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REVIEW ARTICLE

Recent trends in Colon targeted drug delivery system

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ABSTRACT

Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. In addition to local therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. Oral administration of different dosage forms is the most commonly used method due to flexibility in design of dosage form and high patient acceptance, but the gastrointestinal tract presents several formidable barriers to drug delivery.. Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. 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. In the recent times, the colon specific delivery systems are also gaining importance not only for local drug delivery of drugs but also for the systemic delivery of protein and peptide drugs. This review explains the need and approaches to colonic drug delivery through oral route.

Keywords: Colon specific drug delivery system, microspheres, gastrointestinal tract, multiparticulates.

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INTRODUCTION

Now a day, various routes of administration have been explored for the effective delivery of the drug. 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 these 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 (colon cancer, ulcerative colitis, crohn's disease and inflammatory bowel disease) whereby 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. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of g.i.t. previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes & temporary storage of stools. But now it is accepted as important site for drug delivery. Targeted delivery ensures the direct treatment at the disease site, lower dosing, & reduction in 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 and the stability of the drug in the colonic environment is a further factor that warrants attention.

Colon Anatomy

The GI tract is divided into stomach, small intestine and large intestine. 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 [24]. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure .The left colon contain descending colon, splenic flexure and sigmoid. 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 [9]. 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. The colon tissue containing the villi, lymph, muscle, nerves, and vessels [3].

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Physiology of Colon

Colon is divided in to the caecum, ascending colon, transverse colon, rectum and anal canal Fig. 1. The caecum has a dilated portion, which is blinded interiorly and is continuous with the ascending colon superiorly. Ascending colon passes upwards from the caecum to the level of the liver where it bends acutely to the left at the right colic flexure to become transverse colon. The transverse colon, that extends across the abdominal cavity, in front of the duodenum and the stomach to the area of the spleen. The descending colon passes down the left side of the abdominal cavity then bends towards the midline. Pelvic colon describes an S shaped curve in the pelvic, then continuous downwards to become the rectum [9]. Colon consists of layer of tissues, i.e. the longitudinal muscle fiber, submucous layer, mucous membrane lining. Arterial Blood supply in the colon is mainly by superior and inferior mesenteric arteries and venous drainage is mainly by the superior and mesenteric vein [4].

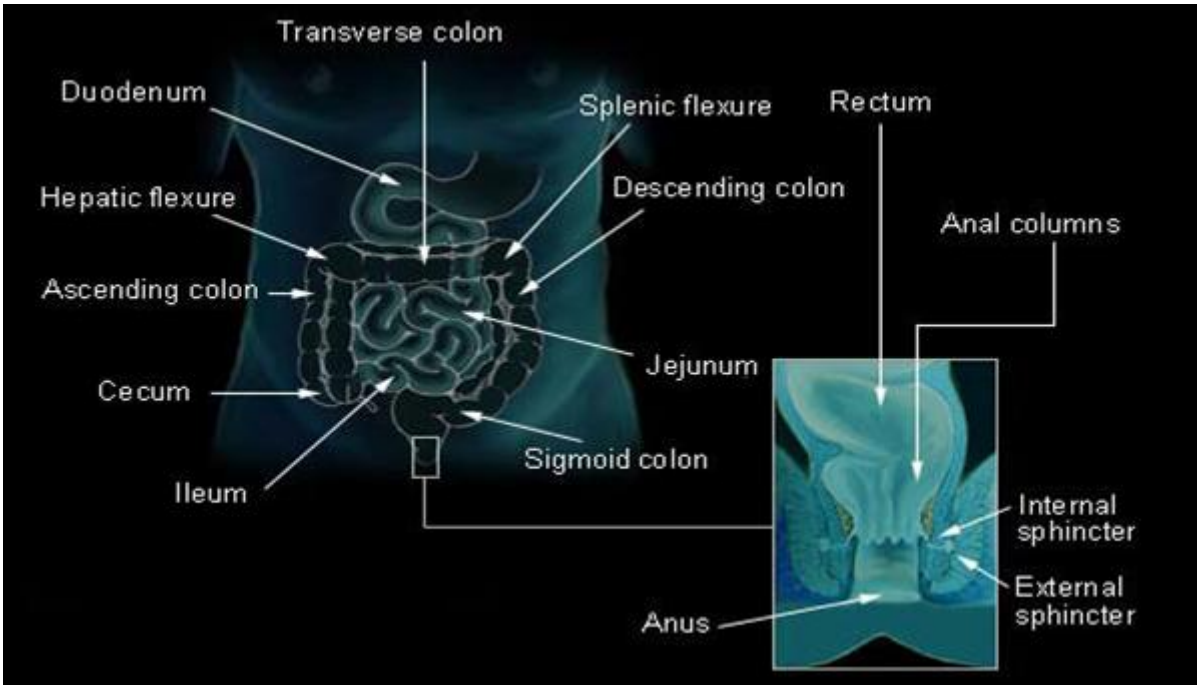

Figure 1: Small and Large Intestine

Factors affecting colon absorption [30, 31]

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

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Colon Target Drug Delivery System

The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon [1].

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Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal [31]. Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity [34].

When the drug is to be delivered into colon without dilution in other regions of gastrointestinal tract then the drug has poor absorption in stomach or small intestine, colonic drug delivery is preferred. The pH in this region varies from 6.4 - 7 and presence of microbial flora plays as important role in drug release especially in this region. Various mechanisms are adopted for drug release in this area are.[30]

- Coating with pH sensitive polymer e.g., Eudragit®S100, Eudragit® L100,
- Biodegradable polymer like polymers which are sensitive to colonic bacteria.
- Polymers which selectively sticks to colonic mucosa e.g., polycarbophils or polyethans.

- Redox sensitive polymers that respond to redox potential in colon which expresses the total metabolic and bacterial action.

Need of Colon Drug Delivery System

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects [4].
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery [11].
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases [11].
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted) [24].
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon [8].
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides [8].

Approaches to Colonic Drug Delivery Through Oral Route

Oral route generally preferred by the patient than the rectal route. Colon is the most distal segment of g.i.t. that's why orally administered drug must retard drug release in the upper g.i.t. but must release promptly on entry into the distal colonic part. In colon due to presence of low fluid volume & viscous nature of luminal content, the drug dissolution & release from the formulation may vary. Colonic microflora also shows impact on the stability of released drug. Inspite of these difficulties various approaches & systems have been developed to target the drug to the colon [13].

pH dependent delivery – In g.i.t. there is presence of pH gradient which approximately ranges from 1.2 in stomach, 6.6 in proximal small intestine, 7.5 in distal intestine & pH of colon is about 6.4. Generally Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0, which results in premature drug release from the system. It is concluded that pH of g.i.t. was not a reliable criteria for colonic targeting. 3 Problem of premature drug release can be overcome by the use of Eudragit FS [13].

Pressure dependent delivery – The pressure controlled colon delivery capsule utilizes the increase in pressure of the luminal contents of the colon. Increase in luminal pressure is due to reabsorption of water in this region. The drug is dispersed in suppository base & coated with

ethyl cellulose for the preparation of such system. Temperature of body is responsible for suppository base to melt & increases the volume which forms balloon of ethyl cellulose filled with liquid. This balloon can withstand with the contraction of small intestine (peristalsis) but ruptures when subjected to intensive contraction in the colon & contents of thicker viscosity. This system is used for the production of single unit system [29].

Bacteria dependent delivery – In this system colonic bacteria are utilized to degrade the substrate. The bacterial amount has been estimated about 10 11 per gram in the colon & having around 400 species (anaerobic in nature). Earlier polymer cross linked with azo aromatic groups was used but due to potential carcinogenic activity now a day's natural polysaccharides are used. Natural polysaccharides generally undergo premature drug release so they are chemically modified or mixed with hydrophobic polymers. This polymer shows good film forming properties, resistant to pancreatic enzymes but they will undergo degradation due to bacterial enzyme [22].

Time dependent delivery (Pulsatile drug delivery) - Pulsatile release systems are formulated to undergo a lag-time of predetermined span of time of no release, followed by a rapid & complete release loaded drugs(s). The approach is based on the principle of delaying the time of drug release until the system transits from mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. This system offers many advantages over conventional oral drug delivery systems like patient compliance, reduced dosage, reduced dosage frequency, avoidance of side effects, avoidance of peak and valley fluctuation, nearly constant drug level at the target site [32].

Colon Disease- There are various colon disease which are listed below-

- Acid Reflux/Heartburn [20]
- Colon cancer [20]
- Crohn's disease [10]
- Ulcerative colitis [10]
- Diverticulitis [20]
- Non-cancerous colon polyps [25]
- Hemorrhoids [25]

DIFFERENT APPROACHES TO TREAT COLON DISEASE

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 [27]. 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 [26].

Different types of conjugates were used to prepare 5-ASA (5-Acetyl salicylic acid) prodrugs, which succeed in releasing the 5-ASA in colonic region. They are biodegradable poly (ether-ester) azo polymers [23], azo-linked polymeric prodrugs [12], acrylic type polymeric prodrugs[28] and cyclodextrin prodrugs. Glucuronide prodrugs were developed for corticosteroid to deliver the drug to the large intestine of colitic rats [16].

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-diisocyanate with a mixture of an aromatic azodiol [7]. Cyclodextrin prodrugs were prepared by conjugating 5-ASA on to the hydroxyl groups of α-, β-, γ-cyclodextris 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. An azo prodrug of 5-ASA with histidine was synthesized for targeted drug delivery to the inflammated gut tissue in inflammatory bowel disease [20].

pH-Dependent System

The basic principle in this method is the coating of the tablets/pellets etc with various pH sensitive polymers, 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[20]. Methacrylic acid esters 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 [10].

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 [21]. 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 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 [15].

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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 bioenvironmental inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms [26]. In this method drugs and/or dosage forms are coated with the biodegradable polymers i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating [6].

Combination of Different Approaches of CDDS

An oral colonic drug delivery system of 5-ASA was developed using combination of pH dependent, time based and enzyme degradable approaches. The pellets were coated with three functional layers i.e. the outer EudragitL30D-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 [14]. 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 gelatin 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 [19]. Pectin based CDDS of 5-fluorouracil was developed using calcium pectinate gel. Calcium pectinate gel beads were prepared by ionotropic gelatin method followed by enteric coating with Eudragit S-100 and evaluated using USP paddle type dissolution apparatus in different simulated mediums [17].A new microbial-triggered colon targeted 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 in situ delivery pores for colon-specific drug release. Cellulose acetate in acetone along with chitosan (as pore forming agent) was coated on tablet as a semi-permeable 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[18]. Hydrogel based CDDS amylase pectin hydrogel beads prepared for colon specific delivery of indomethacin and sulfamethoxazole [21].

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REFERENCES

[1] Akala EO, Elekwachi O, Chase V, Johnson H, Marjorie L, Scott K. Drug Dev Ind Pharm 2003; 29:375-386.
[2] Ardizzone S, Bollani S, Manzionna G, Bianchi Porro G. Eur J Gastroenterology Hepatol 1999; 11: 27-32.
[3] Ardizzone S, Porro G B. Drug Safety 2002;25: 561-82.
[4] Bajpai S K, Bajpai M, Dengree R. J Appl Polym Sci 2003; 89: 2277–2282.
[5] Basit A, Bloor J. Pharmtech 2003; 185-190.
[6] Brigitte Skalsky, Markus Rudolph, Gerhard Renner et al. Eudracol Abstract 2003;112.
[7] Chavan MS, Sant VP and Nagarsenker MS. J Pharma Pharmacol 2001; 53: 895-900.
[8] Chourasia M K, Jain S K. J Pharmaceutical Sci 2003; 6: 33-66.
[9] Colonic Delivery Formulations, Recent Patents on Drug Delivery and Formulation, 2007;12-13.
[10] Davaran S, Rashidi M R and Hashemi M. AAPS Pharm Sci Tech 2010; 4: 1-6.
[11] Encyclopedia of controlled drug delivery, John wiley and sons, Inc. Newyork, 2003, pp 698-726.
[12] Etienne Schacht, An Gevaert, El Refaie Kenawy. J Controlled Release 1996; 39: 327-338.
[13] Evans DF, Pye G, Bramley R, Hardcastle JD. Gut 1988; 29: 35-1041.
[14] Fude C, Lei Y, Jie J. Drug Dev Ind Pharm 2007; 33: 999-1007.
[15] Gang Cheng, Feng An, Mei-Juan Zou. World J Gastroenterology 2004; 10: 1769-1774.
[16] Harold W. Nolen III, Richard N. Biopharmaceutics Drug Disposition 1997; 18:681-695.
[17] Jain A, Gupta Y, Jain SK. J Drug Target 2007; 15: 285-294.
[18] Liu H, Yang XG, Nie SF et al. Int J Pharma 2007; 332: 115-124.
[19] Mastiholimath VS, Dandagi PM, Samata Jain S et al. Int J Pharma 2007; 328: 49- 56.
[20] Mei-Juan Zou, Gang Cheng, Hirokazu Okamoto. World J Gastroenterology 2005; 11: 7457- 7460.
[21] Munjeri O, Collett JH and Fell JT. J Controlled Release 1997; 46: 273-278.
[22] Saffron M, Kumar GS, Sabvariar C, Burnham JC, Williams F, Neckers DC. Sci 1986; 233: 1081-1084.
[23] Samyn C, Kalala.W, Vanden Mooter et al. Int J Pharm 1995; 121: 211-216.
[24] Sarasija S, Hota A. Indian J Pharmaceutical Sci 2000; 62: 1-8.
[25] Shweta Arora, Ali J, Alka Ahuja et al. Indian J Pharma Sci 2006; 68: 295-300.
[26] Sinha V R, Rachana Kumaria. European J Pharma Sci 2003; 18: 3-18.
[27] Sinha, V.R., Kumaria, Rachna. Int J Pharm 2001; 224: 19-38.
[28] Soodabeh Davaran, Jalal Hanaec, Abbas Khosravi. J Controlled Release 1999; 58: 279-287.
[29] Takaya T, Ikada C, Imagawa N, Niwa K, Takada K. J Pharm Pharmacol 1995; 47:474-478.

[30] Vyas SP, Khar RK. Controlled drug delivery, Concepts and Advances, 1s t edition, Vallavbh prakashan ,2002,pp 258-268.
[31] Watts P, Illum L. Drug Dev Ind Pharm 1997; 23: 893- 913.
[32] Wilding IR, Davis SS, Bakhshaee M, Stevens HNE, Sparrow RA, Brennan J. Pharm Res 1992; 9: 654-657.
[33] Wilson and Gisvold's, Textbook of Organic Medicinal and pharmaceutical chemistry Edited by Delgodo J.N., Remers W.A.,1990, 10th Edition, pp 212.
[34] Wood E, Wilson CG, Hardy JG. Int J Pharm 1985; 25: 191-197.