REVIEW ARTICLE

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# Colon-Specific Drug Delivery Systems

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**Colon specific delivery of drugs are of interest for the treatment of colonic diseases, so as to maximize the effectiveness of these drugs. Oral delivery of peptides and proteins are possible because colon provides a more friendly environment than the upper gastrointestinal tract. Colon is also rich in lymphoid tissue so uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies thus helping in vaccine delivery. This review deals with the anatomy and physiology of colon and various aspects of formulations by which colon targeting of drugs can be achieved.**

Formulations that release drug into the colon rather than the upper intestinal tract are beneficial for a number of clinical situations. Delivery of drugs to the colon via, the oral route is valuable in treating diseases of the colon (ulcerative colitis, Chron's disease, carcinomas and infections) whereby high local concentration can be achieved while minimising side effects that occur because of release higher up in the gastrointestinal tract or because of unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies, and this helps in effecient vaccine delivery. Oral delivery of peptides can also be achieved through colon. The colon is a 'friendlier' environment for peptides and proteins compared to the upper gastrointestinal tract. Clinically relevant bioavailability may be achieved if the peptide can be protected from acid and enzymes in the stomach and upper intestine.

## Structure and Function of the Colon[1,2]:

The colon forms the lower part of the gastrointestinal tract and extends from the ileocecal junction to the anus (Fig. 1). The colon is upper five feet of the large intestine and the rectum is the lower six inches. While the colon is mainly situated in the abdomen, the rectum is primarily a pelvic organ. The colon is a cylindrical tube which is lined by a moist, soft pink lining called the mucosa, the pathway is called the lumen and is approximately 2-3 inches in diameter. The junction of the small intestine (ileum) and the colon is in the lower right abdomen. The first portion of the colon is spherical and is called cecum. The appendix hangs off the cecum. The next portion of the colon, in the order in which contents flow, is the ascending (proximal) colon, just under the liver, the angle or bend is known as the hepatic flexure, located just beneath the rib cage. The colon then turns to a long horizontal segment, the transverse colon. Beneath the left rib cage, the colon turns downward at the splenic flexure, to become the descending (distal) colon. In the left lower portion of the abdomen, the colon makes an S-shaped cure from the hip over the midline known as the sigmoid colon. The colon and rectum have an anatomic blood supply. Along these blood vessels are lymph nodes. Lymph nodes are structures found in the circulating lymphatic system of the body that produce and store cells that fight infection, inflammation, foreign proteins and cancer.

The major function of the colon is the consolidation of the intestinal contents into faeces by the absorption

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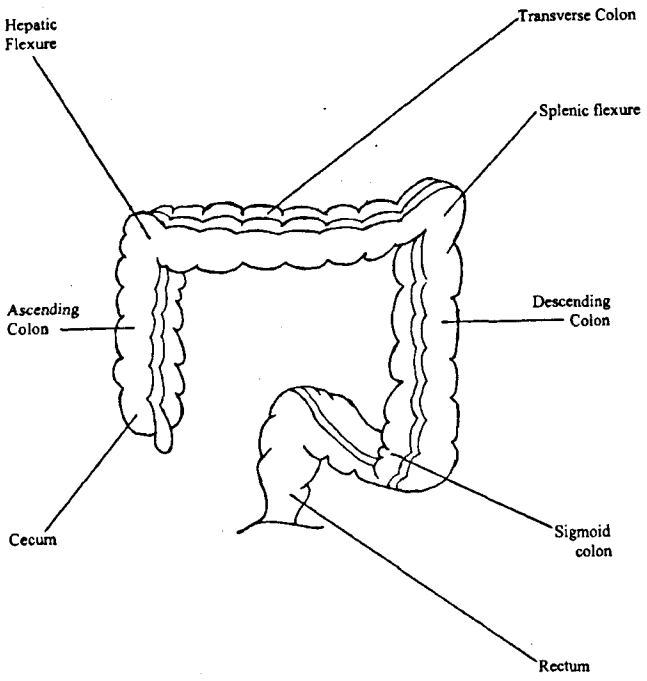


**Fig. 1 : Schematic Diagram of Colon**

of water and electrolytes and to store the faeces until excretion. The absorptive capacity is very high, each day about 2000 ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. In the healthy human colon, sodium and chloride ions are usually secreted[3]. On average, it has been estimated that colon contains only about 220 g of wet material, equivalent to just 35 g of dry matter[4]. The majority of this dry matter is bacteria.

Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements, caused by circular muscle and causing the appearance of the sac-like haustra, predominate and result in mixing of the lumenal contents. Significant propulsive activity, associated with defecation and effected by longitudinal muscle is less common and occurs at an average of three or four times daily.

### Colonic Microflora[5]:

The slow movement of material through the colon allows a large microbial population to thrive there. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus Bacteroides. Most of these isolated bacteria are anaerobic in nature, a small number of fungi are also present. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source. The principal source of nutrition for the colonic microorganisms are carbohydrates arriving in intestinal chyme. The carbohydrates are degraded by the action of polysaccharidase and glycosidase enzymes and the ultimate products of fermentation are short chain fatty acids, carbon dioxide, hydrogen, methane and hydrogen sulphide. In the proximal regions of the colon, carbohydrate fermentation predominates and results in a relatively low pH. In the distal regions, there is little carbohydrate fermentation, resulting in a higher pH (table 1). The bacteria within the colon are predominantly anaerobic and there is a low redox potential (reducing environment)[6,7].

**Table 1**

| Region of Gastrointestinal Tract | Characteristics |
|---|---|
| Large intestine | Length (cm) |
| Cecum | 6-7 |
| Ascending colon | 20 |
| Transverse colon | 45 |
| Desending colon | 30 |
| Sigmoid colon | 40 |
| Rectum | 12 |
| Anal canal | 3 |
| Large intestine | Intestinal diameter (cm) |
| | 6 |
| pH | |
| Cecum and colon | 5.5-7 |
| Rectum | 7 |
| Colon | Redox potential |
| Right | -415 |
| Mid | -400 |
| Left | -380 |

### pH in the Colon:

Radiotelemetry shows the highest pH levels (7.5±0.5) in the terminal ileum. On entry into the colon, the pH

drops 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[8]. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0[9]. *In vitro* fermentation of two other pharmaceutical polysaccharides, isapghula and guar gum, in the presence of faecal bacteria also results in a fall in pH[10]. Colonic pH has been shown to be reduced in disease. In a group of 7 patients with untreated ulcerative colitis the mean pH in the proximal colon was 4.7±0.7, where as in a group of 5 patients receiving treatment it was 5.5±0.4[11].

**Transit of Material in the Colon:**

The presence of food generally increases gastric residence and in some cases with regular feeding, dosage forms have been shown to reside in the stomach for periods in excess of 12 h[12,13,14]. Small intestinal transit is surprisingly constant at 3-4 h and appears to be independent of the type of dosage form and whether the subject is in the fasted or fed state[15].

Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease and drugs[16]. The gastrointestinal transit of a radiolabelled non-disintegrating osmotic tablet formulation was measured in 6 subjects using gamma scintigraphy. The tablets emptied from the stomach in a mean time of 0.8 h. The mean transit time through the small intestine was 3 h. Colonic transit was highly variable with a median transit time of 20.9 h. In one subject the tablet moved through the colon in just 2.5 h, giving a whole gut transit time of only 6 h[17].

The effect of capsule size and density on colonic transit has been investigated. Capsules with a density of 1.1 g/cm$^3$ and a volume of 0.3, 0.8 and 1.8 cm$^3$ and capsules with a volume of 0.8 cm$^3$ and a density of 0.7 and 1.5 g/cm$^3$ were tested. Capsule transit through the ascending colon was not affected by density and although there was a tendency for the transit rate to increase with volume, this effect was not significant[18].

Dependency of dosage form dimensions on colonic transit is demonstrated in a study which compares the colonic transit of 3 mm, 6 mm, 9 mm and 12 mm tablets. In 2 out of 8 subjects, 6 mm tablets moved ahead of 3 mm tablets and in all subjects 9 mm tablets moved ahead of 6 mm tablets. Twelve millimeter tablets moved ahead of 6 mm tablets in only 3 of the subjects. The lower degree of separation between 6 mm and 12 mm compared to 6 mm and 9 mm was explained by the fact that while the 9 mm tablet had a large thickness and diameter compared to the 6 mm, only the diameter of the 12 mm tablet was changed, which perhaps suggest that rate of colonic transit of the tablet is volume-dependent[19].

The results suggest that smaller units travel through the colon more slowly than larger ones. Hence, additional retention of a dosage form within the colon could perhaps be achieved by the use of a multiparticulate formulations, rather than a large single unit, thus ensuring that it does not pass too rapidly through the colon and be excreted before all the drug has been released.

**Effect of diet on colonic transit:**

Dietary fiber influences greatly the colonic motility. Dietary fiber increases faecal weight, partly by retention of water and partly by increasing bacterial mass and reduces colonic transit times. For example, addition of 20 g/day of bran to the diet of group of healthy subjects increased stool weight by 127% and reduced whole gut transit by 73±24 h to 43±7 h[20].

Ingestion of food has been found to stimulate colonic activity in what is termed the gastrocolonic response[21]. The effect of eating a meal on the colonic transit of radiolabelled tablet (5 x 6 mm) shows ingestion of food accelerates the movement of tablet through the ileocecal junction into the colon[22].

Diseases have also been found to affect colonic transit[23]. A study was carried out in volunteers pretreated with codeine and lactulose, to stimulate colon. In subjects treated only with lactulose, the mean transit times of 50% of the administered quantity of 0.2 mm particles and 5 mm tablets through the ascending colon were 5.3±2.5 h and 4.7±3.4 h respectively. Lactulose with codeine-treated subjects showed mean transit time of 7.4±2.5 h and 10.4±7.7 h for the 0.2 mm particles and 5 mm tablets, respectively. Hence codeine slowed down ascending colon transit, but there was no significant difference between the transit rate of the particles and tablets[24,25]. Poorly absorbed substances retain excessive fluid within the intestinal lumen and this is the mechanism by

which substances such as magnesium salts, sorbitol and polyethylene glycols can cause diarrhoea[26].

**Absorption of Drugs from the Colon:**

Drugs are absorbed passively by paracellular or transcellular routes. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, whereas paracellular absorption involves the transport of drug through the tight junctions between cells and is the route most hydrophilic drug takes. Studies in the rat have indicated that paracellular absorption is constant throughout the small intestine, but transcellular absorption appears to be confined to the small intestine, with negligible colonic absorption by these route[27]. The poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight[28]. The slow rate if transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic contents becomes more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa.

Because of the small extent of pracellular transplant, the colon is a more selective site for drug absorption that the small intestine. Drugs shown to be well absorbed include glibenclamide[29], diclofenac[30], theophylline[31], ibuprofen[14], metoprolol[32] and oxprenolol[33]. Drugs shown to be less absorbed include furosemide[34], piretanide[32], buflomedil[36], atenolol, cimetidine, hydrochlorothiazide[37], lithium[38] and ciprofloxacin[39].

The oral absorption of the majority of peptide and protein drugs is limited because of the following reasons:

1. Degradation in the acidic environment of the stomach.
2. Enzymatic degradation in the small and large intestine.
3. Low mucosal permeability.
4. Rapid small intestinal transit.
5. Extensive first pass metabolism by the absorbing membrane and the liver.

It is well recognised that peptides and proteins are well absorbed intact from the gastrointestinal tract, but the bioavailability is invariably extremely low, with exceptions, such as di and tripeptide analogues, cyclosporin[39,40] Suzuki et al. have studied the effects of polyunsaturated fatty acids on insulin absorption from rat intestinal loops *in situ*, using a water-in-oil-in-water (w/o/w) multiple emulsion. Comparing the pharmacological availability, the order of effectiveness with respect to the enhanced absorption of insulin is docosahexaenoic acid ≥ eicosapentaenoic acid> C18 unsaturated fatty acids>> C18 saturated fatty acids[41].

Schnurch *et al.* in their search for a novel bioadhesive polymer for intestinal peptide and protein delivery have found Bowman-Birk inhibitor covalently linked to chitosan-EDTA to be a very useful drug carrier matrix in overcoming the enzymatic barrier to orally administered peptide and protein drugs[42].

**Methods for Targeting Drugs into the Colon (figure 2):**

Colonic targeting is advantageous in treating diseases of colon, oral delivery of proteins and peptides, where a delay in systemic absorption is therapeutically desirable (nocturnal asthma, arthritis).

**1.Utilisation of Bacterial Enzymes :**

Both prodrugs and dosage forms from which the release of drug is triggered by the action of colonic bacteria enzymes have been devised. Enzymes produced by the colonic bacterial are capable of catalysing a number of metabolic reactions which includes reduction (of double bonds, nitro groups, azo groups, aldehydes, sulphoxides, ketones, alcohols, N - axides and arsonic acid), hydrolysis (of glycosides, sulphates, amides, esters, nitrates and sulphonates), deamination, decarboxylation, dealkylation, acetylation, nitrosamine formation, heterolytic ring fission and esterification[43].

**Azo-prodrugs:**

Sulfasalazine is a conjugate of sulphapyridine and 5-aminosalicylic acid (5-ASA), with the molecules linked by an azo bond (-N=N-). In the treatment of inflammatory bowel diseases (IBD), sulphasalazine acts as a 5-ASA prodrug. In the colon sulphasalazine breaks up as 5-ASA and sulphapyridine by azoreductase[44]. To date, the only new generation prodrug of 5-ASA to be introduced into clinical use in olsalazine a dimer of 5-ASA[45]. Other 5-ASA prodrug include balsalazine and ipsalazine in which 5-ASA is azo linked to 4-aminobenzoylglycine and p-aminohippurate, respectively[46]. Prodrugs have also has been prepared by azo-linkage of 5-ASA to polymers[47,48,49].

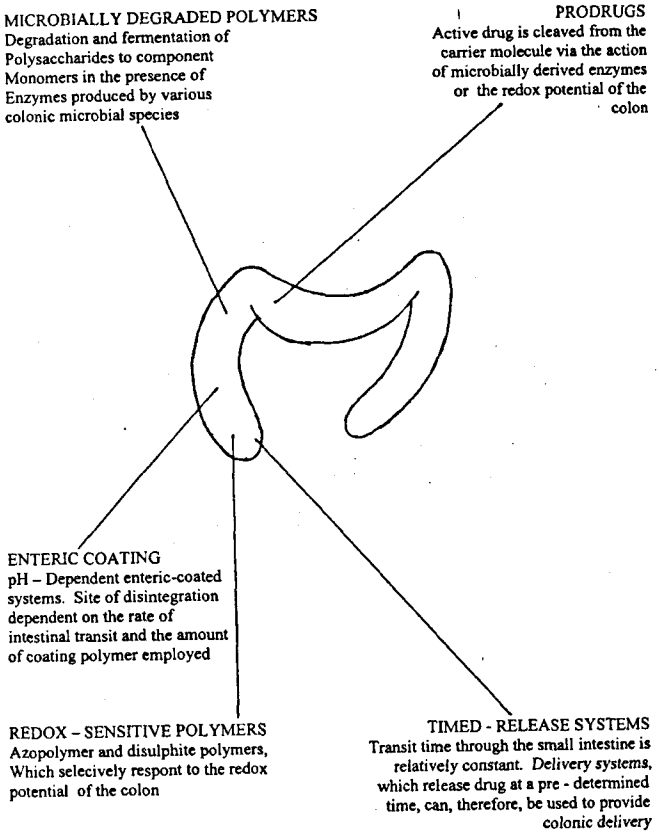


**Fig. 2 : Colon Targeting Mechanisms**

**Azo-polymers:**

Polystyrene and hydroxyethylmethacrylate cross-linked with divinylazobenzene[50] have been used for colon delivery. Hydrophilic azo polymers containing different ratios of methylmethacrylate and hydroxethylmethacrylate (HEMA) have been synthesized and those with high HEMA content, showed greatest susceptibility to colonic degradation[51,52]. Similar results have been reported with azo-containing polyamides[48], azo-containing polyurethane[53].

Hydrogels have been produced based on acrylic acid, N, N-dimethylacrylamide and N-terbutyl-acrylamide cross-linked with azo aromatic compounds[54]. The swelling of the polymer is pH-dependent and swells in the colon to allow access to bacterial azoreductase enzymes.

**Disulphide polymers :**

Synthetic polymers containing disulphide (-S-S-) groups, also reduced in the anaerobic environment of the colon, have been reported. One of these polymers is prepared by copolymerization of 3-3'-dithiodisuccinimidyl propionate with α, ω-bisaminopropylpolytetramethylene oxide and tetraethyleneglycol diamine. Glycosidic prodrugs[35,56,57].

Colon-targeted corticosteroids known as pro-ante drugs have been developed by the attachment of the active agent to glycosidic carriers. The prodrug passes unabsorbed into the colon where the glycoside bonds are cleaved by the action of bacterial glycosidase enzymes making the corticosteroid available for therapeutic action.

**Polysaccharides as matrices/coating Agents:**

The major attraction of most of these materials is that they are already approved for use as pharmaceutical excipients. A mixed coating comprising amylose and ethylcellulose (1:4) has been reported to provide colon specific delivery[58,59]. Pectin has been evaluated as a colon-specific coating material. Studies indicated that the degree of methoxylation of pectin and calcium content of the pectin layer influences the solubility of the layer and its susceptibility to enzymatic degradation[60,61]. Pectin has also been mixed with ethylcellulose and used as a tablet coating. Tablets have been prepared from calcium pectate, guar gum, locust bean gum, tragacanth and xylan. These in combination with methacrylate copolymers (Eudragit®) have also been used to coat tablets. A delivery system based on the mucopolysaccharide, chondroitin, has also been reported. This polymer is found in human colon from sloughed epithelial cells and dietary meat[62].

**2. pH-Triggered Delivery Systems :**

The principal group of polymers utilized for the preparation of colon targeted dosage forms has been the Eudragits (registered trademark of Rohm Pharma, Darmstadt, Germany), more specifically Eudragits L and S. These are anionic polymers which are water impermeable at low pH. Eudragit L100 and S100 are copolymers of methacrylic acid and methyl methacrylate. The ratio of the carboxyl to ester groups is approximately 1:1 in Eudragit L100 and 1:2 in Eudragit S100. The polymers form salts and dissolve above pH 6 and 7 respectively. Eudragit L100-55 is a copolymer of methacrylic acid and ethyl acrylate which dissolves above pH 5-5. This polymer disperses in water to form a latex and thus avoids the use of organic solvents in the coating process. Eudragit L30D-55 is a ready to use aqueous dispersion of Eudragit L100-55. Eudragits L100, S100 and L100-55 are listed in the USP/NF 23 as methacrylic acid copolymer A,B and C respectively.

DanBioSyst has developed a simple-to-manufacture colon targeting system (TARGIT®), that is based on injection molded starch capsules coated with a mixture of Eudragit L and S. The composition and thickness of the coating is such that the capsule does not disintegrate until it reaches the colon.

The drug can also be mixed with carbopol and granulated. The tablets formed is coated with a semipermeable membrane which allows water to enter. At around neutral pH (colon pH) carbopol starts swelling, thus rupturing the coating and releasing the drug.

### 3. Time-Dependent Delivery System (figure 3) :

As discussed earlier, although gastric emptying tends to be highly variable, small intestinal transit times are less so (3±1 h). So various attempts are made to prevent the release of drug until 3-4 h after leaving the stomach.

Pulsincap® is similar in appearance to hard gelatin capsule, the main body is made water insoluble (exposing the body to formaldehyde vapour which may be produced by the addition of trioxymethylene tablets or potassium permanganate to formalin or any other method). The contents are contained within a body by a hydrogel plug which is covered by a water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell, the amount of hydrogel is such adjusted that it pops out only after the stipulated period of time to release the contents[63,64].

Osmotic pumps that provide colon specific drug delivery have also been described. The units are enteric-coated and are activated only in the small intestine. A drug-free layer is adjacent to the delivery orifice and this is released over the first 3-4 h following activation. Therefore, after this period when the unit begins to release drug, it is within the colon.

In another method, an organic acid (succinic acid) is filled into the body of a hard gelatin capsule as a pH adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethylcellulose. The capsules are then coated with a three layered film. The capsules were first coated with an acid soluble polymer (Eudragit E), then with a hydrophilic material {hydroxypropylmethylcellulose (HPMC)} and finally enterically coated with Eudragit L. After ingestion of the capsule, the outermost enteric layer of the

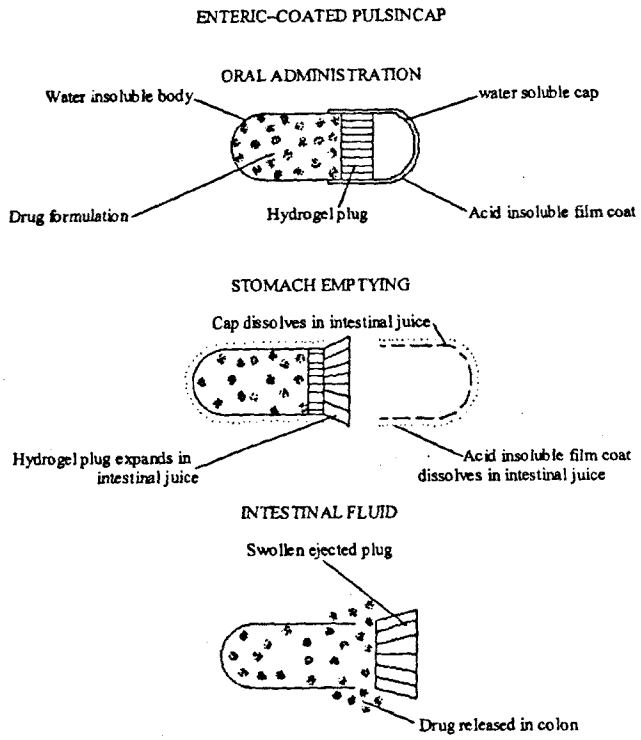


**Fig. 3 : Enteric-Coated Pulsincap**

coating prevents drug release in the stomach. Enteric layer and hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released. Therefore, the onset time of drug release in the intestine can be controlled by the thickness of acid soluble layer[65].

A delivery system, called the Time Clock™, has been developed comprising a solid core coated with a mixture of hydrophobic material, surfactant and water soluble polymer. The coating is designed to slowly erode away and after a predetermined interval, drug is released. An *in vitro* and *in vivo* investigation has been reported using tablets coated with a mixture of carnuba wax, bees wax, polyoxyethylene sorbitan monooleate and HPMC[66].

Another dosage form utilizing a similar concept has also been described. Solid dosage forms are coated with an inner layer of HPMC and an outer layer of enteric polymer. when the layer has dissolved, the inner layer of HPMC gels and slowly erodes away. When erosion has reached a critical level, drug is released from the inner core of the dosage for[67,68].

Takaya *et al.* have developed a preoral dosage form for colon delivery of drugs. The inside surface of a hard gelatin capsule is coated with ethylcellulose, the thickness of the ethylcellulose layer decides where the drug is to be released[69].

In conclusion, it is now appreciated that the colon can be an important site for the absorption and delivery of drugs. Although the surface area in the colon is low compared to the small intestine, this is compensated by the markedly slower rate of transit. The colon appears to be a viable site for the absorption of peptides and proteins. The use of absorption enhancers increases the permeability of the colonic epithelium and facilitating low molecular weight peptide absorption. The various methods described above to achieve colon delivery of drugs are quite promising and further studies are required in these regard to improve the bioavailability of the drug and decrease its toxicity.

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