ABSTRACT:
Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. The delivery of drugs to the colon has numerous therapeutic implications in the field of drug delivery. In the recent past, the colon-specific drug delivery system is also gaining importance not only for local drug delivery of drugs but also for systemic delivery of protein & peptide drugs. The colon, as a site for drug delivery, is also beneficial for the treatment of disease sensitive to circadian rhythms and delivery of poorly absorbable drugs. The various approaches that can be exploited to target the release of drug to the colon including prodrug formation, coating with pH-sensitive polymer, coating with biodegradable polymers, embedding in biodegradable matrices, hydrogel, time release system, osmotic & bio-adhesive system. In this review article will cover both past & present approaches for achieving colon specific drug delivery.

INTRODUCTION
From the last few decades, a great deal of research work has been devoted to the development of the site specific drug delivery systems which offer several benefits over the traditional drug therapies. The principle goal of the site specific delivery is to deliver the drug to the specific organ of body. The colon drug delivery has a number of important implications in the field of pharmacotherapy. The therapeutic advantages of targeting the drug to the diseased organ include:

- Delivery of the drug in its intact form as close as possible to the target site.
- Reduces conventional dose and frequency
- Reduced incidence of adverse side effects.

Various diseases of colon such as ulcerative colitis, Crohn’s disease, carcinoma and infections require local therapy. So, the development of locally acting colon targeted drug delivery systems may revolutionize the treatment of colonic diseases. In the recent times, the colon-specific delivery systems are also gaining importance for the systemic delivery of protein and peptide drugs. The peptide and protein drugs are destroyed and inactivated in acidic environment of the stomach and/or by pancreatic enzymes, the colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine. Further, drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of diseases that have peak symptoms in the early morning such as nocturnal asthma, angina, and arthritis. The colon, as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity, and a much greater responsiveness to absorption enhancers. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancer make the colon a promising site for the delivery of protein and peptide drugs for systemic absorption. Successful colonic drug delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. For instance, regardless of whether a local or systemic effect is required, the administered drug must first dissolve in the luminal fluids 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. Because of the distal location of colon in the GIT, a colon specific drug delivery system should prevent drug
release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into colon. Several approaches have been developed for targeted colonic drug delivery. Most of them utilize the physiological properties of the GIT and colon such as pH of GIT, transit time of small intestine, luminal pressure of the colon, and the presence of microbial flora localized in the colon.

**DRUG RELEASE BASED ON VARIATION OF pH:-**

The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. These enteric polymer coatings are insensitive to the acidic conditions of the stomach but ionize and dissolve at the more neutral pH of 5-6 found in the upper small intestine. This concept has since been adapted and attempted for colonic delivery purposes, using polymers that have a threshold pH for dissolution higher than those used in conventional enteric coating. Most commonly copolymers of methacrylic acid and methyl methacrylate that dissolve at pH 6 (Eudragit® L) and pH 7 (Eudragit® S) have been investigated. Colon targeted drug delivery systems based on methacrylic resins has described for Prednisolone, Mesalazine, 5-ASA, Diclofenac sodium and Paracetamol. Aqoat® AS-HF coated pellets have been used for drug delivery to the distal intestine and the proximal colon. Eudragit-SO coated system showed optimal delivery of insulin in ileum at pH 7.0 and successfully delivered more than 60 % of sulphapyridine in colon. Partially methylated Eudragit-SO that is soluble in slightly higher pH aqueous media can be effective for colon drug delivery. When sites of disintegration of Eudragit™ S-coated single-unit tablets were investigated using a gamma camera they were found to lie between the ileum and splenic flexure. A Site specificity of Eudragit S formulation, both single and multiple units, is usually poor. The polypeptide hormone vasopressin and insulin have been administered to rats orally in Eudragit™ S-coated single-unit capsules. Eudragit™ S-coated insulin capsules have also been administered orally to hyperglycemic beagle dogs.

Contrariwise, failure of enteric-coated dosage forms, especially single-unit dosage forms, because of lack of disintegration has been reported. The decline in pH from the end of the small intestine to the colon can also result in problems. Lengthy lag times at the ileo-caecal junction or rapid transit through the ascending colon can also result in poor site-specificity of enteric-coated single-unit formulations. In fact, the pH in the distal small intestine is usually around 7.5 while the pH in the proximal colon is closer to 6.0. These delivery systems therefore have a tendency to release their drug load prior to reaching the colon. To overcome the problems of Prednisolone premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl methacrylate (Eudragit FS), which dissolve at a slower rate and at a higher threshold pH (7.0- 7.5) has been developed recently.

**Oral preparations for the treatment of inflammatory bowel disease, ulcerative colitis and Crohn’s disease.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Delivery system</th>
<th>Site of release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalazine (Mesalamine)</td>
<td>Asacol MR</td>
<td>Eudragit S-coated tablet (release at pH &gt;7)</td>
<td>Distal small intestine and colon</td>
</tr>
<tr>
<td>Mesren</td>
<td>Ipocol MR</td>
<td>Eudragit S-coated tablet (release at pH &gt;7)</td>
<td>Distal small intestine and colon</td>
</tr>
<tr>
<td>Salofalk</td>
<td></td>
<td>Eudragit L-coated tablet (release at pH &gt;6)</td>
<td>Mid to distal small intestine and colon</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Entocort</td>
<td>Eudragit L100-55-coated ethylcellulose granules (slow release at pH &gt;5.5)</td>
<td>Proximal small intestine to colon</td>
</tr>
</tbody>
</table>
The pH in the gastrointestinal tract varies between and within individuals. It is affected by diet and disease, for example during acute stage of inflammatory bowel disease colonic pH has been found to be significantly lower than normal. In ulcerative colitis pH values between 2.3 and 4.7 have been measured in the proximal parts of the colon. Although a pH-dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve even in the lower small intestine, and the site-specificity of formulations can be poor. The disadvantage of this technique is the lack of consistency in the dissolution of the polymer at desire site. Depending on intensity of the GI motility, the dissolution of the polymer can be in the distal portion of the colon or at the end of the ileum. Moreover, many factors such as the presence of short chain fatty acids, residue of bile acids, carbon dioxide or their fermentation products reduce the colonic pH to approximately 6 and call its pH as a trigger into question.

**DRUG RELEASE BASED ON GASTROINTESTINAL TRANSIT TIME:**

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time-based. In these systems, the site of drug release is decided by the transit time of a formulation in the GI tract, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. Ideally, formulations are designed such that the site of delivery (i.e. colon) is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon. The time of transit through the small intestine is independent of formulation. It has been found that both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine. The rate of transit of solid oral dosage forms through the gastrointestinal tract is largely unpredictable, in part because of the variability in gastric emptying. Depending on the size, shape and density of the dosage form and the feed status of the individual, residence time in the stomach can range from a few seconds to a number of hours. Time-dependent formulations are designed to release their drug load after a predetermined lag time. A nominal lag time of 5 or 6 hours is usually incorporated into the system on the assumption that this is the time required for the dosage form to reach the colon. A number of systems have been developed on this principle, with one of the earliest being the Pulsincap device. Somewhat complex in design, the device consists of an impermeable capsule sealed at one end with a hydrogel plug. On contact with gastrointestinal fluids, the plug hydrates and swells and, after a preset lag time, ejects from the capsule body, enabling drug release to occur. The size and composition of the plug control the lag time from the device. The performance of two different Pulsincap devices, preprogrammed with 5- and 6-hour time delays, was investigated in fasted human volunteers using gamma scintigraphy. To minimize the impact of gastric emptying on the eventual position of time dependent systems at the time of release, the application of an enteric coat has been proposed. This multi-barrier concept now forms the basis for most of these systems. The outer enteric coat dissolves on entering the small intestine to reveal an inner polymeric layer that swells, erodes or dissolves over a period of time sufficient to delay drug release from the core of the formulation. The recently described colon targeted delivery capsule combines both pH and time-based mechanisms for delivery. A mixture of drug and organic acid is encapsulated in a conventional hard gelatin capsule. The capsule is then coated with a three layered film consisting of an acid-soluble layer, a hydrophilic layer and an outer enteric layer. On ingestion, the outer enteric layer remains intact until gastric emptying of the capsule. The enteric film then dissolves followed by the intermediate hydrophilic layer. The inner acid-soluble layer (soluble below pH 5) remains intact in the small intestine but allows the ingress of fluid into the core of the capsule. When the pH inside the capsule decreases by the dissolution of
the organic acid, the acid-soluble layer dissolves and the drug is released. The thickness of the acid-soluble layer, therefore, controls drug release from the system. The performance of the dosage form was evaluated in a crossover study involving fed and fasted volunteers. The site of disintegration of the coated capsule was more consistent in the fasted state (ranging between the ileocaecal junction and the descending colon). In the fed state, gastric emptying and colonic arrival of the capsule was significantly retarded. No capsule disintegration was noted in some volunteers and premature disintegration was observed in the small intestine in some of the others. Due to the inter subject variation in GIT transit times, the onset of initial drug release occurred in the small intestine in some subjects, while in others the formulation passed the ascending colon intact. Additionally, the performance of a time dependent formulation can be affected significantly by the pathophysiological conditions associated with the GI tract. Accelerated transit through different regions of the colon has been observed in the patients with irritable bowel syndrome, the carcinoid syndrome and diarrhea, and the ulcerative colitis. Therefore, time dependent systems are not ideal to deliver drugs colon specifically for the treatment of colon-related diseases including ulcerative colitis. Furthermore, when designing systems for the treatment of such diseases, it will be desirable that the drug is released in a bolus fashion upon entry into colon.

PRESSURE CONTROLLED DRUG DELIVERY SYSTEMS:

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The use of gastrointestinal pressure has been proposed as a method of targeting release in the distal gut. This pressure, which is generated via muscular contractions of the intestinal wall for grinding and propulsion of luminal contents, varies in intensity and duration throughout the gastrointestinal tract. The colon is believed to exert a higher effective luminal pressure via the action of haustral contractions coupled with a viscous environment. Takaya and co-workers have developed a novel capsule that is sensitive to this raised pressure. This pressure controlled colon delivery capsule (PCDC) is composed of drug, dispersed in a suppository base, coated with the water insoluble polymer ethyl cellulose. Once swallowed, the temperature of the body causes the suppository base to melt and increase in volume, and the system resembles a liquid filled ethyl cellulose balloon. The system is able to withstand the luminal pressures of the stomach and small intestine resulting from muscular contraction of the gut wall, since there is sufficient fluid present in the lumen to dissipate this pressure. In the distal gut, reabsorption of water increases the viscosity of luminal contents. As such, the capsule will be directly affected when subjected to the pressure of the intense haustral contractions of the colon and hence will rupture. The use of gastrointestinal pressure provides an innovative approach to targeting drugs to the gut. However, there are limited data on the luminal pressures of different regions of the gastrointestinal tract, and whether these are subject to the inter and intra individual variation as is pH and intestinal transit time.

DRUG RELEASE BASED ON PRESENCE OF COLONIC MICROFLORA:

Much of the recent interest in colonic delivery has focused on the use of gastrointestinal microflora as a mechanism for drug release. Both anaerobic and aerobic micro-organisms inhabit the human gastrointestinal tract. Although bacteria are distributed throughout the gastrointestinal tract, the vast majority are present in the distal gut. The bacterial count has been estimated to be $10^{11}$ per gram in the colon, compared with $10^4$ per gram in the proximal small intestine. Moreover, over 400 different species are present, Colonic bacteria are predominantly anaerobic in nature and secrete enzymes that are capable of metabolizing
endogenous and exogenous substrates, such as carbohydrates and proteins, which escape digestion in the upper gastrointestinal tract. Such materials that are susceptible to bacterial fermentation in the colon, while remaining recalcitrant to the conditions in the stomach and small intestine, could therefore be utilized as carriers for drug delivery to the colon. Carbohydrates arriving from the small intestine form the main source of nourishment for bacteria in the colon. The carbohydrates are split into short-chain fatty acids, carbon dioxide and other products by the enzymes glycosidase and polysaccharidase. In the proximal colon the pH is lower than at the end of the small bowel because of the presence of short-chain fatty acids and other fermentation products. Diet can also affect colonic pH. The first bacteria-sensitive system developed for colonic delivery was Sulfasalazine, a prodrug consisting of the active ingredient Mesalazine linked by an azo bond to a carrier molecule, Sulfapyridine. Mesalazine is rapidly absorbed from the small intestine, but when administered as a prodrug is not absorbed until it reaches the colon where the azo bond is cleaved by colonic bacteria to liberate the active ingredient at the site of inflammation. In the colon Sulphasalazine is split by bacterial azoreduction into 5-ASA and sulphapyridine. Sulphapyridine can cause side effects, and other carriers for delivery of 5-ASA to the colon have therefore also been investigated. Olsalazine consists of two molecules of 5-ASA linked by an azo bond. Ipsalatsine and balsalatsine are other 5-ASA containing prodrugs. Polymers and polyamides containing azo groups have been used to convey 5-ASA to the large intestine. Azo polymers have been used as colon specific film coatings. Colon targeting by means of azo polymers is associated with many problems. Microbial degradation of azo polymers is usually slow and drug delivery can be incomplete and irregular. Not enough is yet known about the safety of azo polymers. In vivo absorption studies with azo polymers have mostly been carried out using rats. No results of studies in human beings are available. Although the gastrointestinal microflora of rats and humans differ, results of in vivo experiments with rats can give some indications regarding biodegradation of azo polymers. Dextran ester prodrugs have been investigated as means of transporting drugs to the colon. When the bioavailability of naproxen after administration of dextran-naproxen prodrug was assessed in pigs, lag times of two to three hours were observed. Dextran esters of fatty acids have been used to form colon-specific film coatings. Hydrogels containing azo aromatic cross links have been investigated in connection with site specific drug delivery of peptide and protein drugs. Colonic delivery system based on cross linked hydrogels, which contains azo bonds and exhibit pH-dependent swelling. In the low pH range of the stomach the gels have a low equilibrium degree of swelling and the drug is protected against digestion by enzymes, but at high pH levels they swell. So in the stomach a drug will be protected, but released in the colon, where cross-links become degraded. In addition to azo-polymers, disulfide bond containing polymers have been utilized as carriers for colon-specific delivery. The use of natural polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as pharmaceutical excipients in formulations. These formulations are considered safe because they utilize materials that are taken as dietary fiber. Issues with regard to safety, toxicity and availability are therefore much simplified. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature and swell under exposure to upper gastrointestinal conditions, which would result in premature drug release. To overcome this problem the natural polysaccharides are either chemically modified or mixed with hydrophobic, water insoluble polymers. This has the effect of limiting the swelling in the upper gastrointestinal tract, but still permitting a partial solubilisation of the matrix or coating in the colon due to bacterial degradation, resulting in drug release. Examples of various polysaccharide carriers are such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrants, guar gum, inulin, amylose, sodium alginate. Various enzymes that are involved in the degradation of some of these polymers are amylase, chitosanase, pectinase, inulinase, xylanase, dextranase, galactomannanase etc. Pectin is a
polysaccharide, found in the cell walls of plants. It is
totally degraded by colonic bacteria but is not
digested in the upper gastrointestinal tract. Ashford et
al. investigated the ability of a direct compression
coat of pectin to achieve colon delivery. Tablets were
manufactured by directly compressing a high
methoxy grade of pectin around a core tablet. A
minimum of 700mg pectin was needed to prevent
release of a model drug, fluorescein, in simulated
mouth to colon conditions. When tested in humans,
the coated tablets all disintegrated in the colon, in
regions varying from the caecum to the splenic
flexure after a time of between 5.5 and 8.8 hours.
Although the system was successful in vivo, the
method of manufacture is not conducive for
scaleup, and patient acceptability would be poor because of
the cumbersome nature of the tablets; a
proportionally large amount of pectin (700mg) is
needed to control release from a core tablet weighing
only 120mg. A more practical system was produced
by the same group, consisting of a film composed of
a mixture of pectin, chitosan and hydroxypropylmethylcellulose coated onto placebo
tables. The film coating process provides a more
expeditious method of manufacture than compression
coating. The chitosan component of this coat offers
an additional substrate for the colonic bacteria. An
overcoat of enteric polymer was also applied to the
tablets prior to administration. The tablets were
radiolabelled with technetium-99m and administered
to healthy volunteers. By using scintigraphy the
tablets were observed to pass through the stomach
and small intestine intact, and then break in the colon.
Pectin in the form of its water-insoluble calcium salt,
calcium pectinate has also been evaluated as a
colonic carrier. This material has been investigated in
the form of a matrix formulation and compression
coat. Amidated pectin is more tolerant to pH
variations and fluctuations in calcium levels. They
are well susceptible to enzymatic degradation. Pectin
has also been investigated in combination with an
additional biodegradable polysaccharide, galactomannan, in the form of a coating on tablets
and soft gelatin capsules. The two polysaccharides
form a complex in aqueous solution above pH 7. The
resultant film is insoluble in gastric and small
intestinal fluids, but remains susceptible to bacterial
degradation. On assessing their performance in vivo it
was found that in the majority of cases the site of
initial disintegration of the formulation was the
colon, irrespective of whether the tablet or soft
gelatin capsule was administered. A combination of
locust bean gum and chitosan has been evaluated in vitro and in vivo as a vehicle for colonic delivery.
These polysaccharides were mixed in different ratios
and applied to tablet cores. A direct correlation was
found between the quantity of locust bean gum in the
coat and the rate of degradation. A coat composition
of four parts locust bean gum and one part chitosan
was more extensively fermented in the presence of
rat caecal contents. This also translated into a high
bioavailability of Mesalazine from this formulation in
humans. Chondroitin sulphate is a soluble
mucopolysaccharide, which is utilized as a substrate
for bacteria (Bacteroides thetaiotaomicron and B.
ovatus) in large intestine. Chondroitin breakdown
occurs by the enzyme chondroitin sulphate lyase.
Natural chondroitin sulphate is cross-linked and has
higher water solubility. The hydrophillicity may be
altered by varying the degree of cross-linking. Inulin
is a naturally occurring carbohydrate found in many
plants such as onion, garlic, artichoke and chicory. It
consists of a mixture of oligomers and polymer
containing 2 to 60 or more D-fructose molecules
which are linked by β (2-1) bonds. It is generally
accepted that inulin can resist hydrolysis and
digestion in upper GI tract. In the colon, it is
fermented by the colonic microflora, more
specifically by Bifidobacteria and Bacteroide. Inulin
HP (high degree of polymerization) incorporated in
Eudragit RS film was evaluated as a possible
biodegradable coating for colonic drug delivery. A
new single-unit technology named CODES requires
the presence of a polysaccharide in its core to activate
drug release. The system consists of a core tablet
containing the active agent and a biodegradable
polysaccharide such as lactulose. The tablet is coated
with three separate film layers: (i) an inner acid-
soluble layer; (ii) an intermediate hydrophilic
polymer; and (iii) an outer enteric coat. On passage
down the gut the outer enteric layer is insoluble in the
stomach but dissolves in the small intestine. This is
followed by the dissolution of the hydrophilic polymer. The acid-soluble layer (pH <5) remains intact, although it is slightly permeable to water. On arrival in the colon, the lactulose inside the core will dissolve and diffuse through the coat. The local bacteria will degrade the polysaccharide into organic acid, which will lower the local pH sufficiently to initiate dissolution of the coating and drug release. Scintigraphic studies in healthy volunteers have validated the design concept of this technology, with disintegration occurring in the colon. The thickness of the acid soluble layer and the concentration of lactulose in the core are the main factors that affect its performance. This system therefore works on the principle of pH, time and bacteria for release. The polysaccharide amylose has been exploited as a colonic carrier Amylose is one of the two major components of starch, the other being amyllopectin accounting for 15–25% of the total weight. A number of forms of starch were shown to survive passage through the human small intestine. These are classified as forms of resistant starch. Resistant starch can be further subdivided into four types: (I) physically inaccessible starch; (ii) resistant starch granules; (iii) retrograded starch; and (iv) chemically modified starch. In vivo, all four types of resistant starch totally resist digestion in the small intestine and become available for fermentation in the large intestine. The glassy amorphous form of amylose, a type of retrograded starch, is resistant to pancreatic enzymes and can be formed into films that are biodegradable by colonic bacteria. Amylose is fermented by a broad range of colonic bacteria, with more than 50% of the bacterial population showing a tendency to digest amylase. Amylose films swell in aqueous media and, therefore, require the addition of a water-insoluble polymer, ethylcellulose, to act as a structuring agent. These mixed coatings can be applied directly to solid dosage forms by conventional coating methods with equipment that is widely available and so is amenable to industrial scale up. The film coating remains intact in the stomach and small intestine. On arrival in the colon, the amylose component of the film is digested, producing pores through which the drug is released. The ratio of amylose to ethylcellulose in the film and the thickness of the coat control the drug release rate. Amylose has been used in coatings of colon-specific formulations. Amylose, a major component of starch, swells too much on its own, but amylose-ethylcellulose coatings have been investigated in connection with targeting of drug release on the colon. From the results of in vitro studies it was concluded that amylose-ethylcellulose coatings could be suitable for colon-specific formulations. Chitosan is a high-molecular-weight polysaccharide that is degraded by colonic bacteria and 5-ASA has been administered to rats in enteric-coated chitosan capsules. A multiple-unit formulation containing chitosan and drug has also been prepared. This formulation depended for drug delivery on both variations in gastrointestinal pH and the presence of colonic microflora. Microflora. Cross-linked guar gum has been used as a drug carrier in matrix tablets. It was concluded that guar gum is suitable for preparation of colon-specific formulations and is particularly suitable as a carrier of drugs that are not very soluble in water. However, the guar gum formulations mentioned have only formed the subjects of in vitro dissolution studies and in vivo evaluation in rats.

CONCLUSION:
Colon targeted drug delivery systems are exploited to selectively target the drug release to the colon. Several approaches have been investigated to achieve site specificity to the colon.

REFERENCE: