World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

A COMPREHENSIVE REVIEW ON COLON TARGETED DRUG DELIVERY SYSTEM, ITS CURRENT CHALLENGES AND FUTURE PROSPECTIVE

Gurpreet Kaur*, Ashita Pawaiya, Damandeep Kaur, Anuradha Kumari and Preetinder Kaur

M. Pharmacy (Pharmaceutics), Assistant Professor, Rayat Bahra Institute of Pharmacy, VPO Bohan, Education City, Hoshiarpur.

***Corresponding Author: Prof. Gurpreet Kaur**
M. Pharmacy (Pharmaceutics), Assistant Professor, Rayat Bahra Institute of Pharmacy, VPO Bohan, Education City, Hoshiarpur.

Article Received on 13/06/2024 **Article Revised on 03/07/2024** **Article Accepted on 24/07/2024**

ABSTRACT
Drug administration can occur in the colon both locally and systemically. Colonic drug delivery has become more and more important, not only for the delivery of medications to treat localized diseases of the colon, such as Crohn's disease, ulcerative colitis, etc., but also for the systemic delivery of therapeutic peptides, proteins, anti-diabetic, anti-asthmatic, and antihypertensive medications. The drug must be protected from deterioration, release, and absorption in the upper GI tract in order to successfully target the colon. It must also be guaranteed to release rapidly or under control in the proximal colon. In contrast to more recent Colon Targeted Drug Delivery System (CTDDS) methods like pressure-controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery (ORDS-CT), which are unique in terms of achieving in vivo site specificity and manufacturing process feasibility. This review primarily compares the primary approaches for Colon Targeted Drug Delivery System (CTDDS), namely prodrugs, pH and time dependent systems, and microbial triggered systems. These methods achieved limited success and had limitations. If a medication could be given directly to the colon, treatment might be more successful. The benefits and drawbacks of the various strategies and assessments for site-specific drug administration to the colon are also covered in this article.

KEYWORDS: Colon, Targeted drug delivery system, pH, Biopolymer, Microflora, Novel strategies.

INTRODUCTION

The oral route of administration has garnered the greatest interest for the Colon Targeted Drug Delivery System (CTDDS), while it can also be modeled after a sustained or controlled drug delivery system. This is due to the fact that the dose form intended for oral administration is more flexible than the parenteral route because.

I. Patients accept oral drug administration pretty well.
II. Compared to parenteral administration, this method of medication administration is comparatively safe, and there is less chance of side effects at the administration site.

For the treatment of colonic disorders, the majority of traditional medication delivery methods such as inflammatory bowel diseases i.e. Ulcerative colitis, Crohn's diseases, Colon cancer and Amoebiasis are failing because the medication is not concentrated enough to reach the site of action. For these colonic treatments to be safe and effective colon-specific medication administration is required.[1] Colon-specific medication administration is becoming a difficult task for pharmaceutical technologists**. Figure 1** describes location of inflammatory bowel disease.

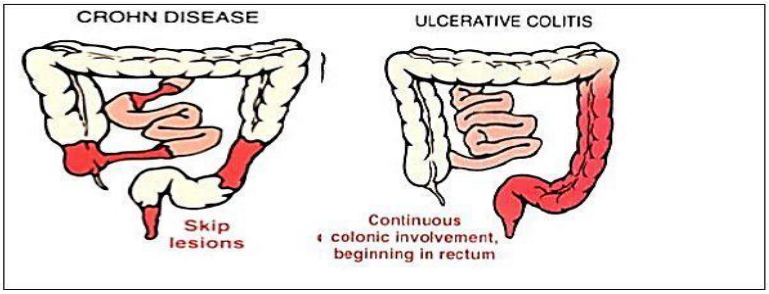

Figure 1: Location of inflammatory bowel disease.

Targeting a medication to the affected organ has several therapeutic benefits.

a) The ability to reduce the standard dosage.
b) A decreased risk of adverse effects at site of action.
c) Delivering the medication as close to the target areas as feasible in its intact state.

In order to prevent medication release and absorption in the stomach and small intestine, retain bioactive agents, and permit drug release exclusively in the colon, the Colon Targeted Drug Delivery System (CTDDS) must be able to protect the drug while it is being delivered to the colon. The colon is thought to be a suitable site for peptide and protein medication absorption for the following reasons.

(i) Digestive enzymes are less intense and diverse.
(ii) The mucosa of the colon has significantly less proteolytic activity than the mucosa of the small intestine. As a result, CTDDS shields peptide medications from hydrolysis and enzymatic breakdown in the duodenum and jejunum, releasing the medication in the ileum or colon to increase systemic bioavailability.
(iii) The colon exhibits a prolonged residence time of up to five days, and it responds favorably to absorption enhancers.[2]

Although other routes for CTDDS may potentially be employed, the oral route is the most practical and recommended route.

Advantages[3]: Therapeutic benefits of colon-specific drug delivery systems include the following.

1. Decrease in side effects during colonic illness therapy, such as Crohn's disease, Ulcerative Colitis, and Colorectal Cancer,
2. Avoids first pass metabolism of the steroids,
3. Preventing the gastrointestinal irritation that results from taking NSAIDs orally,
4. Drugs used to treat conditions like Rheumatoid Arthritis, Asthma, and Angina are release gradually,
5. Less frequency of drug administration and better compliance by patients,
6. Offers an ideal environment for peptides and proteins that are sensitive to stomach fluid and digesting enzymes
7. Bioavailability of poorly absorbable drugs is increased.

Limitations[4]

1. Individual differences exist in the pH levels of the colon and small intestine, which may permit drug release at an undesirable CTDDS site. Individual differences in the drug release pattern could lead to unsuccessful therapy,
2. The caecum and small intestine have similar pH levels, which lessens the formulation's site specificity,
3. Poor site specificity is the main drawback of colonic medication administration,
4. Low loading dose and increased excipient requirements,
5. Colic microflora can be impacted by diet and illness, which can have a negative impact on how well drugs target the colon. Meal composition in the GIT can influence the pharmacokinetics of a drug,
6. An excessive slow rate of enzymatic degradation may disrupt the breakdown of polymers, changing the drug's release profile,
7. In the case of a time-dependent colonic drug delivery system, a significant fluctuation in the gastric retention period may result in drug release at the undesirable site,
8. Need of improved technology.

Need of colon targeted drug delivery[5]

1. Local delivery of drugs to the colon, which aims to treat the disease directly at the site with less dose and fewer systemic side effects,
2. Colon-specific formulations extend the duration of drug delivery, and site-specific or targeted drug delivery systems would enable oral administration of peptide and protein medications,
3. The use of colon-targeted drug delivery systems is advantageous in treating colon disorders,
4. Topical treatment of inflammatory bowel diseases, such as ulcerative colitis or crohn's disease, can be accomplished through local or systemic drug delivery through the colon.

Glucocorticoids and Sulphasalazine are typically used to treat such inflammatory disorders. If drugs were directed towards the colon, diseases such as colorectal cancer would potentially be treated more successfully. Formulations intended for colonic distribution are also appropriate for the delivery of medications that are polar and/or vulnerable to hepatic metabolism-related chemical and enzymatic degradation in the upper gastrointestinal tract, including therapeutic proteins and peptides. Colon targeted diseases; drug and their site of action are given in **Table 1.**

Table no. 1: Colon targeted disease, drug and sites.

Target sites	Disease condition	Drug and active agents
Topical Action	Inflammatory Bowel Disease, Irritable bowel disease, Crohn's disease	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Balsalazide
Local Action	Pancreatactomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements, 5-Flourosil
Systemic Action	To prevent gastric irritation, To prevent first pass metabolism of orally ingested drug, For oral delivery of peptides, For oral delivery of vaccines	NSAID Steroids Insulin Typhoid

Anatomy of colon

The gastrointestinal tract is divided into upper and lower GIT segments, extending approximately 5 meters from the mouth to the anus. The colon is roughly 1.5 cm in length, covers the majority of the large intestine. The colon is made up of the i) sigmoid colon, ii) ascending colon, iii) hepatic flexures, iv) transverse colon, v) splenic flexure, and vi) descending colon. The ascending colon extends from the bend on the right side, beneath the liver and the caecum, for about 20 centimeters. The hepatic flexure connects the ascending and transverse colons at a right angle, and it is located on the side closest to the liver. The transverse colon, which is the longest and movable portion of the colon at 45 cm, allows the ascending and descending colons to attach by traversing the abdominal cavity. It also has the highest absorption rate at this location.[6] Various parts of colon are mentioned in **Table 2**. Structure of colon is described in **Figure 2**.

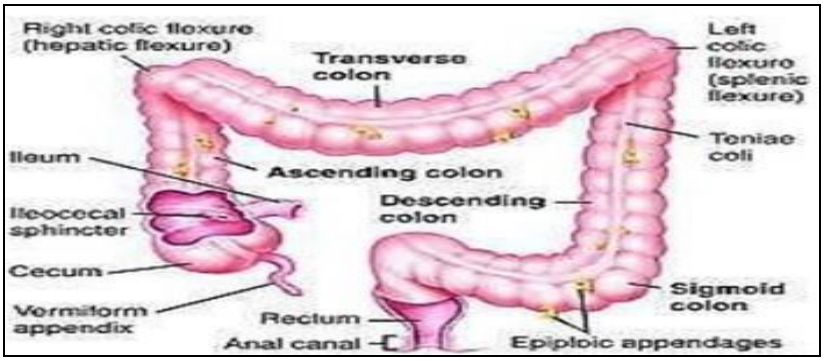

Figure 2: Structure of Colon.

Table No. 2: Parts of Colon.

Parts of colon	Description
Ascending colon	20–25cm long located behind the peritoneum hepatic flexure lies under right lobe of the liver
Cecum(Proximal right colon)	20–25cm long located behind the peritoneum hepatic flexure lies under right lobe of the liver
Transverse right colon	Lies anterior in the abdomen, attached to gastro colic ligament splenic flexure near tail of pancreas and spleen
Descending colon	10–15cm long located behind the peritoneum. After it enters the true pelvis it is known as thesigmoid colon
Sigmoid colon	This part describes an S-shaped curve in the pelvis that continues downwards to becomethe rectum
Rectum	This is a slightly dilated section of the colon about 13cm long. It leads from the sigmoid colon and terminates in the anal canal
Anal canal	This is short passage 3.8 cm long and leads from rectum to the exterior

The serosa (external coat), muscularis externa, submucosa, and mucosa are the four layers that constitute up the colon wall.[7] Different layers of colon are given in **Table 3**. Variations in the physiology of Human Gastro-intestinal Tract is also mentioned in **Table 4**.

Table no. 3: Different layers of colon.[16]

Layers of colon	Description
Serosa	Exterior coat of the large intestine
Muscular external	Major muscular coat of the large intestine which composed of an inner circular layer of fibers surrounding the bowel and an outer longitudinal layer.
Submucosa	A layer of connective tissue lies immediately beneath mucosa lining the lumen of the colon
Mucosa	The mucosa has three parts: epithelium, lamina propria, and muscular mucosa

Table 4: Variations in the Physiology of Human Gastro-intestinal Tract.

Organ	Contents	pH
Stomach	Thin soluble mucus, HCl, intrinsic factor, pepsin, lipases, gastrin, histamine, serotonin, somatostatin	1–1.5
Small Intestine	Chyme (from stomach), alkaline mucus, intestinal juice which is mostly water, motilin, cholecystokinin, brush border enzymes (maltase, sucrose, lactase, enterokinase and carboxypeptidase) Bile (which contains electrolytes, fatty substances, bile salts and pigments), pancreatic juice (a bicarbonate-rich f luid containing enzymes)	5–7.5
Cecum	Mucus, enteric bacteria, vitamins, food residue, gases such as carbon dioxide and methane	5.5–7
Ascending Colon	Mucus, enteric bacteria, vitamins, food residue, gases such as carbon dioxide and methane	5.7–6.9
Transverse Colon	Mucus, enteric bacteria, vitamins, food residue, gases such as carbon dioxide and methane	5.8–7.4
Descending Colon	Mucus, enteric bacteria, vitamins, food residue, gases such as carbon dioxide and methane	6.3–7.7
Rectum	Undigested food residues, mucus, epithelial cells from the intestinal lining, numerous bacteria (millions), some remaining water	~7

FACTOR TO BE CONSIDERED IN THE DESIGN OF COLON-SPECIFIC DRUG DELIVERY SYSTEM[6,8]

The colon is the body's "black box," therefore it can be challenging to target a specific location.

The development of a Colon Targeted Drug Delivery System (CTDDS) and the drugs' colonic bioavailability can be influenced by a number of factors. A quick discussion of a few of these factors is given below.

1. Intrinsic Factors

a) Intestinal colonic transit time
b) pH of colon
c) Colonic microflora and enzymatic metabolism
d) Mucus barrier

2. Extrinsic factors

a) Drug candidate
b) Polymeric drug carrier

1. Intrinsic Factors

a) Colonic micro flora and their enzymes[9]

Drug release is triggered by intestinal enzymes in different regions of the gastrointestinal tract. These enzymes are often produced by gut microflora, which are abundant in the colon. These enzymes are used to liberate drugs from prodrugs and break bindings between an active agent and an inert carrier, as well as to breakdown coatings and matrices. There are around 400 different kinds of bacteria known to exist, with 20–30% belonging to the genus Bacteroides. Grampositive facultative bacteria predominate in the upper portion of the GIT, where there are relatively few other types of bacteria. Most commonly found intestinal anaerobic and aerobic bacteria is given in **Table 5.[10] Table 6** mentions drug metabolizing enzymes in the colon that catalyze reactions.

Table 5: Most commonly found intestinal anaerobic and aerobic bacteria.

Aerobic genera	Anaerobic genera
Escherichia	Bifidobacterium
Enterococcus	Clostridium
Streptococcus	Bacteriodes
Klebsiella	Eubacterium

Table 6: Drug metabolizing enzymes in the colon that catalyze reactions.

Enzymes	Microorganism	Metabolic reaction catalyzed
Nitroreductase	*E. coli*, Bacteroides	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, *E. coli*	Reductive cleavage of azo compounds
Esterase, amidases	*E.coli, P.vulgaris, B. subtilis, B. mycoides*	Cleavage of esters or amidases of carboxylic acids
Glycosidase	Clostridia, Eubacterium	Cleavage of β-glycosidase of alcohols and phenols
Glucuronidase	*E. coli, A. aerogenes*	Cleavage of β-glucuronidases of alcohols and phenols

b) pH in the colon[11]

The pH varies in the GI tract from the mouth cavity to the large intestine. Numerous factors, including diet, food intake, intestinal motility, and illness conditions, can cause pH variations in the stomach, small intestine, and large intestine. This pH fluctuation along the GIT is used by the colonic drug delivery system to target the drug. The stomach has a pH gradient of 1.2, the proximal small intestine has a pH gradient of 6.6, and the distal small intestine has a pH gradient of roughly 7.5. The pH values of the right, mid, and left colon are roughly 6.4, 6.6, and 7.0, respectively. The small intestine's pH can reach 8 or 9.2, but the colon's pH is often lower. pH range found in GIT is given in **Table 7**.

Table 7: pH range in GIT.

Portion of GI Tract	pH Range
Oral cavity	6.2-7.4
Oesophagus	5.0-6.0
Stomach	Fasted condition: 1.5-2.0, Fed condition: 3.0-5.0
Small intestine	Jejunum: 5.0-6.5, Ileum: 6.0-7.5
Large intestine	Right colon: 6.4, Mid colon and left colon: 6.0-7.5

b) Mucus barrier[12]

Mucus is a hydrogel layer that is rich in mucin and glycoproteins. It prevents the gastrointestinal tract from absorbing the drugs. Human mucus is composed of three layers: the basal layer, the thinner, and the luminal layer. The primary functions of mucus are chyme lubrication and epithelial cell protection against infections and mechanical damage. The mucosal layer causes the medication to have a poorer therapeutic effect because the mucus's adhesive quality binds the medication to its surface, which is only removed in feces. This restricts how long the drug is delivered to the place of action.

c) Intestinal colonic transit time[13]

The colon transports everything through the digestive tract more slowly than other parts of the body. The transit time is dependent on several factors, including food, amount of dietary fiber, movement, stress, illness, and medication use. The duration of colonic transit varied from 50 to 70 hours. Different transit time of dosage form in GIT is mentioned in **Table 8**.

Table 8: The transit time of dosage form in GIT.

Organ	Transit time(h)
Stomach	≤1(fasting) ≥3(fed)
Small intestine	3-4
Large intestine	20-30

2) Extrinsic factors[14]

a) Drug candidate: Those drugs are selected for CTDDS that are:

- Drugs, especially peptides, with poor intestinal or stomach absorption,
- Drugs for colon cancer, IBD, diarrhea, and ulcerative colitis are frequently given locally,
- Drugs for colon use that work locally to treat GIT diseases, drug for colon cancer,
- Pharmaceuticals that are poorly absorbed from the upper gastrointestinal tract,
- Drugs that are targeted,
- Drugs that experience significant first-pass metabolism.

b) Polymeric drug carrier[15]

The physiochemical composition of the drugs and the condition for which the system is intended to be utilized determine which carrier is best for a certain drug candidate. The carrier selection is influenced by various parameters, including the drug's chemical composition, stability, and partition coefficient, as well as the type of absorption enhancers selected. Additionally, the drug molecule's functional groups influence the drug carrier selection. The release characteristics and effectiveness of the systems may be impacted by the carriers that include additives such hydrogels as coating agents and polymers as matrices.

Approaches for colon targeted drug delivery[16]

1) Primary approaches for colon targeted drug delivery

a.pH sensitive polymer coated drug delivery system
b.Delayed release drug delivery system
c. Microbially triggered drug delivery
- Prodrug approach
- Polysaccharide based system

2) New approaches for colon targeted drug delivery
a. Pressure controlled drug delivery system (PCDDDS)
b.CODE
c. Osmotic controlled drug delivery system (OROS-CT)
d. Pulsatile
- Pulsincap system
- Port system

e. Azo hydrogels
f. Multiparticulate system based drug delivery

a)pH sensitive polymer coated Drug Delivery to colon[17,18]

Principle: Dosage forms (e.g., tablets/pellets) are coated with pH-sensitive polymers for delayed release and upper GIT protection. The most often used pH-dependent coating polymers are methacrylic acid copolymers, also known as Eudragit S, specifically Eudragit L and S. These polymers are insoluble at low pH levels, but they become more soluble as pH increases. **Figure 4** describes pH dependent release.[20]

A drawback with this strategy is the
- variability in gut pH, which can be influenced by diet and disease conditions.
- Low site specificity (starts to disintegrate even in the lower small intestine).

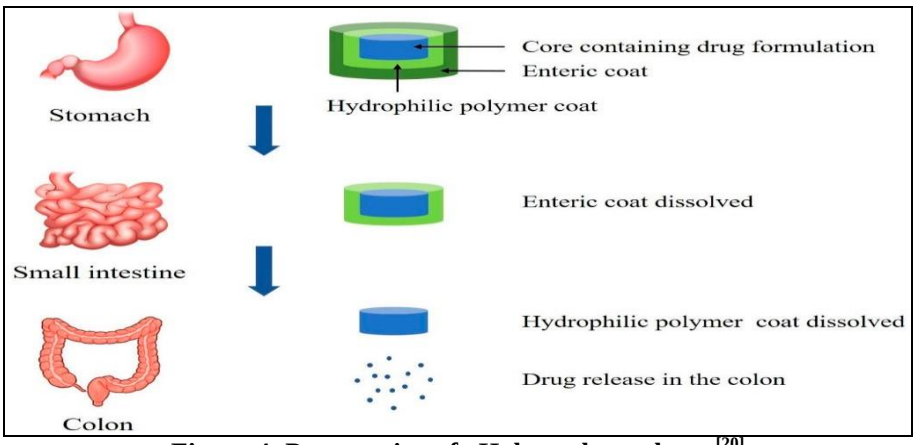

Figure 4: Presentation of pH dependent release.[20]

b) Delayed (Time-Controlled Release System) Release Drug Delivery to Colon

Principle The drug should be released from the dosage form after a specified lag period. This ensures that the drug reaches the correct site of action at the appropriate time and amount. Lag time is around 5 hours.

Design of enteric coated timed- release press coated tablet is described in **Figure 5**.

Disadvantages
- Variation in gastric emptying time between subjects and also depends on type and amount of food intake.

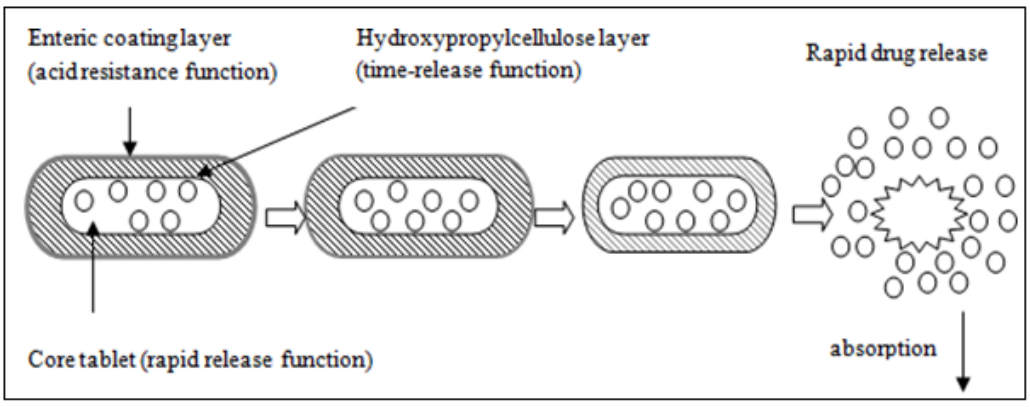

Figure 5: Design of enteric coated timed-release press coated tablet.

c) Microbially Triggered Drug Delivery to Colon

Because the colon is rich in bacteria, drug release occurs through degradation of biodegradable polymers coated on dosage forms. These dosage forms are shielded from upper GIT because there is very little microbial degradable activity in upper GIT, which is inadequate to cleave the polymer coating.

- **Prodrug Approach for Drug Delivery to Colon**[1,18,19]

For colonic administration, the prodrug (a pharmacologically inactive derivative of a parent drug molecule) is engineered to undergo minimal hydrolysis in the GIT's upper tracts before undergoing enzymatic hydrolysis in the colon, releasing the active drug moiety from its carrier.

The colon contains a range of bacterial enzymes that carry out biotransformation. Enzymes commonly targeted for colon drug administration include azoreducatase-galactosidase, β-xylosidase, nitroreductase, and glycosidase deaminase. Prodrug approach for CTDDS is given is **Figure 6.**

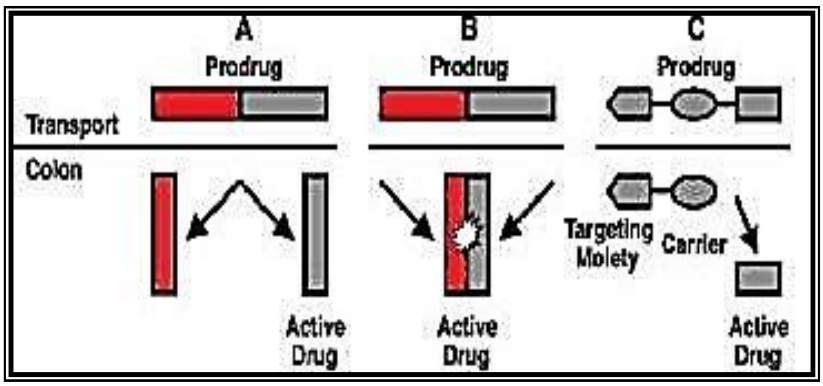

Figure 6: Prodrug approach for CTDDS.

Limitations include a non-versatile strategy that relies on the functional group on the drug moiety for chemical bonding. Additionally, carriers require thorough testing before usage.

- **Polysaccharide-Based Delivery System**[18,19,26]

Naturally occurring polysaccharides are employed to target the colon because they are abundant, cheap, and come in a range of forms with different characteristics. They are chemically adaptable, very stable, safe, non-toxic, hydrophilic, and biodegradable. These polysaccharides are derived from plants (guar gum, inulin), animals (chitosan, chondroitin sulphate), algae (alginates), and microbes (dextran). The microbes in the gut can break down the polysaccharides into simple saccharides. Therefore, they fit into the category of "generally regarded as safe" (GRAS).

Polysaccharides are biodegradable substances that occur naturally. They originated by microbes (dextran) or plants (guar gum, inulin), as well as by animals (chitosan, chondroitin). Colon-targeting delivery systems find these extremely desirable since colonic bacteria enzymes break them down. They are also widely distributed, possess a wide range of structures, are very stable, safe, and biodegradable, and may be chemically altered with ease. When using polysaccharides individually for colon targeting, the combination of polysaccharides produced greater outcomes. Cellulose and its derivatives are mostly utilized for colon targeting because they are not absorbed orally. Enteric cellulose esters and non-enteric cellulose esters are the two categories of cellulose esters. The solubility of the nonenteric cellulose esters varies with pH and they are insoluble in water. They dissolve in alkaline pH conditions but are insoluble in acidic ones Due to their ease of breakdown by colon enzymes and safety for living things, polysaccharides including chitosan, pectin, and chondroitin are frequently employed instead of other polymers for colon-targeting delivery methods. Thin coating films were developed to ensure that the medication reached the desired locations. Various polysaccharides used in CTDDS are given in **Table 9**.

Table 9: Polysaccharides investigated for use in CTDDS.

Polysaccharide	Source	Properties
Starch	Plant	Starch hydrolyzed readily by enzymes through the acetal link
Amylose	Plant	Amylose stays resistant to pancreatic α-amylase while degrading by the bacterial enzymes present in the colon.
Cellulose	Plant	Colonic bacteria can produce endo-as well as exo-enzymes due to the colon being an anaerobic environment. These form complexes that degrade cellulose to form carbohydrate nutrients.
Inulin	Plant	The inulin has incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GI tract but digested in the human fecal medium by the action of *bifidobacteria* and *bacteroides*.
Locust bean gum	Plant	Cross-linked galactomannan leads to water-insoluble film forming product-showing degradation in colonic microflora.

Guar gum	Plant	Guar Gum shows degradation in the large intestine due the presence of microbial enzymes.
Alginate	Algae	The alginate beads have the advantage of being non-toxic, and dried alginate beads re-swell in the presence of dissolution media and can function as controlled release systems.

2) New approaches for colon targeted drug delivery system

A) Pressure controlled drug delivery system (PCDDDS)

Principle: Digestion in the GI tract involves stomach contractions and peristaltic motions to propel intestinal contents. The large intestine uses powerful peristaltic movements, known as mass peristalsis, to transfer contents from the ascending colon to the transverse. The colon experiences powerful peristaltic waves three to four times per day. However, they briefly increase luminal pressure in the colon, which is used to develop pressure-controlled devices. Peristaltic action causes higher luminal pressure in the colon than in the small intestine due to the viscosity of the contents. In the stomach and small intestine, digestive juices are fluid, whereas in the colon, water reabsorption and feces production increase the viscosity of the contents.

b) Novel Colon Targeted Delivery System (CODESTM)[21]

CODESTM is a CTDDS technique designed to address issues with pH and time-dependent systems. It is a combination of pH-dependent and microbial-triggered CTDDS. The drug uses lactulose to trigger site-specific medication release in the colon. The system consists of a lactulose-based tablet core coated with Eudragit E acid soluble material, followed by Eudragit L enteric material. The enteric coating preserves the tablet, but it dissolves fast after gastric emptying. The enteric coating protects the tablet while it is in the stomach and then dissolves fast after gastric emptying. The coating protects the preparation while it goes through the small intestine, which has an alkaline pH. When the tablet reaches the colon, microbes breakdown the polysaccharide (lactulose) into organic acid. This lowers the pH of the surrounding system, causing the acid-soluble coating to dissolve and the drug to be released. The conceptual design of CODES is explained in **Figure 7**.

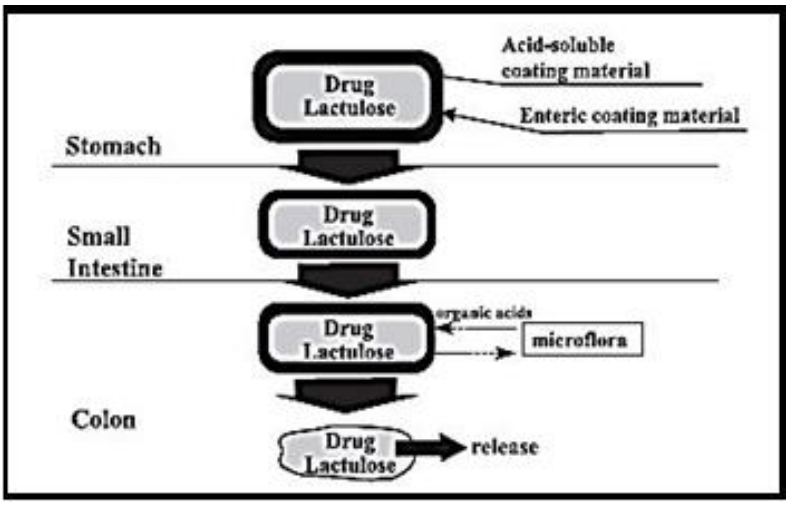

Figure 7: Schematics of the conceptual design of CODES.

c) Osmotic controlled drug delivery system (OROS-CT)[22]

One system that is controlled by osmotic pressure is the OROS-CT. It is made by using a hard gelatin capsule that dissolves in the small intestine's pH to allow water into the device. It then swells as a result, forcing the medication out. But as the capsule reaches the small intestine's higher pH, this coating dissolves and water seeps in. A semipermeable membrane that encloses a drug compartment and an osmotic push compartment is present within the intestinal covering. Water pushes through an aperture in the membrane next to the drug compartment, causing the push compartment to swell and forming a gel that is driven out.

The rate at which water enters determines the rate at which the drug exits. These systems can also be made so that there is a delay between the time the enteric coating dissolves and the drugs is released, which would prevent drug release in the small intestine. The conceptual design of OROS-CT is described in **Figure 8**.

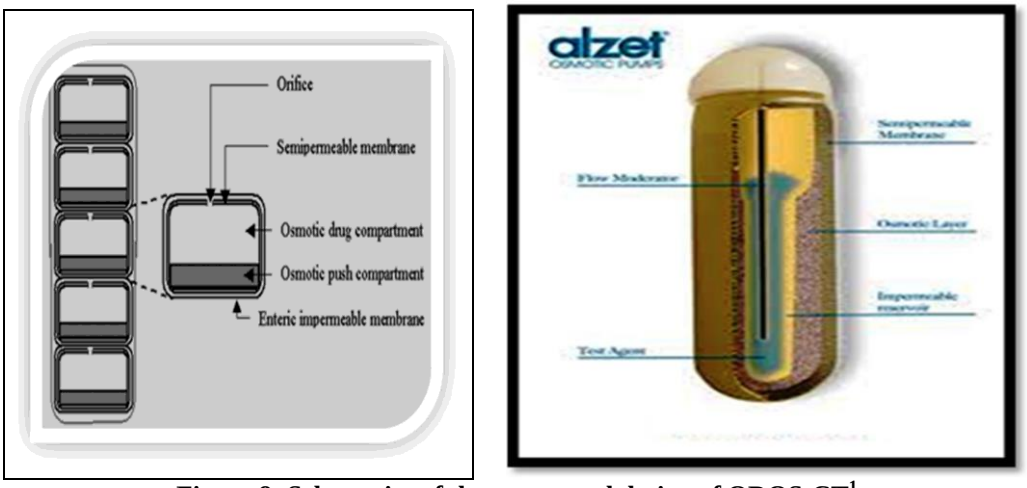

Figure 8: Schematics of the conceptual design of OROS-CT[1]

d) Pulsatile Drug Delivery system[22]

i) Pulsin Cap: This system mostly relies on the time-dependent method, of which PulsinCap® is the most widely used. The novel technique consists of an insoluble half-capsule body that is filled with an active substance, an open end that is sealed with a fixed amount of hydrogel plug, a water soluble cap coated on the plug, and an enteric polymer film covering the entire capsule. . The coating dissolves as it through the small intestine, where the pH is higher than 7. When the drug enters the colon, it is released with the help of water entry, which causes the drug compartment to form a flow able gel and the osmotic push compartment develop. PulsinCap technology[23] is explained in **Figure 9**.

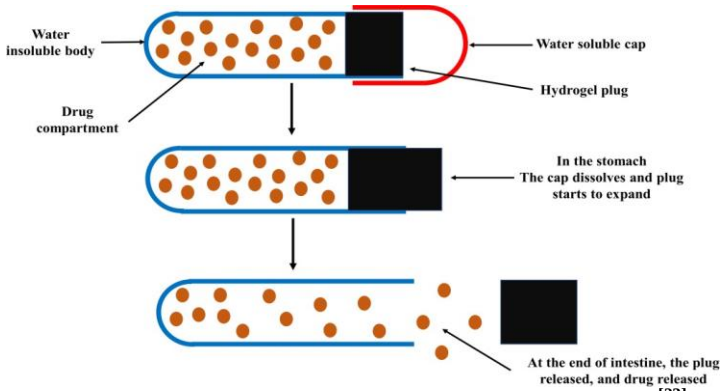

Figure 9: Schematic diagram of PulsinCap technology.[23]

ii) Port system[24]: When developing port systems, the capsule is encased in a membrane that is semipermeable. It is made up of a gelatin casing with semipermeable membranes made of derivatives of cellulose and acetic acid. The drug's formulations and active ingredient are contained in an insoluble plug found inside the capsule. When the capsule's pressure rises as a result of coming into touch with the dissolving fluid, the medication is released from it. The drug is expelled from the capsule due to the semipermeable membrane allowing fluid to enter the capsule's body. The capsule's contents are released one after the other at predetermined intervals separated by a set amount of time. Mechanism of action of port system drug delivery is explained in **Figure 10**.

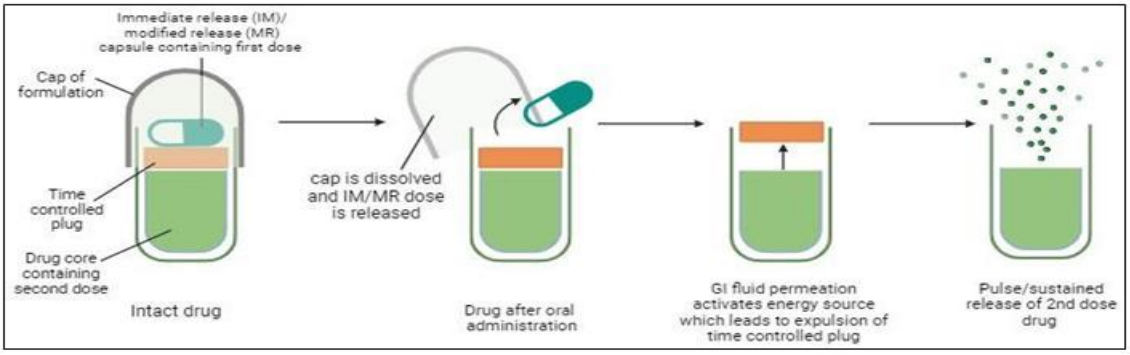

Figure 10: Mechanism of action of port system drug delivery.

e) Prodrug approach for colon drug delivery[25]

A prodrug is a parent molecule that is pharmacologically inactive and needs to undergo enzymatic transformation in the biological environment in order to release the active ingredient at the intended location. With this method, the medication and its carrier are covalently linked so that, when taken orally, the drug's moiety stays intact in the stomach and small intestine and, once it reaches the colon, are renewed by enzymatic cleavage.

i) Azo-polymeric pro drugs: The use of polymers as drug carriers for colon drug administration is the focus of more recent methods. For this reason, polymers that exist naturally as well as synthetic ones have been employed. To create polymeric prodrugs having an azo connection between the polymer and drug moiety, sub-synthetic polymers have been employed. For CTDDS, these have been assessed. Several azo polymers have also been considered for use as coating materials on top of drug cores. It has been discovered that coating of peptide capsules with polymers cross-linked with azo-aromatic groups protects the drug from being broken down in the stomach and small intestine. The drug is released in the colon where the azo bonds are broken down.

ii) Multiparticulate system based drug delivery[23,26]: Multiple tiny, distinct units are packed into a sachet or crushed into a tablet matrix, such as pellets, granules, beads, microparticles, or nanoparticles. Because of its extremely small size, these dosage forms allow the system to avoid deterioration in the upper gastrointestinal tract. More consistent GIT dispersion and a uniform drug release mechanism are ensured by smaller and more uniform particle sizes. The primary benefit of this approach is reduced variability in gastrointestinal transit time both within and between subjects since the smaller particle size has less of an impact on the time it takes for the stomach to empty. Multiparticulates are employed as drug carriers in time-dependent, pH-sensitive, and microbially controlled systems that target the colon. When compared to traditional single units for controlled release technologies, multiparticulate systems offer a number of benefits, including less localized side effects and more predictable stomach emptying than single unit tablets or capsules.

Evaluation of CTDDS

***In vitro* Evaluation[27]**: There is no standardized method for evaluating CTDDS because the optimal in vitro model would have the same GIT circumstances as the real thing, including pH, volume, stirring, bacteria, enzymes, enzyme activity, and other dietary ingredients. Designing a criticized in vitro model is challenging since these variables are typically altered by food and physical stress. *In vitro* model used for CTDDS are.

***i) In vitro* dissolution test**

The USP-described dissolution procedures cannot perfectly mimic in vivo conditions, such as those related to pH, bacterial environment, and mixing stresses. This is because controlled-release formulations utilized for colonspecific medication administration typically have complex dissolution processes. The traditional basket method can be used to conduct CTDDS-related dissolution experiments. Dissolution studies of a formulation specific to the colon done in a range of media that mimic the pH levels and times that are likely to be experienced at different points in the gastrointestinal tract. For instance, pH 1.2 has been chosen to replicate gastric fluid, pH 6.8 to represent the jejunal area of the small intestine, and pH 7.2 to represent the ileal segment. A gradient dissolution research has been conducted in three buffers to study enteric-coated capsules for CTDDS. Examine in vitro whether coatings and carriers are intact in conditions that mimic the stomach and intestine. Two hours (mean gastric emptying time) of drug release research in 0.1 N HCl Three hours of phosphate buffer drug release trial (mean small intestine transit time).

***In vitro* enzymatic test:** For this there are 2 tests.

- The carrier drug system should be incubated in a fermenter that has been designed to support bacteria (*Streptococcus faccium or B. ovatus*). The amount of drug released at various intervals will be assessed.
- The buffer medium used for drug release studies contains enzymes (enzyme pectinase, dextranase), as well as the caecal contents of rats, guinea pigs, or rabbits. The amount of drug released at a given time is calculated and is closely correlated with the polymer carrier's rate of breakdown.

***ii) In Vivo* Evaluation[28]**

Many species, including dogs, guinea pigs, rats, and pigs, are used to assess drug transport to the colon because their anatomical and physiological characteristics, as well as the microbiology of the human gastrointestinal tract, are similar to those of these animals. The relative model for the colonic disorders should be taken into consideration while selecting a model for testing a CTDDS. For instance, guinea pigs are frequently employed as experimental models for IBD. Rat and rabbit GIT azoreductase and glucouronidase activity distributions are similar to human GIT distributions. A unique structure for the quick assessment of CTDDS has been brought forward. This technique involves transplanting human fetal bowel onto the back of thymic nude mice as a subcutaneous tullel. The tullel vascularizes in 4 weeks, develops, and is capable of establishing a host-derived mucosal immune system.

iii) Drug Delivery Index (DDI)[29] and Clinical Evaluation[30]

DDI is a pharmacokinetic parameter that is determined after oral colonic pro-drugs are administered once or more. The relative ratio of RCE, or relative colonic tissue exposure to the drugs, to RSC, or relative systemic exposure to the drug, is known as the DDI. Better intestinal medication delivery is indicated by a high drug DDI value. Colonoscopy and intubation are used to

evaluate the absorption of drugs from the colon. In order to assess colon medication delivery systems, gamma scintigraphy and high frequency capsules are now the most popular methods used.

- **High frequency capsule**[31]

This method is important for study absorption properties of drug in colon. This method is used for to check the bioavailability of the drug in the colonic site. High frequency capsule is used for evaluating the relative bioavailability of the CTDDS. Drug release at various sites of GIT and advantages of relative bioavailability are evaluated and compare the absorption parameters A smooth plastic capsule that is eaten orally and contains a small latex balloon, drugs, and radiotracer. Generator with high frequency is the trigger system. An impulse causes the drug and radiotracer to be released, and radiological localization is used to track the release in various GIT regions. It examines the drug's capacity for absorption in the colon.

- **Gamma Scintigraphy**[31]

This technique is used to investigate how long drugs take to transit through the GIT. This approach is used to measure the passage time. Because pharmacokinetic studies use Scintigraphy, they are able to identify the locations of drug absorption. The crystal that develops from the subject detects gamma radiation. When the energy is converted to light scintillation and amplified, they provide the digital result. This method is noninvasive and uses minimal radiation on individuals. A valuable technique for researching food and drug clearance from the GIT is Gamma Scintigraphy. This method is also useful for comprehending how drugs are delivered.

Limitations and challenges in colon targeted drug delivery

1) Developing a suitable dissolution testing procedure to assess the intended system in vitro is one of the challenges in the development of colon-specific drug delivery systems. This is because there are many different reasons for using a colon-specific drug delivery system.
2) The colon provides a nearly neutral pH, a long transit time, decreased digestive enzyme activity, and enhanced receptivity to absorption enhancers as a site for drug delivery; yet, the process of delivering medications to the colon is highly intricate. The colon is quite challenging to access because of its position in the distal portion of the alimentary canal. The gastrointestinal system contains a variety of enzymes and a wide range of pH values, which make it more difficult for the dosage form to be reliable and efficient when it comes to distribution.
3) The drug must also be in solution before entering the colon for this route of delivery to be successful. Alternatively, the drug may dissolve in the luminal fluids of the colon, but this may not be possible for poorly soluble drugs due to the colon's higher viscosity and much lower fluid content than the upper GI tract.
4) The drug's stability is another issue that needs to be taken into account while developing the delivery system. The medication may attach itself to mucus, feces, intestinal fluids, or leftovers from food in a particular way.
5) Through the drug's metabolic breakdown, the local microbiota may also have an impact on colonic function. Reduced surface area and the relative "tightness" of the colon's tight junctions can also limit the amount of drugs that can pass through the mucosa and enter the bloodstream. There is evidence in the literature that the colonic mucosa is less active in the cytochrome P-450(3A) class of drug metabolizing enzymes. Drugs with a longer residence time—three to five days—have greater plasma levels and, thus, are generally more bioavailable. This is particularly true for medications that function as substrates for this particular class of enzyme.

Future Prospective

One of the most important areas of research is colon targeting because of its specificity, which can be used to treat conditions like inflammatory bowel illnesses locally or to achieve maximum drug absorption if the desired amount is attained without leaking to a particular colonic region. Certain medication molecules that are poorly absorbed may find better bioavailability in the colon, according to recent studies. By comparison with the stomach and small intestine, the distal colonic portion is found to have a lower enzyme activity and a less hostile ecosystem. One of the biggest issues for oral peptide delivery in the pharmaceutical industry is developing formulations that can increase the oral absorption of peptide and protein medications, which have relatively low bioavailability due to instability in the GI tract (due to pH or enzymatic breakdown). Drug moieties like as proteins, peptides, oligonucleotides, and vaccines can be delivered spatially using colon focused multiparticulate systems like microspheres and nanoparticles. However, the goal of oral administration is not drug release. It is necessary to address the bioavailability of protein medications administered at the colon location. The use of drug absorption enhancers in drug delivery systems is anticipated to improve therapeutic efficacy. Drug transporters that regulate drug influx and efflux as well as substances that can improve drug absorption have become crucial to the digestive system's drug absorption process. Nature intended the colonic portion of the GIT primarily for the purpose of excreting metabolic products rather than absorbing nutrients. Consequently, more studies on the specificity of medication absorption at the colon location are required. These kinds of investigations will play a big role in the future advancement of colon focused medication delivery.

REFERENCES

1. Vinay K Gupta, et al A Review Article on Colonic Targeted Drug Delivery System, The Pharma Innovation, 2012; 7(1): 14-24.
2. Gaurav Tiwari, et al Primary and novel approaches for colon targeted drug delivery – A review, International Journal of Drug Delivery, 2010; 2: 01-11.
3. Obot Solomon Sunday. Colon-targeted drug delivery systems: design, trends and approaches. Universal Journal of Pharmaceutical Research, 2017; 2(4): 53-57.
4. Mr. Sandeep Vishnu Gapat *et al.* A REVIEW ON COLON TARGETED DRUG DELIVERY: AN INNOVATIVE APPROACH. *Indo American Journal of Pharmaceutical Research, 2015; 5(10): 3115-3127.*
5. Altamash M. et al Colon targeted drug delivery system: A review on current approaches. Indian J. Pharm. Biol. Res, 2013; 1(4): 130-147.
6. Tahseen et al. Colon Specific Drug Delivery System: Innovative Approaches to Treat Colonic Ailments SGVU Journal of Pharmaceutical Research & Education, 2018; 3(2): 338-351.
7. T M Litto et al Colon Targeted Drug Delivery: - A Review J. Pharm. Sci. & Res, 2020; 12(10): 1326-1331.
8. Seth Amidon, et al Colon-Targeted Oral Drug Delivery Systems: Design Trends and Approaches, AAPS PharmSciTech, August 2015; 16(4): 731-741.
9. Asha Patel, et al Colon Targeted Drug Delivery System: A Review System JPSBR, July-August 2011; 1(1): 37-49.
10. Patel Parul K. et al Bacteria aided biopolymers as carriers for colon specific drug delivery system: A Review Int. J. Pharm Tech Res, 2012; 4(3): 1192-1214.
11. Gurmeet Singh et al Emerging Techniques and Challenges in Colon Drug Delivery Systems Journal of Applied Pharmaceutical Science, 2012; 02(03): 139-147.
12. Manan Patel et al Colon targeted drug delivery system: Recent approaches International Journal of Bioassays, 2021; 10.1: 5763-5777.
13. Prasanth V.V et al Colon Specific Drug Delivery Systems: A Review on Various Pharmaceutical Approaches Journal of Applied Pharmaceutical Science, 2012; 02(01): 163-169.
14. Preetha Mathew et al Novel Approaches to Colon Targeted Drug Delivery-An overview Int. J. Pharm. Sci. Rev. Res, July - August 2020; 63(1): Article No. 09, Pages: 52-59.
15. Ratnaparkhi Mukesh P et al Colon Targeted Drug Delivery System International Journal of Pharma Research & Review, August 2013; 2(8): 33-42.
16. Sharma Ankush et al A Review On Novel Approaches For Colon Targeted Drug Delivery System, IJPCBS, 2014; 4(2): 241-249.
17. Rutuja P. Bugad A Comprensive Review On Colon Targeted Drug Deliver System, IJCRT, July 2021; 9(7): 225-237.
18. Anita, Singh A and Dabral A: A review on colon targeted drug delivery system. Int J Pharm Sci & Res 2019; 10(1): 47-56. doi: 10.13040/IJPSR.0975-8232.10(1).47-56.
19. Philip AK, *et al.* Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches *OMJ, 2010; (*25): 70-78.
20. Sang Hoon Lee et al Strategic Approaches for Colon Targeted Drug Delivery: An Overview of Recent Advancements *Pharmaceutics*, 2020; *12*: 68: 1-20.
21. Apninder Kaur et al Polymeric Drug Delivery Approaches for Colon Targeting: A Review, *Drug Delivery Letters*, 2014; *4(1): 38-48.*
22. Risa Widiani Batubara et al Current Update on Clinical Therapeutic Strategies for Colon Targeted Delivery Systems Pharmaceutical Sciences and Research (PSR), 2024; 11(1): 1-17.
23. Milad Reda Qelliny et al Colon Drug Delivery Systems for the Treatment of Inflammatory Bowel Disease, J. Adv. Biomed. & Pharm. Sci, 2019; 2: 164-481.
24. Rozhan Arif Muhammed et al A Review On Development Of Colon Targeted Drug Delivery System, *Int J App Pharm, 2024; 16(2): 12-27.*
25. Ashwini Sopan Bansode et al Colon Targeted Drug Delivery System : An Overview, *Int. Imperial J. Pharmaceutics & Cosmetology, July 2012; 2(2): 001-007.*
26. Madhu E N *et al.*, Novel Colon Specific Drug Delivery System: A Review, IJPSR, 2011; 2(10): 2545-2561.
27. Malik K et al A Review on Colon Targeting Drug Delivery System: Novel Approaches, Anatomy and Evaluation, The Pharma Innovation, 2012; 1(9): 1-12.
28. Asha Patel et al Colon Targeted Drug Delivery System: A Review System, JPSBR, July-August 2011; 1(1): 37-49.
29. S.Pradeep Kumar et Al Novel Colon Specific Drug Delivery System: A Review International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(1): 22-29.
30. *Reddy et al.* Colon Targeted Drug Delivery System: A Review, *IJPSR, 2013; 4(1): 42-54.*
31. Karishma Mahajan et al Overview On Colon Targeting Drug Delivery System, 2021 JETIR February 2021; 8(2): 2120-2137.
32. Abdul B, John B. Perspectives on Colonic Drug Delivery, Business Briefing, Pharmatech, 2003; 185–190.
33. Bajpai S K, Bajpai M, Dengree R. Chemically treated gelatin capsules for colontargeted drug delivery: a novel approach, J. Appl. Polym.Sci, 2003; 89: 2277–2282.
34. M.Najmuddin, Vishal Patel, Aejaz Ahmed, Shelar and T. Khan. Preparation and evaluation of flurbiprofen for colonic drug delivery system.

IJPPS, 2010; 2(2).
35. Ranamazumder, Lila K Nath, Anwarul Haque, Taras Ankar Malty, K. Prasanta. Formulation and invitro evaluation of natural polymers based on microspheres for colonic drug delivery system. IJPPS, 2010; 2(2).
36. Chourasia M K, Jain S K. Pharmaceutical Approaches to Colon Targeted Drug Delivery, Journal of pharmaceutical sciences, 2003; 6(1): 33-66.
37. Sarasija S, Hota A. Colon-specific drug delivery systems, Indian journal of pharmaceutical sciences 2000; 62(1): 1- 8.
38. Cole ET, Scott RA, Connor AL, Wilding IR, Petereit HU, Schminke C, Beckert T, Cadé D. Enteric coated HPMC capsules designed to achieve intestinal targeting. Int J Pharm 2002; 231(1): 83-95.
39. Mooter VG, Kinget R. Oral colon-specific drug delivery: A review: Drug Delivery 1995; 2: 881-931.
40. Tozer T.N., Friend D.R.; McLeod A.D., "Kinetics Perspectives on colonic delivery", STP Pharma Sci., 1995, 5: 5-12.
41. Kost J, Langer R. " Responsive polymeric delivery systems", Adv. Drug Delivery Rev, 2001; 46: 125-48.
42. Vyas S.P., Roop K.Khar, "Controlled Drug Delivery Concepts and Advances", Vallabh Prakashan, 1st ed., Delhi, 2002; 218-225.
43. Jain N.K., "Controlled and Novel drug Delivery", CBS publication, 1st edition, New Delhi, 2002; 89-111.
44. Vijay Kumar and Gilbert S. Banker, "Modern Pharmaceutics", 4th edition, Marcel Dekker, 529- 530.
45. Yeh P.Y.; Berenson M.M., Samovitz W.S., Kopecek.J., "Site specific drug delivery and enhancement in gastrointestinal tract", J.control. release, 1994; 36: 109-124.
46. Lee V.H., Yamamoto A., Advanced Drug Del. Review, 1990; 4: 171-207.
47. http: //www.medicalnewstoday.com/articles/150496.php
48. http: //www.cancer.gov/cancertopics/pdq/treatment/pancreatic/Patient/page2
49. Gupta, V.K.; Gnanarajan, G.; Kothiyal, P. A Review Article on Colonic Targeted Drug Delivery System. *Pharm. J.*, 2012; *1*(7): 14-24.
50. Sharma, M.; Joshi, B.; Goswami, M. Colon specific delivery system: The local drug targeting. *Int. Res. J. Pharm.*, 2011; *2*(12): 103-107.
51. Koteshwara, K.B.; Anup, N.; Madhavan, N. Colon targeted drug delivery system. A Review. *Int. J. Res. Ayurvedic. Pharm.*, 2011; *2*(1): 60-65.
52. Kumar, V.; Kumar, T.S.; Tamizhmani, T. Colon targeting drug delivery system: A review on recent approaches. *Int. J. Pharm. Biomed. Sci.*, 2011; *2:* 11-19.
53. Sinha, V.R.; Kumria R. Colonic drug delivery: prodrug approach, Pharmaceutical research. *Int. Res. J. Pharm.*, 2001; *224*(1-2): 19-38.
54. Wilson, P.J.; Basit, A.W. Exploiting gastrointestinal bacteria to target drugs to the colon: an *in vitro* study using amylose coated tablets. *Int. J. Pharm*, 2005; *300:* 89-94.