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COLON SPECIFIC DELIVERY SYSTEM: THE LOCAL DRUG TARGETING

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ABSTRACT
Oral administration of different dosage forms is most commonly used method due to greater flexibility in design of dosage form and high patient acceptance, but gastrointestinal tract presents several formidable barriers to drug delivery. The colon is a site where both local and systemic delivery of drugs takes place. Local delivery could, for example, allow topical treatment of inflammatory bowel diseases. In colon specific drug delivery system, colon has a large amount of lymphoma tissue (facilitates direct absorption into blood), negligible brush border membrane activity, and much less pancreatic enzyme activity as compared with small intestine. Colon specific drug delivery has gained potential for delivery of proteins and therapeutic peptides. Different approaches are designed based on prodrug formulation, pH sensitivity, time dependency, microbial degradation and osmotic pressure etc. But these systems have limited success. Newly developed CDDS are developed which includes pressure controlled colonic delivery capsules, osmotic controlled drug delivery systems which are unique in terms of achieving in vivo site specificity and feasibility of manufacturing process.
Keywords – Colon specific drug delivery system, microbial degradation, osmotic pressure, pH sensitivity, prodrug, time dependency

INTRODUCTION

Colonic delivery refers to targeted delivery of drugs into lower GI tract, which occurs primarily in large intestine (i.e colon) . In the past two decades, the pharmaceutical scientists are extensively investigated in the area of colonic region for targeted drug delivery system. Targeted drug delivery system to colon is highly desirable for local treatment of a variety of bowel diseases such as (Ulcerative colitis, Crohn's disease), amoebiasis, colonic cancer and for local treatment of colonic pathologies and the systemic delivery of protein and peptide drugs[3]. The colon is believed to be a suitable site for absorption of peptides and protein drugs for following reasons-

1. Less diversity and intensity of digestive enzymes.
2. Comparatively proteolytic activity of colon mucosa is much less than thatobserved in small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradation in duodenum and jejunum and eventually releases drug in ileum and colon which leads to greater systemic bioavailabilty.
3. Colon has a long residence time (upto 5 days).[4]

Oral route is most convenient and preferred route[5] but other routes for CDDS may also be used. In 1942, Svartz discovered that sulphasalazine, the sulphanilamide prodrug of 5 amino salicylic acid (5-ASA) is effective in treatment of rheumatoid arthritis and anti-inflammatory diseases. The exact mode by which the drug target itself to the colon was elucidated in 1970 i.e colon specific azoreductase splits sulphasalzine causing the release of active moiety of 5-ASA.

Why Is Colon Targeted Drug Delivery Needed?

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
2. Site specific delivery would allow oral administration of peptide and protein drugs, colon specific formulation could also be used to prolong the drug delivery.
3. Colon specific drug delivery system is considered to be beneficial in treatment of colonic disease. For ex. Colorectal cancer.
4. Colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel diseases e.g. ulcerative colitis or crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids.
5. Formulation for colonic delivery are suitable for delivery of drugs which are polar and/ or susceptible to chemical and enzymatic degradation in upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.
6. Preventing gastric irritation produced by oral administration of NSAIDs.
7. Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.
8. Minimize extensive first pass metabolism of steroids.

Limitations Of Colon Targeting

1. Location at distal portion of alimentary canal, the colon is difficult to access.
2. Successful delivery requires the drug to be in solution before it arrives in the colon, but fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
3. Lower surface area and relative tightness of tight junctions in colon can restrict drug transport across mucosa into systemic circulation.

Rationale Of Colon Specific Drug Delivery System

1. Treatment of local pathologies.
2. Chronotherapy (asthma, hypertension, cardiac arrhythmias, arthritis or inflammation).
3. Greater responsiveness to absorption enhancers.
4. Less enzymatic activity.
5. Site for delivery of delicate drugs (Proteins and peptides).
6. Oral delivery of vaccines as it is rich in lymphoid tissue.

Colon Anatomy

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from ileocaecal junction to the anus with a length of 1.5 meters (adults) is divided into three main parts. These are the colon, the rectum and anal canal. Colon is upper 5 feet of large intestine and is situated in the abdomen. The colon is cylindrical tube lined by the mucosa. The colon consists of the caecum, colon ascends, colon transversal, colon descendens and rectosigmoid as shown in the figure 1. Colon is made up of four layers- serosa, muscularis externa, sub mucosa and mucosa. The colon does not have villi, but due to the presence of plicae semilunares (cresentric folds), the intestinal surface of colon is increased to 1300 cm^2. CDDS is dependent on following physiological factors: these are pH level, transit time and microbial environment in the colon which govern the release rate of drug from different design of CDDS (Vyas and Roop, 2006, Vincent et al. 2002). Different enzymes are present in colon, which are responsible for microbial degradation , were reported by Vincent et al (2002).

Colonic Absorption Of Drugs

The surface area of colon is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). The transport of drug in colon is affected by different factors.

- Passes through colonocytes (Transcellular transport)
- Passes through adjacent colonocytes (Paracellular transport)

Transcellular absorption involves the passage of drugs through the cells and thus the route for most of lipophilic drugs , whereas paracellular absorption involves the transport of drug through the tight junction between the cells and is route of most hydrophilic drugs.

Criteria For Selection Of Drugs For CDDS

The criteria for selection of drugs for colon specific drug delivery is explained in table-1.

- Pathology and pattern of the disease, especially the affected parts of lower GI tract.
- Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at intended site of delivery and desired release rate of active ingredient.
- The pH of intestinal fluids affects the efficacy of colon specific drug delivery systems hence it is most common physiological factor that is considered in design of delayed release formulation.
- The best candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides.
- Drug carrier is another factor which influence CDDS. The selection of carrier for particular drug depends on physicochemical nature of drug as well as the disease for which the system is to be used . Factors such as chemical nature, partition co efficient, stability of drug and type of absorption enhancer chosen influences the carrier selection.
- Choice of drug carrier depends on functional groups of the drug molecule. For e.g. Aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond.

General Consideration For Design Of Colonic Formulation

- The proper selection of a formulation approach is dependent upon several important factors given below:
- Pathology and pattern of the disease especially affected parts of lower GI tract or physiology and physiological composition of healthy colon is not intended for localized treatment.
- Physiochemical and biopharmaceutical properties of drug such as solubility, stability and permeability at the intended site of delivery.
- The desired release profile of the active ingredient.

Drugs Suitable For CDDS

1. The following different categories of drugs are suitable for colon drug delivery.
2. Drugs used to treat irritable bowel disease (IBD) require local delivery of drug to colon. Ex.- sulphasalazine, olsalazine, mesalazine, steroids like fludrocortisones, budesonide, prednisolone, dexamethasone.
3. Drugs to treat colonic cancer require local delivery. Ex. 5- fluoro uracil, doxorubicin, methotrexate.
4. Protein and peptide drugs- eliminating drug degradation. Ex.- growth hormone, calcitonin, insulin, interleukin, interferon, erythropoietin.
5. To treat infectious disease (amoebiasis, helminthiasis)- require site specific delivery. Ex.- metronidazole, mebendazole, albendazole.
6. To treat rheumatoid arthritis (NSAIDs), nocturnal asthma, angina require delay in absorption due to circadian rhythm.
7. Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport. Ex.- gilbenclamide, diclofenac, theophylline, ibuprofen, Metoprolol, oxyprenolol.

Different Approaches For The Colon Targeting

[A] Primary approaches for CDDS[16]

a) pH sensitive polymer coating drug delivery to colon
b) Delayed (time controlled release system) release drug delivery to colon
c) Microbially triggered drug delivery to colon
   i. Prodrug approach
   ii. Polysaccharide based approach

[B] Newly developed approaches for CDDS[15]

a) Pressure controlled drug delivery system (PCDCS)
b) CODES TM (a novel colon targeted drug delivery system)
c) Osmotic controlled drug delivery to colon (OROS-CT)
d) Pulsincap system
e) Port system
f) Time clock system
g) Chronotropic system
h) Colal-pred system
i) Target technology
j) Ticking capsule
k) Enterion capsule technology

pH dependent delivery system

In stomach., pH ranges between 1-2 during fasting but increases after eating[12]. The pH is 6.5 in proximal small intestine and about 7.5 in distal small intestine. From the ileum to the colon pH declines significantly. It is about 6.4 in the caecum. pH values as low as 5.7 have been measured in ascending colon in healthy volunteers[13]. The pH in transverse colon is 6.6, in descending colon 7.0 . Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in stomach and proximal small intestine, it may start to dissolve even in lower small intestine, and the site specificity of formulations can be poor. Enteric coated dosage forms are designed to remain intact in the stomach and release the active substance in intestine. pH sensitivecoating can be used to deliver the drugs to the colon. Unit dosage forms and multiparticulate dosage forms have been coated with pH dependent polymers to provide site specific release[14].

Time controlled drug delivery system

In this system, site of drug release is divided by transit time of a formulation in GI tract, which makes it challenging to colon. Dosage form is also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours[17]. Time controlled formulation for colonic delivery include a pH dependent (enteric coat) component because the transit time of a formulation in GI tract is influenced by gastric emptying rate. Enteric coating is also used for preventing the lipid swelling and disintegration in upper GIT since other controlled release components based on mechanisms of swelling (gelling), osmosis as a combination of two or often included in the time release.

Microbially targeted drug delivery to colon

The microflora of colon is in the range of 1011-1012 CFU/ml[18]. Consisting mainly of anaerobic bacteria. Ex.: bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and pnemicoccus etc. , thus vast microflora fulfills its energy needs by various types of substrates that have been left undigested in small intestine.Ex. di and trisaccharides polysaccharides etc[19] for this fermentation in microflora, produces a vast number of enzymes like glucuroidase, xylosidase, arabinosidase, galactosidase, nucleoreductase, azoreductase, deaminase. Because of presence of biodegradable enzymes only in the colon, the use of biodegradable enzymes only in the colon, the use of biodegradable polymers for colon specific drug delivery seems to be more specific approach as compared to other approaches. These polymers shield drug from the environment of stomach and small intestine and are able to deliver

the drug to the colon. On reaching colon they undergo assimilation by micro organism as degradation by enzyme as breakdown of polymer backbone leading to subsequent reduction in their molecule weight and thereby loss of mechanical strength[20-24]. Various materials used in formulation of colon specific drug delivery system is explained in table-2.

Prodrug approach

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vitro to release active drug. For colonic delivery, the prodrugs are designed to undergo minimal absorption and hydrolysis in upper GIT and undergo enzymatic hydrolysis in colon, thereby releasing the active drug moiety from drug carrier, metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic process[25]. A number of other linkages. susceptible to bacterial hydrolysis especially in colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucuronic acid, glucose, galactose etc. limitation of prodrug approach is that it is not very versatile approach as its formulation depends upon functional group available on drug moiety for chemical linkage.

Polysaccharide based drug delivery system

Use of naturally occurring polysaccharide is of attention for drug targeting to colon since these polymers are found in abundance, inexpensive and are available in variety of structures with varied properties. They are highle stable, non toxic, hydrophobic, biodegradable and gel forming. They are broken down by colonic microflora to simple saccharides[26]. So, these fall into the category of "Generally Regarded As Safe" (GRAS). The advantages and disadvantages of various colon specific drug delivery methods are shown in table-3.

NEWLY DEVELOPED APPROACHES FOR CDDS

PRESSURE CONTROLLED DRUG DELIVERY SYSTEM

As a result of peristalsis , higher pressures are encountered in colon in small intestine. Takaya et al. (1995) have developed pressure controlled colon delivery capsules prepared by using an ethyl cellulose, which is insoluble in water[27]. In such systems, drug release occurs following disintegration of water insoluble polymer capsule as a result of pressure in the lumen of colon. The thickness of ethyl cellulose membrane is the important factor for disintegration of formulation[28-29]. System also depends on capsule, size and density. Because of re-absorption of water from colon, the viscosity of luminal content is higher in colon than small intestine. So, drug dissolution in colon could present a problem in relation to colon specific drug delivery system.

NOVEL COLON TARGETED DRUG DELIVERY SYSTEM (CODESTM)

CODESTM is a unique CDDS technology that was designed to avoid inherent problems associated with pH or time dependent systems[30-31]. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. System consists of traditional tablet core containing lactulose; which is over coated with an acid soluble material, Eudragit E, and then overcoated with an enteric material, Eudragit L. Once the tablet arrives in colon, bacteria enzymatically degrade polysaccharide (lactulose) into organic acid.

OSMOTIC CONTROLLED DRUG DELIVERY (OROS-CT)

The OROS-CT can be used to target the drug locally to colon for treatment of disease or to achieve systemic absorption that is otherwise unattainable[32]. The system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within hard gelatin capsule[33]. Each bilayer push unit contains an osmotic push layer and a drug layer surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to drug layer. Immediately after OROS-CT is swallowed, gelatin capsule containing push-pull units dissolve.because of its drug impermeable enteric coating, each push pull unit is prevented from absorbing water in acidic aqueous environment of stomach, hence no drug is delivered. As the unit enters small intestine, coating dissolves in this higher pH environment, water enters the unit, causing osmotic push compartment to swell, and concomitantly creates a flowable gel in drug compartment. Swelling of osmotic push compartment forces drug gel out of orifice at a rate precisely controlled by rate of water transport through the semipermeable membrane.

PULSINCAP SYSTEM

This system comprises of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal drug contents into capsule body[34]. When this capsule came in contact with dissolution fluid, it swells, after a lag time, the plug pushed itself outside the capsule and rapidly release drug. Polymers used for designing of hydrogel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly vinyl acetate, polyethylene oxide. Length of the plug and its point of insertion into capsule controlled lag time.

PORT SYSTEM

It consists of an insoluble plug consisting of osmotically active agent and drug formulation[35]. System shows good *in- vitro* and *in-vivo* correlation in humans.

TIME CLOCK SYSTEM

It is a delivery device based on solid dosage form that is coated by an aqueous dispersion[36]. This coating is a hydrophobic surfactant layer to which a water soluble polymer is added to improve adhesion to the core. Once in contact with dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying thickness of film. After the lag time, i.e ; the time required for rehydration, the core immediately releases the drug.

CHRONOTROPIC SYSTEM

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time and drug releases at once after this lag time. Chronotropic system consists of a core containing reservoir coated by a hydrophilic polymer HPMC[37-39]. An additional enteric coated film is given outside this layer to overcome intrasubject variability in gastric emptying rate[40].

COLAL-PRED SYSTEM

It has arisen from combining alizyme properitary colonic drug delivery system, COLAL, with an approved generic steroid (Prednisolone sodium metasulfobenzoate). It is an effective treatment for ulcerative colitis without the typical side effects of steroids. It has a coating that is broken down only in colon, by locally occurring bacteria**.**

TARGIT TECHNOLOGY

It is for site specific delivery of drugs in GIT and in particular, targeted release into the colonic region. The technology is based on the application of pH sensitive coatings onto injection moulded starch capsules.

TICKING CAPSULE

It is a chronotropic device employing some electrical means of controlling pulsatile drug release coupled with electronic timing. It is divided into three compartments- Porous Si- based drug delivery module; Electronic control module and battery. Many human illnesses and their symptoms show a regular pattern : hypertension (early morning); arthritis pain (mid afternoon) ; heart attack (early morning+ late afternoon) and asthma attack (night).

ENTERION CAPSULE TECHNOLOGY

It is a 32 mm long, round ended capsule and contains a drug reservoir with volume capacity of approximately 1 ml. Capsule can be loaded with either a liquid formulation or a particulate formulation through an opening 9mm in diameter, which is then sealed by inserting a push on cap fitted with a silicone O- ring. When capsule reaches target location in gastrointestinal tract, the

contents are actively ejected by external application of an oscillating magnetic field. The frequency of magnetic field is set in low MHz region, low enough so that there is negligible absorption of energy by body tissues but sufficiently high enough to induce unable power in a turned coil antenne embedded in capsule wall. Power induced in coil by magnetic field is fed to tiny heater resistor located within separate sealed electronics compartment inside the capsule. Small size of heater (less than 1mm^3) means that heat build up is extremely rapid. Heater resistor is in direct contact with the restraining filament, causing it to softer and breaks with the increase in temperature. This inturn, releases the spring and driver the piston. Resulting increase in pressure within the drug reservoir forces off the o-ring sealed cap and rapidly ejects the drug in GI fluid.

EVALUATION OF CDDS

The drug release in colonic region from different CDDS is evaluated by different methods in vitro and in vivo release studies, which slow success rate of different designs of colon drug delivery systems. Successful colon specific drug deliverysystem is one that remains intact in physiological environment of stomach and small intestine, but releases drug in colon.

In vitro evaluation

In *in-vitro* evaluation ability of coats/carriers to remain intact in physiological environment of stomach and 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 3 hours (mean small intestine transit time) using USP dissolution apparatus. In case of microflora activated system, release rate of drug is tested in vitro by incubating in buffer medium in presence of either enzymes (ex. Pectinase, dextrinase) or rat/ guinea pig/ rabbit caecal contents.

In vivo evaluation:

When the system is concerned and prototype formulation with acceptable *in vitro* characteristics is obtained, *in vivo* studies are conducted to evaluate site specificity of drug release and to obtain relevant pharmacokinetic information of delivery system. Animal models have obvious advantages in assessing colon specific drug delivery system; human subjects are increasingly utilized for evaluation of this type of delivery system. Gamma –scintigraphic studies were conducted in human volunteers with technetium-99m-DTPA as tracers in sodium chloride core tablets compression coated with guar gum showed that guar gum protects the drug from being released in stomach and small intestine. On entering the ascending colon, tablets commenced to release tracer indicating breakdown of gum coat by enzymatic action of colonic bacteria (Krishnaiah et al. 1998a).

CONCLUSION

Concept of targeting the delivery of specific drugs to colon is self explanatory and sufficient scientific rationale is available to support justification. Various approaches are being researched in attempts to understand and achieve the desired goal of targeting delivery to a specific organ, the colon. All available approaches have their own limitations and advantages and extensive research is being focused on these to improve further. Time dependent systems are not very practical solution due to variable GI tract transit time but may have role in diseases that are subjected to circardian rhythm. Pressure controlled system hold some promise but currently little is known about luminal pressures of different regions of GI tract. Only system available as of today is based on pH but these systems can possibly deliver the drug at all. That day is not far off when new, improved polymers will replace existing available polymers with improved performance. Bacterially activated systems seem to have the greatest enzyme activity is most unique and exploitable in this region. Amylase based COLOL is the leading product in the later phases of clinical evaluation and has a promise for commercial manufacturing. Another area that still needs to be understood is human physiology and inter/ intra subject variability. Once this aspect of human system is understood, gained knowledge can be applied to focus research on identifying suitable analytical tools that can predict in vivo performances of developed system. At the end of the day, the need of today's business and patient community is to identify appropriate approach that can result in delivery of drugs in a safe, effective and less expensive manner with minimum fluctuations in terms of release of drugs at target site.

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Table 1:- Criteria for selection of drugs for colon specific drug delivery system:

Criteria	Pharmacological class	Non- peptide drugs	Peptide drugs
Drugs used for local effects in colon against GI diseases	Anti-inflammatory drugs, Nifedipine	Oxyprenolol, Metoprolol	Amylin, Antisense oligonucleotide
Drugs poorly absorbed from upper GIT	Anti hypertensive and anti-anginal drugs	Isosorbides, Theophylline, Ibuprofen	Cyclosporin, Desmopressin
Drugs for colorectal cancer	Anti neoplastic drugs	Pseudoephederine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Proteins and peptides	Bromophenaramine, 5-FU, Doxorubicin	Gonadoreline, Insulin, Interferon
Drugs that undergo extensive FPM	Nitroglycerine and Corticosteroids	Bleomycin and Nicotine	Protirelin, Sermorelin, Saloatonin
Drugs for targeting	Anti arthritic , Anti asthmatic drugs	Prednisolone, Hydrocortisone	Somatropin, Urotoilitin

Table 2- : Materials used in the formulation of CDDS

Prodrug conjugates	**pH sensitive polymers**	**Materials used in Time dependent System**	**Microbial degradable polymers**
Azo bond conjugates	Eudragit L-100, Eudgrgit S-100	Hydroxyl propyl methyl cellulose	Chitosan
Amino acid (polypeptide conjugates)	Eudragit L-30 D, Eudragit L-100-55	Hydroxy ethyl cellulose	Pectin, Lactulose, Cyclodextrin
Glycoside conjugates	Eudragit F S 30 D	Ethyl cellulose	Guar gum
Glucuronide conjugates and sulphate conjugates	Poly vinyl acetate phthalate, Cellulose acetate phthalate	Microcrystalline cellulose	Dextran, Alginates
Polymeric conjugates	Hydroxyl propyl ethyl cellulose phthalate	Hydroxyl propyl methyl cellulose acetate succinate	Inulin, Amylose
Cyclodextrin conjugates, dextran conjugate	Hydroxy propyl methyl cellulose cellulose phthalate 50	Lactose/ behinic acid	Locust bean gum, Boswellia gum

Table 3:- Advantages and disadvantages of various methods of oral colon- specific drug delivery

Method	Advantages	Disadvantages
Time dependent systems	Small intestine transit time fairly consistent	Substantial variation in gastric retention time. Transit through the colon more rapid than normal in patients with colon disease.
pH dependent systems	Formulation well protected in the stomach	pH levels in the small intestine and colon vary between and within and within individuals pH levels in the end of small intestine and caecum are similar. Poor site specificity.
Microflora activated systems	Good site specificity with prodrugs and polysaccharides.	Diet and disease can affect colonic microflora. Enzymatic degradation may be excessively slow.

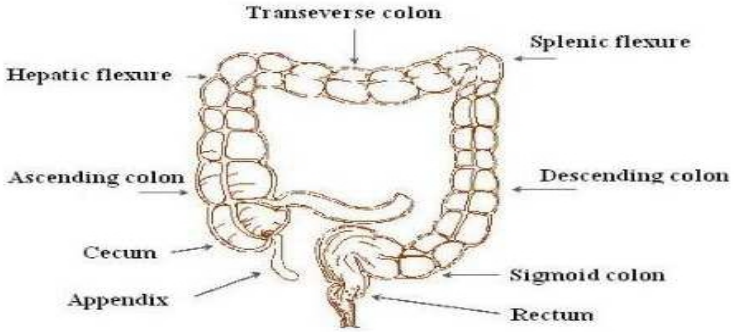

Figure 1 : Structure of colon.