offers the following therapeutic advantages [1, 2, 10 & 11]:

1. Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn's disease etc.)
2. By producing the 'friendlier' environment for peptides and proteins when compared to upper gastrointestinal tract.
3. Minimizing extensive first pass metabolism of steroids.
4. Preventing the gastric irritation produced by oral administration of NSAIDS.
5. Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.
6. Drugs which are destroyed by the stomach acid and/or metabolized by pancreatic enzymes are slightly affected in the colon [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 & 23].

Different approaches to target the Colon:

TABLE 3: APPROACHES FOR THE DEVELOPMENT OF COLON TARGETED DRUG DELIVERY [24]

Approach	Basic feature
I. Chemical Approaches	
1. Azo conjugates	The drug is conjugated via an azo bond
2. Cyclodextrin conjugates	The drug is conjugated with cyclodextrin
3. Glycosidic conjugates	The drug is conjugated with glycoside
4. Glucuronide conjugate	The drug is conjugated with glucuronate
5. Dextran conjugates	The drug is conjugated with dextran
6. Polypeptide conjugates	The drug is conjugated with polypeptide
7. Polymeric prodrugs	The drug is conjugated with polymer
II. Pharmaceutical Approaches	
1. Coating with polymer	
i. Coating with pH-sensitive polymer	Formulation coated with enteric polymers release drug when pH moves towards alkaline range
ii. Coating with biodegradable polymer	Drug is released following degradation of the polymer due to the action of colonic bacteria
2. Embedding in matrices	
i. Embedding in biodegradable polysaccharides	The embedded drug in polysaccharide matrices is released by swelling and biodegradable action of polysaccharides.
ii. Embedding in pH sensitive matrices	Degradation of pH sensitive polymer in the GIT releases the embedded drug
3. Timed released systems	
4. Redox-sensitive polymers	
5. Bioadhesive system	Drug coated with bioadhesive polymer that selectively provides adhesion to colonic mucosa.
6. Coating of miroparticles	Drug is released through semipermeable membrane
7. Osmotic controlled delivery	Osmotic pressure

Chemical or Prodrug Approach: A prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous enzymatic transformation *in vivo* to release the active drug [25]. In this method, the prodrugs are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the carrier.

Different types of conjugates were used to prepare 5-ASA prodrugs, which are succeed in releasing the 5-ASA in colonic region. They are biodegradable poly (ether-ester) azo polymers [26], azo-linked polymeric prodrugs [27], acrylic type polymeric prodrugs [28] and cyclodextrin prodrugs [29]. Glucuronide prodrugs were developed for corticosteriod to deliver the drug to the large intestine of colitic rats [30]. Azo-containing urethane analogues synthesized for colon drug delivery.

A urethane-based analogue containing an azo aromatic linkage in the backbone was synthesized by reacting touline- 2, 6- di- isocyanate with a mixture of an aromatic azodiol [31].

Cyclodextrin prodrugs were prepared by conjugating 5-ASA on to the hydroxyl groups of α-, β-, γ-cyclodextrins through an ester linkage and investigated the release in cecum and colon. After oral administration in rats the conjugate passed through stomach and small intestine without degradation or absorption and in the cecum and/or colon site-specific degradation of conjugate released 5-ASA [32]. An azo prodrug of 5-ASA with histidine was synthesized for targated drug delivery to the inflammated gut tissue in inflammatory bowel disease. The synthesized prodrug was found to be equally effective in mitigating the colitis in rats, as that of sulfasalazine without the ulcerogenicity of 5-ASA and adverse effective of sulfasalazine [33].

In a recent study by Yunjin *et al*., (2006), explained the potential of 5- amino salicyliltaurine as a colon specific prodrug of 5-ASA by *in vivo* evaluation to treat experimental colitis. The prodrug was prepared by conjugating 5-ASA with taurine and tested in 2,4,6, trinitrobenzene sulfonicacid (TNBS) induced colitis rats.

Taurine conjugation of 5-ASA greatly reduced absorption of 5-ASA from the intestine. Oral administration of the conjugate not only increased the colonic delivery efficiency of 5- ASA but also decreased the systemic absorption of free 5-ASA as compared to other conjugates prepared with glycine and asparticacid.

Taurine conjugate of 5-ASA is slightly more effective than sulfasalazine in alleviating the colonic inflammatory induced by TNBS. N-Nicotinoylglycyl-2-(5- fluorouracil-1-yl)-D, L-glycine was synthesized as a prodrug of 5-fluorouracil colon specific drug delivery [34].

pH-dependent system: The basic principle in this method is the coating of the tablets/pellets etc with various pH sensitive polymers (**Table 4**), which will produce delayed release and also give protection from gastric fluids. Selection of polymers is important thing. The selected polymers to colon targeting should be able to withstand the pH of the stomach and small intestine. Methacrylic acid esters are the most commonly used polymers for colon targeting because they are soluble at above pH 6.

The ideal polymer should be able to withstand the lower pH of the stomach and of the proximal part of the small intestine but able to disintegrate at neutral or shortly alkaline pH of the terminal ileum and preferably at ileocecal junction. Eudragit L and Eudragit S are widely used in the colon targeting because Eudragit L is soluble at pH 6 or above and Eudragit S is soluble at pH 7 or above and the combination of these polymers give the desirable release rates.

A novel colon-specific drug delivery system was developed with methacrylate derivatives of 5-ASA using pH sensitive swelling and drug release properties [35].

Composite film coated tablets of 5-ASA were prepared for colon specific delivery. In this method 5-ASA core tablets were prepared and coated with dispersion containing Eudragit RS and dessterrifed pectin, polygalacturonic acid, or its potassium and sodium salts. Negligible drug release occurred during first five hours where the coated tablets were in the stomach and small intestine.

After that, the release of 5-ASA from coated tablets occurred linearly as a function of time due to the action of pectinolytic enzymes [36]. A comparison study of the usual enteric-coated polymers viz. Eudragit, Cellulose acetate phthalate with Shellac and Ethyl cellulose as carriers for colon specific drug delivery was conducted to select a suitable carrier.

In this study, lactose based indomethacin tablets were prepared and coated with one of the above coating polymers to a varying coating thickness. From the dissolution data, at a coat concentration of 3% shellac provided the most appropriate polymer coat for colon-specific drug delivery. Variation in the shellac coat thickness can facilitate drug delivery to terminal ileum, distal or proximal colon [37].

EUDRACOLTM is a novel pH and time controlled multiple unit colon drug delivery systems in which the pellets coated with Eudragit RL/RS and Eudragit FS 30D. Caffeine is used as marker drug for pharmacokinetic studies using the multi particle principle and delayed release in the colon; reduction of dosing frequency may be achieved. Due to its specific coating structure, the Eudracol system offers a new dimension for colon drug targeting via the oral route [38].

5-ASA pellets were coated with the enteric coating solution containing different ratios at Eudragit L-100 and Eudragit S-100 for colon drug delivery. The release of 5-ASA is depending on the thickness of the layer and the ratio of Eudragit copolymers [39]. pH-sensitive hydrogels were prepared for colonic delivery of therapeutic peptides, proteins. New pH-sensitive glycopolymers were developed by free radical polymerization of methacrylic acid and 6-hexandiol diacrylate and 6- hexandiol propoxylate diacrylate [40].

TABLE 4: LIST OF PH DEPENDENT POLYMERS [41, 42 & 43]

pH dependent polymers	Threshold pH
Polyvinyl acetate phthalate (PVAP) (Coateric®)	5.0
Cellulose acetate phthalate (CAP) (Aquateric®)	6.
Cellulose acetate trimellitate (CAT)	5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	
LF Grade	≥5.5
MF Grade	≥6.0
HF Grade	≥6.8
Hydroxypropyl methylcellulose phthalate (HPMCP)	
HP-50	≥5.0
HP-55 and HP-55S	≥5.5
Shellac (MarCoat 125 & 125N)	7.0
Eudragit® FS 30D	≥7.0
Methacrylic acid copolymer, Type A (Eudragit®L-100 and Eudragit® L12, 5)	≥6.0
Methacrylic acid copolymer, Type B (Eudragit®S-100 and Eudragit® S12, 5)	≥7.0
Methacrylic acid copolymer, Type C (Eudragit® L100-55)	≥5.5
Methacrylic acid copolymer dispersion (Eudragit® L30D)	5.6

Time-dependent system: The basic principle involved in the system is the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount [44]. Colon targeting could be achieved by incorporating a lag time into formulation equivalent to the mouth to colon transit time. A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. In this method the solid dosage form coated with different sets of polymers (listed in **Table 5**) and the thickness of the outer layer determines the time required disperse in aqueous environment.

Colon drug delivery system of diclofencac sodium (DS) was developed using time dependent approach. In this, diclofencac sodium tablets were coated with ethylcelluese in ethanol solution cooling diethyl phthalate as a plasticizer and PEG 400 as channeling agent. The lag time of DS release was primarily controlled by thickness of ethycellulose coating layer. By increasing the thickness of the coating layer, longer the lag time of DS release [39]. Formulation of fast release enteric coated tablets for colon drug delivery using two different approaches. The first one is using super disintegrate and the second one is based on osmogen.

In the first approach core tablets (celicoxib as a model drug) were prepared using different concentrations of super disintegrates like cross-linked PVP. In second approach core tablets were prepared using potassium chloride, sodium chloride as osmogen. Then they are coated with Eudragit L-100:Eudragit S-100 in the ratio of 1:5 to achieve a desired thickness. The tablets with super disintegrates are fast released where the tablets with osmogen are sustain released. The coat weight determines the lag phase that required eliminating the release in stomach and small intestine [45].

Hydroxy Propyl Methyl Cellulose compression coated tablets of 5-fluorouracil were studied for colon drug delivery that based on time-dependent approach. In this, the core tablet was prepared by wet granulation method and then coated with 50% of HPMC/lactose coat powder by compression-coating method. Drug release characteristics were evaluated in distilled water by using a Chinese pharmacopoeia rotatable basket method [46].

Micro Flora Activated System: The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by release of drug load in colonic region because the bioenvironment inside the

human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms [37] (Sinha, Rachana, 2003). In this method, drugs and/or dosage forms are coated with the biodegradable polymers (Table 5) i.e., the polymers degrade due to influence of colonic microorganisms.

When the dosage form passes through the GIT, it remain intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating.5-ASA pellets were coated with amylose for colon drug delivery, in which amylose coating solution was prepared along with Ethocel, Eudragit RS/RL 30D and Aquacoat ECD 30 [47]. Chitosan capsules were developed for colon specific delivery of insulin and its absorption was improved by addition of absorption enhancers (sodium glycocholate, sodium oleate) and protease inhibitors like bacitracin, aprotinin [48].

Low swelling guar gum prepared by corsslinking with glutaraldehyde that is used as a colon-specific drug carrier [49]. Chitosan succinate and chitosan phthalate were synthesized by reacting the chitosan separately with succinic anhydride and phthalic anhydride. These semisynthetic polymers produced stable matrices of diclofencac sodium for colon specific delivery that had more resistance to acidic condition and improved drug release profile under basic conditions [50].

Organic acids like succinicacid, tartaricacid and citricacid were used as excipients in matrix granules to modify the drug release for colon-specific drug delivery [51]. Amylose-Ethylcellulose film coatings obtained from organic-based solvents were investigated as potential vehicles for colon drug delivery.

In this method, amylose-butanol dispersion and ethycellulose in ethyl-acetate/ethnol/propanol with dibutylsebacate as plasticizer were mixed in various proportions and coated on 5-ASA pellets to achieve desired thickness. The drug release regulating parameters are thickness of coating and ratio of amylose to ethylcellulose. The release of drug is irrespective of the solvent used for coating. Formulation containing 1 part amylose and 1 part ethylcelluose of coating thickness, 15% TWG, gives desired release profiles of 5-ASA for colon targeting [52].

Phosphated cross-linked guar gum was prepared for colon-specific drug delivery. Guar gum cross-linked with increasing amounts of trisodiumtri-metaphosphate to reduce its swelling properties for use as a vehicle in oral delivery formulations, especially drugs aimed at localizing in the distal portions of the small bowel. Swelling of guar gum in artificial GI fluids was reduced from 100-120- fold to 10-35-fold depending on the amount of cross linker used [53].

Colon target drug delivery system for mebendazole was developed using guar gum as a carrier. In this method mebendazole matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder. From the results 20% and 30% guar gum tablets were provided targeting of mebendazole for local action in the colon [54]. The α-cyclodextrin derivate of prednisolone-21-succinate showed anti-inflammatory activity with low adverse effects when compared to prednisolone alone by intra colonical administration to rats with 2,4,6, trinitrobenzene sulfonicacid-induced colitis. The conjugate can alleviate the systemic adverse effect of prednisolone while maintaining the therapeutic activity of prednisolone [55].

A chitosan-dispersed system (CDS) was developed for colon- specific drug delivery, in which the capsule containing acetaminophen was coated with the suspension containing chitosan powder and Eudragit RS, formed a drug release-regulating layer around the capsule. Outer enteric coating layer prevent the dissolving of chitosan under acidic pH. The resultant enteric-coated CDS capsules reached the large intestine with in one to three hours after oral administration and they were degraded at the colon in beagle dogs [56, 57 & 58] were studied about the lactulose as a carrier for colon-specific drug delivery by microbial degradation in colon.

Enteric-coated pectin based matrix tablets were prepared for colonic delivery of theophylline. This approach takes advantage of the combination of pH-sensitive method and microbial-triggered system. In this method theophylline-colon biodegradable pectin matrix tablets were prepared and coated with enteric coating solution (Eudragit S100 in acetone) to overcome the poor compactability of pectin.

Emdex, a hydrophilic directly compressible material was used to prepare tablets by direct compression [59]. The new quaternized chitosan i.e. triethyl chitosan (TEC) is evaluated in pharmaceutical approaches and proved that there is a significant increase in absorption of poorly absorbed compounds in colon specific drug delivery system [60].

Calcium pectinate beads were prepared for colon specific delivery of therapeutic peptides like bovine serum albumin (BSA) by extruding BSA-loaded pectin solution to an agitating calcium chloride solution and gelled spheres were formed instantaneously by an ionotropic gelation reaction. The drug release was regulated by concentration of pectin, concentration of calcium chloride and total drug loading [61]. The HPMA Copolymer (N-(2-hydroxy propyl) methacrylamide)-9 amino camptothein conjugate containing a spacer was synthesized and characterized for oral colon specific drug delivery. The drug delivery system has potential in the treatment of colon cancer [62-63]. Zinc pectinate beads formed the strongest network matrix in comparison with calcium pectinate and suggested the zinc pectinate beads as efficient carriers for specific drug delivery to colon [64].

Metronidazole tablets were prepared using various polysaccharides like guar gum, xanthan gum, pectin, carrageenan, β-cyclodextrin for colon specific drug delivery to treat ameobiasis [65] Mundargi *et al*., 2007). 5-Fluorouracil compression coated tablets were prepared for colonic release of drug using xanthan gum, boswellia gum and HPMC as the coating materials [66].

CDDS of 5-fluorouracil was developed using pectin-ethyl cellulose as a film coat with Fluidized bed coater [67].

TABLE 5: MATERIALS USED IN FORMULATION OF CDDS

Prodrug conjugates	pH-Sensitive Polymers	Materials used In Time-Dependent System	Microbial degradable polymers
Azo bond conjugates	Eudragit L-100	Hydroxy Propyl Methyl Cellulose	Chitosan
Amino acid (Polypeptide) conjugates	Eudragit S-100	Hydroxy Ethyl Cellulose	Pectins
Glycoside conjugates	Eudragit L-30 D	Ethyl Cellulose	Guar gum
Glucuronide conjugates and Sulphate conjugates	Eudragit L-100-55	Microcrystalline Cellulose	Dextrans
Polymeric conjugates	Eudragit F S 30 D	Hydroxy Propyl Methyl Cellulose Acetate Succinate	Inulin
Cyclodextrin conjugates	Poly Vinyl Acetate Phthalate	Lactose/Behinic acid	Lactulose
Dextran conjugates	Hydroxy Propyl Methyl Cellulose Phthalate 50		Amylose
	Hydroxy Propyl Methyl Cellulose Phthalate 55		Cyclodextrins
	Hydroxy Propyl Ethyl Cellulose Phthalate		Alginates
	Cellulose Acetate Phthalate		Locust bean gum
	Cellulose Acetate Trimellate		Chondroitin sulphate
			Boswellia gum

Combination of different approaches of CDDS: An oral colonic drug delivery system of 5-ASA was developed using combination of pHdependent, time-based and enzyme degradable approaches. The pellets were coated with three functional layers i.e., the outer Eudragit L 30D-55 layer for protection against GI fluids, the intermediate layer of ethyl cellulose to inhibit the drug release during passage through the small intestine and the inner layer of pectin for swelling and enzyme-degradation. In vitro release studies indicated that the coated pellets completely protected the drug release in 0.1M HCl while the drug release was delayed for three to four hours in pH 6.8 phosphate buffer [68]. Pulsatile device was formulated to achieve time- or site-specific release of theophylline based on chronopharmaceutical consideration.

The basic design consists of an insoluble hard gelation capsule body filled with Eudragit microcapsules of theophylline and sealed with a hydrogel plug and finally the enteric device was enteric coated. In this approach, pH sensitive and time dependent delivery systems were combined. In this the thickness of enteric coat is a measure of protection from stomach and intestine pH. Different hydrogel polymers were used as plugs to maintain a suitable lag period.

The hydrophilic polymer content is a measure of delayed release of theophylline from microcapsules [69].

Pectin based CDDS of 5-fluorouracil was developed using calcium pectinate gel. Calcium pectinate gel beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S-100 and evaluated using USP paddle type dissolution apparatus in different simulated mediums [70].

A new microbial-triggered colon targated osmotic pump (MTCT-OP) was developed for CDDS based on chitosan for a model drug, budesonide. The combination of osmotic technology and microbial-triggered mechanism had a high potential to deliver to drug load in colonic region. In this method the core tablet of budesonide was prepared with chitosan, which is used to produce osmotic pressure, and to form the insitu delivery pores for colon-specific drug release.

Cellulose acetate in acetone along with chitosan (as pore forming agent) was coated on tablet as a semipermiable membrane and finally coated with Eudragit L-100-55 in ethanol as an enteric coating layer that could prevent cellulose acetate membrane from forming pore or rupture before reaching colon region. Budesonide release from developed system was inversely proportional to the osmotic pressure to the release medium [71].

Hydrogel based CDDS: Amydated pectin hydrogel beads prepared for colon specific delivery of indomethacin and sulfamethoxazole [72]. Glutaraldehyde cross-linked dextran capsules were prepared for colon targeting. Along with magnesium chloride and PEG 400 in water the capsule caps and bodies were prepared on nylon molding pins.

Then, the dextran capsules were filled with model drug (Hydrocortisone) and drug release was studied. The drug release pattern was suitable for colon specific delivery [73]. The hydrogels formed by cross-linked polyvinyl alcohol were suitable for colon specific drug delivery systems. In this method polyvinyl alcohol of different molecular weights was corss-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel-forming polymers. The hydrophilic drugs like diclofencac sodium, propranolol hydrochloride and vitamin B6 hydrochloride were used as model drugs [74].

Methacrylated inulin hydrogels designed for colon targeting the proteins like Bovine serum albumin or Lysozyme. Organic redox-initiated polymerization technique was used to fabricate pH responsive hydrogels for colon specific delivery [75].

Glutaraldehyde corss-linked guar gum hydrogel discs were prepared as vehicles for colon specific drug delivery of ibuprofen. Percent drug release increased with glutaraldehyde concentration. Cross-linking decreased the swelling of guar gum. The fabricated hydrogels discs may prove to be beneficial as colon-specific drug delivery vehicles for poorly water-soluble drugs like ibuprofen [76].

Novel complex hydrogel beads were prepared using pectin and zein for colon-specific drug delivery. Pectin/Zein complex hydrogel beads showed the capability to protect incorporated drugs from premature release into stomach and small intestine. The inclusion of a small portion of zein (a protein from corn) in to the pectin efficiently suppressed the swelling behavior of pectin, thus stabilizing the structural property of the pectin networks.

Like wise, the pectin networks protects the bound zein from protease digestion. These properties made pectin/zein complex beads a promising system for colon specific drug delivery [77]. Cross-linked HPMC hydrogels were synthesized and used to develop 5-ASA colon drug delivery system [78].

Novel Drug Delivery Systems for CDDS: Now a days the basic CDDS approaches are applied to formulate novel drug delivery systems like Multiparticulate systems, Microspheres, Liposomes, Microencapsulated particles etc.

Multiparticulate systems: Multiparticulates (pellets, non-peariles etc.,) are used as drug carriers in pH-sensitive, timedependent and microbially control systems for colon targeting. Multiparticulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such asmore predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules [79].

A multiparticulate dosage from was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB). Microspheres loaded by an enteric polymer (Eudragit S). Here the enteric coating layer prevents the drug release below pH 7. After that CAB microspheres efficiently. controlled the release of budesonide, which is depended on the polymer concentration in the preparation [80].

Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and Eel calcitonin [81]. A multiparticulate chitosan dispersed system (CDS) was prepared for colon drug delivery and it was composed of the drug reservoir and the drug release-regulating layer, which was composed of water insoluble polymer and chitosan powder.

The drug reservoir was prepared by drug containing multiparticulates like Non peariles in the study. In this study the multiparticulate CDS was adopted not only for colon specific drug delivery but also for sustained drug delivery [82].

A multiparticulate system combining pH sensitive property and specific biodegradability was prepared for colon targated delivery of metronidazole. The multiparticulate system was prepared by coating cross-linked chitosan microspheres explorting Eudragit L-100 and S-100 as pH sensitive polymers.

The *in-vitro* drug release studies shows that no release of drug at acidic pH and higher drug release was found in presence of rat caecal contents indicating susceptibility of chitosan matrix to colonic enzymes released from rat caecal contents [83]. High-Amylose cornstarch and Pectin blend microparticles of diclofencac sodium for colon-targeted delivery were prepared by spray drying technique.

The blending of high-amylose cornstarch with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition from pectinbased microparticles. The drug released in colonic region by the action of pectinase from microparticles [84] investigated the effect of sodium glycocholate as an absorption promoter on orally administrated insulin absorption utilizing a colon-targeted delivery system. A novel insulin colon-targeted delivery system (Insulin- CODES) contains insulin, lactulose as a trigger for colon-specific release, citricacid as a solubilizer of insulin, meglumine as a pH adjusting agent andsodium glycocholate as an absorption promoter.

Microspheres of Anti-Cancer Drugs: Cross-linked guar gum microspheres containing methotrexate were prepared and characterized for local release of drug in the colon for efficient treatment of colorectal cancer. In this method glutaraldehyde was used as a cross-linking agent and guar gum microspheres were prepared by emulsification method. From the results of in vitro and in vivo studies the methotrexate loaded cross linked guar gum microspheres delivered most of the drug load (79%) to the colon, where as plain drug suspensions could deliver only 23% of there total dose to the target tissue [85].

Colon specific microspheres of 5-fluorouracil were prepared and evaluated for the treatment of colon cancer. In this method, core microspheres of alginate were prepared by modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The results showed that this method had great potential in delivery of 5-fluorouracil to the colon region [86].

Advantages of Microspheres:

1. Provide selective passive targetting to tumour tissues.
2. Flexibility to couple with site-specific ligands to achieve active targetting.
3. Increased efficacy and therapeutic index.
4. Increased stability via encapsulation.
5. Reduction in toxicity of the encapsulated agent.
6. Improved pharmacokinetic effects.

Evaluation of CDDS: The drug release in the colonic region from different CDDS is evaluated by different methods of in vitro and in vivo release studies, which show the success rate of different designs of colon drug delivery systems. Depending upon the method of preparation different evaluation methods are proposed. A successful colon specific drug delivery system is one of that remains intact in the physiological environment of stomach and small intestine, but releases the drug in the colon.

***In-vitro* Evaluation:** Different in vitro methods are used to evaluate the colonic drug delivery systems. In in-vitro studies the ability of the coats/carriers to remain intact in the physiological environment of the stomach & small intestine is assessed by drug release studies in 0.1N HCl for two hours (mean gastric emptying time) and in pH 7.4 phosphate buffer for three hours (mean small intestine transit time) using USP dissolution apparatus. In case of micro flora activated system dosage form, the release rate of drug is tested in vitro by incubating in a buffer medium in the presence of either enzymes (e.g., pectinase, dextranase) or rat/guinea pig/rabbit caecal contents. The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study [87].

***In-vivo* Evaluation:** Like other controlled release delivery systems, the successful development of the CDDS is ultimately determined by its ability to achieve release in colonic region thus exerts the intended therapeutic effect. When the system design is concerned & prototype formulation with acceptable in-vitro characteristics is obtained, in vivo studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetic information of the delivery system.

Although animal models have obvious advantages in assessing colon specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems. The preferable animals to evaluate CDDS are rats, guinea pigs and dogs [87]. γ-scintgraphic studies were conducted in human volunteers with technetium-99m-DTPA as tracers in sodium chloride core tablets compression coated with guar gum showed that the gum coatprotect the drug (tracer) from being released in the stomach and small intestine. On entering the ascending colon, the tablets commenced to release the tracer indicating the breakdown of gum coat by the enzymatic action of colonic bacteria [88]. Technetium-99m-DTPA was used as a tracer for γ- scintigraphy evaluation of colon specific guar gum directly compressed matrix tablets in human volunteers [89]. The scintgraphic evaluation conducted for capsule type colon specific drug delivery system in human healthy volunteers [15].

In a study by Krishnaiah *et al*., (2001) [90], showed the effect of metronidazole and tinidazole (antimicrobial agents) on the release of albendazole from guar gum based colon specific matrix tablets. The active antimicrobial agents (7 days) treatment of rat caecal content decreased the release of albendazole due to decreased levels of anaerobic bacteria present in rat.

CONCLUSION: From past two decades, considerable amount of research work has been carried out in the area of colon targeting. The advantages of targeting drugs specifically to the diseased colon are reduced incidence of systemic side effects, lower dose of drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site.

By considering the advantages of CDDS like providing friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc.,

Different approaches are designed to develop colonic drug delivery system. The release of drug load in colon region is depended on pH of GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule.

The preferred CDDS is that should release maximum drug load in colon region. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially

activated system and others. Different polymers are used to prepare CDDS by various approaches and are evaluated for their efficiency and safety.

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