REVIEW ON -REVIEW ON TRADITIONAL AND INNOVATIVE APPROACHES FOR COLON-TARGETED DRUG DELIVERY

Mr. Zalte A. J, Prof. Surawase R. K, Prof. Kothawade P. K, Dr. Khushwaha R. K, Mr. Nikam A. S

Department of pharmaceutics, Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Tal-Kalwan, Dist-Nashik(423501) Maharashtra, India

Abstract

Drugs can be administered locally or systemically through the colon. For example, local distribution could make it possible to treat inflammatory bowel disease topically. If medications could be administered specifically to the colon, the effectiveness of the treatment may be increased. Additionally, systemic side effects could be reduced. Oral delivery of peptide and protein medicines, which are often inactivated in the upper gastrointestinal tract, may also be possible using colon-specific methods. Prodrugs, pH and time dependent systems, and microbially triggered drug delivery systems are some of the primary techniques for CDDS (Colon Specific Drug Delivery), which have had little success and have several limitations. newly established CDDS, which consists of osmotic controlled drug delivery, novel colon focused delivery method, and pressure controlled delivery system.

KEY WORDS: Colon Targeted Drug Delivery, colon, ,Primary approaches, Platform Technologies

INTRODUCTION

It is difficult to find a pharmacological target for colonic illnesses in this area. Due to different pH conditions, most colon-specific medications fail to maintain their concentration at the target location and demonstrate optimal therapeutic action with fewer adverse effects. The ideal medication should be packaged in a way that allows it to remain stable at different pH levels, release in a regulated manner when a certain illness state arises, and exhibit appropriate therapeutic action.(Kaur et al., 2014)1The frequency of colonic disorders has grown over the past several decades, necessitating the effective local treatment of colonic diseases for more effective and secure pharmacological therapy. In terms of colonic illnesses, colon cancer (CRC) is the one that causes the third-highest majority of cancer diagnoses globally and more than 200,000 cancer-related deaths each year in Europe. The prevalence of inflammatory bowel disease is also fast increasing in historically low-incidence countries, such as Asia (IBD).(Lee et al., 2020)

Due to the following factors, the colon is regarded as a desirable absorption location for protein medicines and peptides:

• The small intestine has stronger proteolytic activity than the colon mucosa;

• It has a lower diversity and intensity of digesting enzymes.

Therefore, CDDS stops the amides reaction and catalyst in the duodenum and jejunum and releases the medication into the colon, increasing its overall bioavailability. Ultimately, this is because the colon spans a lengthy duration of up to 5 days and is particularly sensitive to absorption enhancers. It should be possible for the CDDS to release the medication into the colon. The poorly absorbed medication is more readily absorbed by the colon, increasing the drug's bioavailability.(Verma, 2018) Since the colon's surface area for drug absorption is much less than that of the small intestine and has a low water content, it is not thought to be an ideal location for drug absorption. However, colon serves as a more preferred location for protein drug absorption since colon has lower hydrolytic enzyme activity than the small intestine. As a result, peptide and protein medication delivery takes place in the colon.

The characteristics of the medicine, the kind of delivery mechanism, and how it interacts with a healthy or sick gut must all be carefully considered for successful colonic drug administration. The colon's luminal fluids must first help the supplied medication dissolve. Poorly water-soluble medications may have difficulty dissolving in the colon since there is often less free fluid there than in the small intestine. In these circumstances, it may be necessary to give the medication in a presolubilized form or to the proximal colon. A single unit (tablets and capsules) or multi-unit (pellets and granules) design is often the foundation of modified release formulations. The two architectures exhibit substantially distinct biopharmaceutical performances. Due to their compact size and split structure, multi-unit systems frequently display more consistent gastrointestinal transit and absorption properties. It would also be favourable for colonic delivery if multi-units passed through the colon at a slower rate. However, single unit systems are typically easier to construct from a financial standpoint. (Pdvvpf, n.d.)

NEED FOR COLON-TARGETED DRUG DELIVERY SYSTEM

The GIT's colonic area has grown in significance as a venue for the administration and absorption of medications. Patients can benefit from CDDS' therapeutic effects in both local and systemic treatments. Systems make use of natural materials that have a high economic viability and are broken down by a colonic bacterial enzyme. It guarantees direct disease-site therapy, lower dosages, and less systemic adverse effects. A formulation tailored to the colon may potentially be employed to extend medication delivery.

Sulphasalazine and glucocorticoids are typically used to treat such inflammatory disorders. Drugs that are polar and/or sensitive to chemical and enzymatic breakdown in the upper GI tract that are significantly impacted by hepatic metabolism, in particular therapeutic proteins and peptides, can be delivered using formulations for colonic distribution. Additionally, it offers a chance to define the mechanism of action of various non-steroidal anti-inflammatory medicines (NSAIDs), such sulfide, which are metabolised in the colon to their active moiety

and inhibit the growth of colon polyps, the early stage of colon cancer, most likely in a local manner. Potential location of protein drug absorption is the large intestine.(Raghuvanshi et al., n.d.)

- Direct therapy of the disease site, reduced dosage, and less systemic adverse effects would all be guaranteed by targeted medication delivery to the colon.

- Oral administration of peptide and protein medications would be possible using site-specific or targeted drug delivery systems. Colon-specific formulations might also be employed to extend the duration of the drug delivery.

- Treatment of colon disorders is thought to benefit from colon-specific medication delivery systems.

- Drugs directed towards the colon may also be able to treat a variety of other major disorders of the colon, such as colorectal cancer, more successfully.

- Using formulations for colonic distribution, drugs that are polar and/or vulnerable to chemical and enzymatic breakdown in the upper GI tract, which is significantly influenced by hepatic metabolism, can be administered. This includes therapeutic proteins and peptides.(Choudhary et al., 2020)

COLON ANATOMY AND PHYSIOLOGY

Colon Organ System

The lower portion of the digestive system, called the colon, extends from the ileocecal junction to the anus. It consists of the ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus as its proximal section (Fig. 1). Although the surface area of the colon is less than that of the small intestine, because to the presence of villi, microvilli, and a prolonged residence period, efficient absorption occurs. The colon is a cylindrical tube that is 2 to 3 inches in diameter and is coated with mucosa, a moist, soft pink lining. Anatomically speaking, the colon and rectum have a blood supply. Blood vessels can also be seen in the lymph nodes.

Segmenting and propelling actions make up the majority of colon activity. The luminal contents are mixed as a result of the segmenting motions that are primarily produced by the circular muscle that gives rise to the sac-like haustra. Significant propulsion, which is less frequent and happens on average three to four times per day, is connected with faeces and is influenced by longitudinal muscle.(Gupta et al., 2010) The four components of the colon have the same structure and function.

a) Ascending colon: It measures almost 12.5 cm in length. From the caecum to the hepatic flexure, it reaches.

b) Transverse colon: The ascending colon continues as the transverse colon from the hepatic flexure to the future spleen.

c) Descending colon: A descending colon is formed when a transverse colon descends.

d) Sigmoid colon: The descending colon continues as an S-shaped sigmoid colon and comes to an end at the rectum.(Gaur et al., 2019)
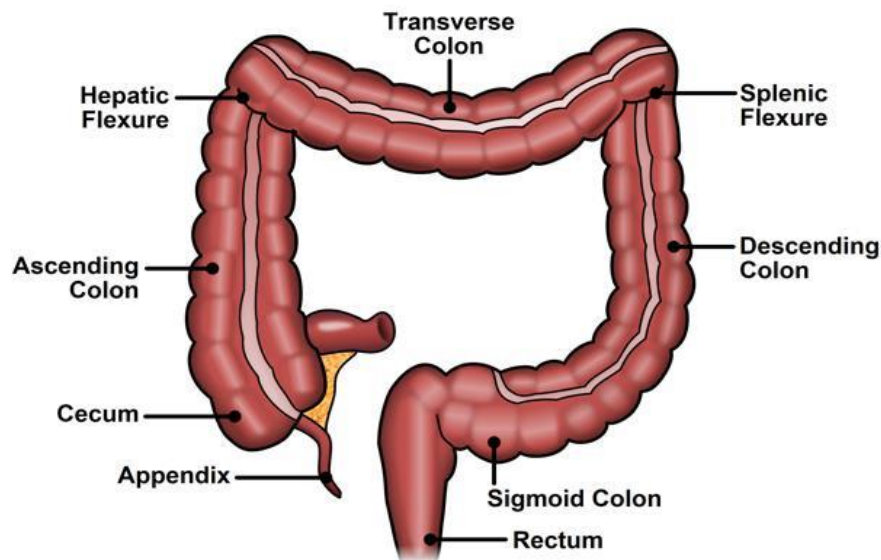
Fig No.1. Small and Large Intestine

Region of Gastrointestinal Tract		Length (cm)	Ph	Internal diameter (cm)
Small intestine	Duodenum	20-30	6.1(fasted) 5.4(fed	3-4
	Jejunum	150-200	5.4	
	Ileum	200-350	7-8	
Large intestine	Cecum	6-7	5.5-7	6
	Ascending colon	20		
	Transverse colon	30		
	Descending colon			
	Sigmoid colon	40		
	Rectum	12		
	Anal rectum	3	7-8	
Stomach			1.5-3 (fasted) 2-5 (fed)	

Table 1: Brief description of the small intestine and colon's structural and physiological characteristics(Choudhary et al., 2020)
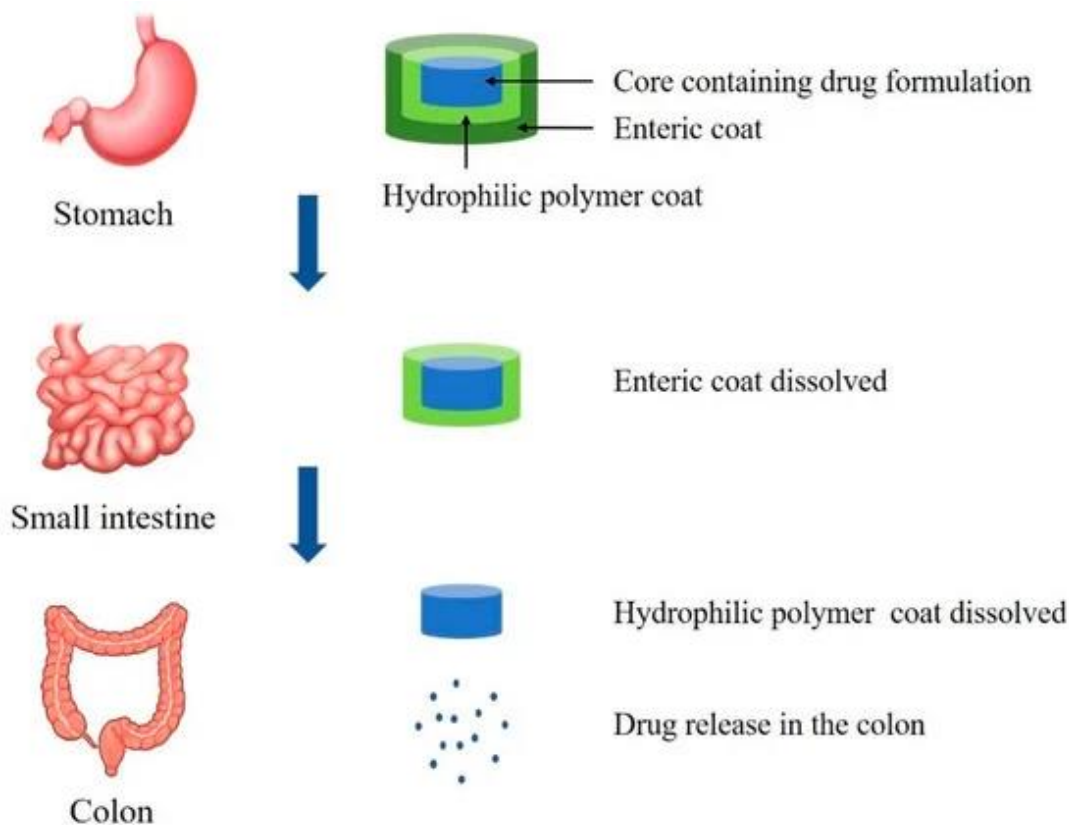
Fig No 2. Drug release in the colon from pH-sensitive polymer-based system

THE SELECTION CRITERIA FOR POTENTIAL DRUGS FOR COLONIC MEDICATION DELIVERY

Drug Candidate

- It should have a low absorption rate from the stomach and small intestine, such as peptides.
- It should quickly biotransform in the large intestine and be compatible with the carrier molecule.
- It must be stable at the GIT's alkaline pH.
- Both local and systemic effects should be present.
- 5.Medications such as sulfasalazine, olsalazine, mesalazine, and steroids like fludrocortisone, budesonide, prednisolone, and dexamethasone are ideal candidates for local colon delivery in the treatment of various intestinal disorders such as ulcerative colitis, amoebiasis, colon cancer, inflammatory bowel disease, and diarrhoea.(Sunday, 2017)

Drug Carrier

The physiochemical nature of the medicine and the disease it is intended to treat both have a role in the choice of carrier for a specific therapeutic candidate. There are several variables that affect the choice of carrier.

- Chemical nature
- Stability
- The drug's partition coefficient
- The choice of absorption enhancer

Similarly, The choice of drug carrier is determined by the functional groups of the drug molecule.For example, a drug's aniline or nitro groups may be employed to form an azo bond connecting it to another benzene group. The release qualities and effectiveness of the systems are influenced by the carriers, which comprise additives such polymers (which may be utilised as matrices, hydrogels, or coating agents).(Kumar Sharma et al., 2011)

COMPENSATIONS

- The colon is a perfect location for the introduction of agents to treat the local disorders of the colon.
- Local therapy has the benefit of using less medication.
- Decreases dose frequency. Consequently, pricey medications are now less expensive.
- 4.The colon is a desirable location where poorly absorbed medication molecules may have increased bioavailability.
- Ignore the first pass metabolism.
- It has a longer retention duration and seems to be very receptive to substances that improve the absorption of medications that are not well absorbed.
- Possibly resulting in a decreased frequency of adverse effects and medication interactions.
- Increase patient compliance.
- A targeted medicine delivery method.(Amritpal et al., n.d.)

HINDRANCES

- a number of production stages
- incompleteness of releases.
- Drug bioavailability is poor.
- Through the metabolic breakdown of drugs, local bacteria may potentially influence intestinal function.
- Low dose loading.
- Excipients are needed in greater amounts.
- many process variables
- demand for cutting-edge technologies
- Colonic medication delivery system manufacture requires skilled personnel.(Gaur et al., 2019)

COLON-TARGETED DRUG DELIVERY: LIMITATIONS AND DIFFICULTIES

1. It is extremely difficult to focus medication for the colon. The colon can be particularly challenging to reach since it is situated at the furthest reaches of the alimentary canal. The vast variety of pH values and various enzymes present throughout the gastrointestinal system, which the dosage form must pass through before reaching the target location, further hinder the efficacy and dependability of distribution.

2. Additionally, the drug's stability is a factor that must be taken into account while constructing the delivery system. The medicine might perhaps attach inadvertently to food residues, digestive fluids, mucus, or faeces.

3. The metabolism of the medicine by the local bacteria may potentially have an impact on colonic function. Drug transport over the mucosa and into the systemic circulation can also be hampered by the tight junctions' relative "tightness" and lower surface area in the colon.

4. The establishment of an adequate dissolution testing procedure to assess the planned system in-vitro is a barrier in the development of colon-specific drug delivery systems. This is a result of the wide variety of justifications for colon-specific medication delivery systems.

5. The medicine must also dissolve in the colon's luminal secretions or be in solution before it enters the colon. The fluid concentration in the colon is significantly lower and more viscous than in the upper part of the GI tract, which can be a limiting issue for drugs that are poorly soluble.(Amritpal et al., n.d.)

Sr. no.	Criteria	Pharmacological class	Drug and active agent
1	Poor upper GIT absorption of the drug	Antianginal and Antihypertensive drugs	Cyclosporine A*, Desmopressin*, Ibuprofen,Isosorbides, Theophylline.
2	local impact in the colon	Anti-inflammatory Drugs	Amylin*,Oligonucleotide*, Antisense*,Oxyprenolol, Budesonide,Metoprolol, Nifedipine, Diclofenac sodium.
3	Crohn's Syndrome	5-aminosalicylic acid, corticosteroids	Sulfasalazine,Olsalazine, Mesalazine,Hydrocortisone, Budenoside, Prednisolone.
4	Ulcerative colitis	5-aminosalicylic acid, Purine antagonist,	Sulfasalazine, Balsalazine, Mesalamine, Mercaptopurine.
5	Medications that go through a lot of first pass metabolism	Nitroglycerin and corticosteroids .	Protirelin*,Sermorelin*, Saloatonin*,Nimustine, Bleomycin, Nicotine, Dexamethasone, Molgramoatim.
6	Medicines that break down in the stomach and small intestine	Peptides and Proteins	Gonadoreline*,Insulin*, Interferones*, Bromophenaramine, 5flurouracil, Doxorubicin

7	Diverticulitis	Nitroimidazole	Metronidazole, Bactrim, Sulfatrim, Flagyl.
8	Irritable bowel syndrome	Antispasmodic, Antidiarrheal, Anticholinergic, Antidepressant	Loperamide, Osmotic laxative, Dicyclomine,Mebeverine, Hyoscyamine, Amitriptyline.
9	Hirschsprung's Disease	Glycopeptide, Nitroimidazole, Antidiarrhea .	Loperamide,Metronidazole Vancomycin .

Table 2: Colon-targeting medications (Denotes peptide medicines.)(Trivedi, 2017)

COLON-SPECIFIC DRUG DELIVERY MECHANISMS

1) Primary Approaches

a) Delivery of Drugs to the Colon Using pH-Sensitive Polymers

The stomach's pH ranges from 1 to 2 when one is fasting, but it rises after eating. 18 The pH of the distal small intestine is about 7.5, whereas the proximal small intestine is closer to 6.5. From the ileum to the colon, pH drastically drops. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been seen in healthy people's ascending colons. 20 While it is 6.6 in the transverse colon, pH is 7.0 in the descending colon. The utilisation of pH-dependent polymers is based on these fluctuations in pH levels. The polymers that are classified as pH-dependent, when it comes to colon-specific drug delivery, are insoluble at low pH levels but gradually become soluble as pH rises. In the stomach and proximal small intestine, a pH dependent polymer can retain a formulation, but in the lower small intestine, it may start to disintegrate and the site-specificity of formulations may be poor. The pH fall that takes place from the end of the small intestine to the colon can lead to issues such as long lag durations at the ileo-cecal junction or fast transit through the ascending colon, which can also affect the site-specificity of enteric-coated single-unit formulations.(Philip & Philip, 2010)

b) Microbially Triggered Drug Delivery to Colon

The majority of the anaerobic bacteria in the colon, which vary in concentration from 1011 to 1012 CFU/mL, including bifidobacteria, eubacteria, enterococci, clostridia, and ruminococcus.This enormous microflora produces the energy it requires by fermenting a variety of substrates that were not fully digested in the small intestine, such as di- and tri-saccharides and polysaccharides. A wide range of enzymes, including urea dehydroxylase, nitroreductase, azareductase, galactosidase, xylosidase, arabinosidase, and are produced by the microflora for this fermentation.The use of biodegradable polymers for colon-specific medication administration appears to be a more site-specific method as opposed to other techniques since the biodegradable enzymes are only present in the colon. These polymers are able to carry the medicine to the colon while protecting it from the stomach and small intestine environments. They are broken down by enzymes, microorganisms, or the polymer's backbone once they reach the colon, which causes their

molecular weight to drop and their mechanical strength to decrease. They are then unable to contain the drug entity for much longer.(K. I. Singh et al., 2012)

In contrast, the colon's lengthy transit time and rich nutritional content promote the colonisation of around 400 distinct bacterial species. The bacteroides, bifidobacteria, eubacteria, clostridia, and gram-positive cocci are the most common anaerobic bacterial species in the colon. Due to their oxygen consumption, the facultative bacteria are to blame for the colon's low redox potential. The extensive microflora of the colon has been employed as a highly selective strategy for medication targeting by altering redox potential. Drug transport to the colon has been made possible through the use of azo group-containing polymers and their degradation by azoreductases generated by the colonic microbiota.(A. Jain et al., 2007)

Prodrug

The active drug must be released in vivo by spontaneous enzymatic transformation of a prodrug, which is a medication molecule's parent derivative that is pharmacologically inactive. The prodrugs utilised in this method are designed to have minimal absorption and enzymatic hydrolysis in the colon, liberating the active drug moiety from the carrier, and little absorption and hydrolysis in the upper GIT.The 5-ASA prodrugs that successfully release the compound in the colonic area were made using a variety of conjugates. They include cyclodextrin prodrugs, azo-linked polymeric prodrugs, acrylic type polymeric prodrugs, and biodegradable poly (ether-ester) azo polymers.

These have undergone CDDS evaluation. Several azo polymers have also been studied as covering materials over medication cores. The large bowel enzyme azo reductase has been shown to be similarly able to cleave them. The drug cannot be digested in the stomach or small intestine when peptide capsules are coated with polymers cross-linked with azo aromatic groups. The drug is released in the intestines as the azo connections are broken. (Periyasamy & Pandey, 2013)

- **Azo bond conjugat**

The diverse and mostly constant community of microorganisms that make up the intestinal microflora play critical roles in health and illness. Many of these microorganisms have physiological activities. The indigenous microflora are in charge of   a range of metabolic activities, including the reduction of nitro and azo groups in environmental and medicinal substances. They also guard patients from potentially dangerous bacteria colonising their digestive tracts.(S. K. Jain & Chourasia, 2003)

- **Glycoside conjugates**

A novel colon-targeted medication delivery method is built on steroid glycosides and the distinct glycosidase activity of the colonic microbiota. Since drug glycosides are hydrophilic, the small intestine cannot effectively absorb them. Once such a glycoside enters the colon, bacterial glycosidases can break it, releasing the medication for absorption by the colonic mucosa.(Periyasamy & Pandey, 2013)

TIMED RELEASE SYSTEMS

It is difficult to create a formulation that can provide a precise medication release in the colon since in these systems the transit duration of a formulation in the GIT determines the drug release. The gastric emptying time, small intestine pH, and the presence of anaerobic bacteria in the colon of each individual are not expected to have an impact on the location of delivery (the colon) when using time release devices. An oral dose form typically needs two hours to digest in the stomach and three hours to transit the whole length of the small intestine to the start of the colon. A time release method depends on the small intestine transit time since it is more reliable than stomach emptying rate. The drug release from these systems may be precisely designed to achieve a desired lag phase by choosing an appropriate mix of controlled-release mechanisms. For time-released formulations of colonic administration, pH-dependent (enteric coat) components are typically included since the transit of a formulation in the GIT is greatly controlled by the stomach emptying time. Controlled release ingredients based on osmosis, swelling (gelling), or a mix of the two are frequently used in time-release formulations.(Bansal et al., 2014)

Time-released drug formulations are available as bilayered tablets or capsules. The balance between the tolerability and thickness of a water-insoluble membrane and the quantity of a swellable excipient, such as sodium starch glycolate and low substituted hydroxypropyl cellulose (L-HPC), which determines the speed at which a medication releases from formulations. The formulation's ethyl cellulose (EC) capsule shell has a thickness of around 12014 millimetres and has micropores at the body's bottom. The substance is packed with a solid medication dispersion formulation. Additionally, an EC capsule body and a direct compression made tablet containing L-HPC are used.
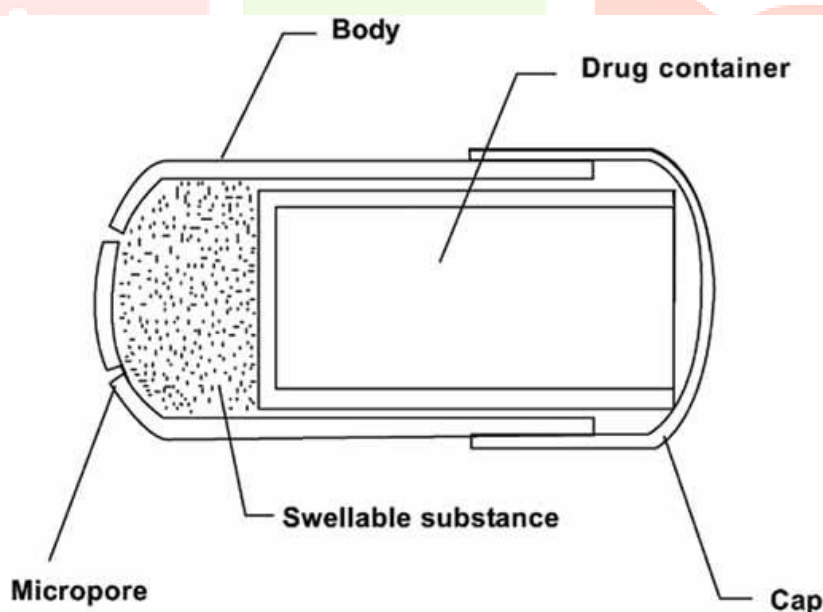

Fig No 3: Time-controlled capsule for colonic delivery(D & H, n.d.)

Method	Advantages	Disadvantages
Time – dependent systems	Consistent transit time in the small intestine	Patients with colon illness transit through the colon more quickly than usual
		significant differences in gastric retention times.
pH-dependent systems	formulation that is stomach-friendly	Individual and intra - individual differences exist in the pH of the small intestine and colon.
		The pH levels at the caecum and small intestine ends are comparable.
Microflora- activated systems	Prodrugs and polysaccharides have good site-specificity	Disease and poor diet may have an impact on colonic microflora.
		Enzymatic degradation might occur too slowly.

Table 3: Advanced research on colon specific drug delivery(Bhowmik, 2013)

B. Platform Technologies

1. Pressure Controlled Delivery system

Compared to the small intestine, the colon is under higher strain. By causing the medication's water-insoluble polymer coating to dissolve, this pressure aids in the process of the drug being released. In order to produce this system, it is crucial to take the polymer's thickness into consideration. Ordinary gelatin capsules are coated with a water-insoluble polymer, like ethyl cellulose, to create pressure-controlled drug delivery capsules (PCDC). Tests of the 5-ASA delivery system produced findings that were consistent with the success of the medication being absorbed at the proper time based on the location of the colon. However, due to increased pressure created by peristalsis in human studies, the medication was shown to release prematurely in the small intestine.(Iswandana et al., n.d.)

2. Osmotic Controlled Delivery system

Although the idea of osmotic controlled drug delivery has been known for a while, the use of this technology in the development of oral dosage forms specifically for the colon has only recently been popular, during the last ten to fifteen years. An example of a system that is controlled by osmotic pressure is the OROS-CT. It is made up of a hard gelatin capsule that dissolves in the small intestine's pH and lets water into the device. This makes it swell, which forces the drug out. There may be up to five or six units in each capsule, and each unit is encased in a drug-impermeable enteric coating that keeps water out of the stomach's

acidic environment. Once the capsule enters the small intestine, where the pH is greater, the coating dissolves and water enters. A semipermeable membrane that includes an osmotic push compartment and a medication compartment is located within the enteric coating. When the push compartment is filled with water, the drug compartment creates a gel that is forced through an opening in the membrane adjacent to it and out of the push compartment. The rate at which the medicine flows out is governed by the rate at which water enters. To avoid drug release in the small intestine, these systems can also be designed so that there is a lag time between the enteric coating dissolving and the release of the medication.
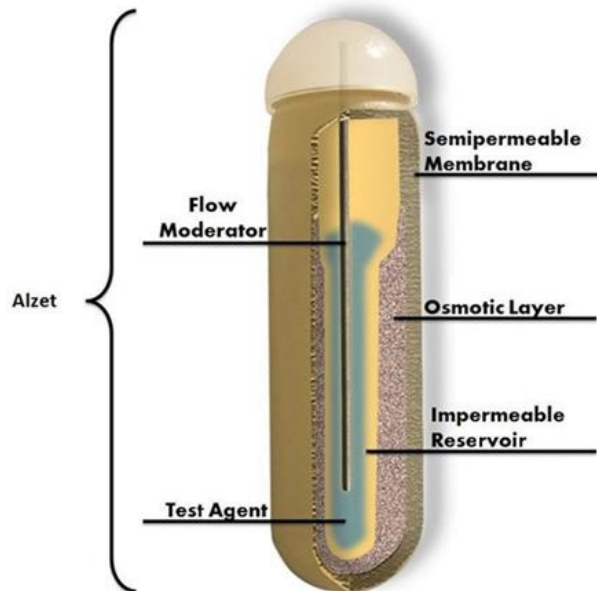

Fig No: 4 Osmotic pressure controlled system

3. Pulse Colonic Delivery System

Microspheres are created by combining the appropriate polymer materials with medicines, tracers, electromagnetic or ultrasonic sensitive components. Microspheres are generated by an electromagnetic or ultrasonic wave in vitro when they reach the site of action, releasing the medication to meet the goal of release point control. This is monitored in vivo following oral delivery. This approach is very appropriate for chemotherapy for colon cancer treatment. This might effectively regulate the typical systemic and gastrointestinal toxicity of chemotherapy medicines.(Dong et al., 2015)

4. Pulsincap System

R.R. Scherer International Corporation, located in Michigan, US, developed this method to attack water-insoluble capsules. This formulation has a seal coat and a hydrogel plug that can expand to enclose the drug reservoir in the capsule body. When a capsule came into touch with the breakdown fluid at a specific moment, swelling occurred and the medication released quickly. The hydrogel plug was created using polymers of various grades and viscosities, including polymethyl methacrylate, hydroxypropyl methyl cellulose, poly vinyl acetate, and poly ethylene oxide. The length and location of insertion of the plug, which were investigated in human volunteers, regulated the lag time of the Pulcinicap capsule.(G. Singh et al., n.d.)

5. Port System

This method, developed by Therapeutic System Research Laboratory in Arm Arbor, Michigan, USA, uses an insoluble drug plug and an osmotically active substance that are covered in a semi-permeable capsule membrane. Attention deficit hyperactivity disorder (ADHD) is treated in people using a system that delivers methylphenidate to school-age children and has good in-vivo and in-vitro correlation.(Malik K & Goswami, 2012)

6. Novel colon targeted delivery system (CODESTM)

The unique CDDS technology known as CODES was created to get beyond the issues that come with pH- or time-dependent systems. CODES is a hybrid technique that combines pH-dependent and microbe-triggered CDDS. It was created via a special mechanism involving lactulose, which works as a trigger for drug release at a specific spot in the colon. The technique is shown in Figure 4. It starts with a conventional tablet core made of lactulose, which is then covered with an acid-soluble substance called Eudragit E and an enteric material called Eudragit L. The idea behind the technique is that the tablet is shielded by the enteric coating while it is in the stomach, and that coating then dissolves fast after gastric emptying. The preparation is then shielded by the coating's acid-soluble substance when it passes through the small intestine's alkaline pH. As soon as the tablet enters the colon, microorganisms begin to enzymatically break down the polysaccharide (lactulose) into organic acid. This sufficiently lowers the pH around the system to have an impact on the dissolving of the acid-soluble coating and subsequent medication release.(Tiwari et al., 2010)

It was developed by employing a novel technique that uses lactulose as the core tablet and acts as a catalyst for site-specific medication release in the colon. The tablet is protected by the enteric coating while it is in the stomach, and it swiftly dissolves after gastric emptying as a result of this technology. The method comprises of a typical tablet core made of lactulose, coated in an acid-soluble substance called Eudragit E, and then covered with an enteric material called Eudragit L.The preparation is then shielded by the coating's acid-soluble substance as it travels through the small intestine's alkaline pH. Once the tablet reaches in the colon, the bacteria will enzymatically breakdown the polysaccharide (lactulose) into organic acid.(Roy et al., 2012)
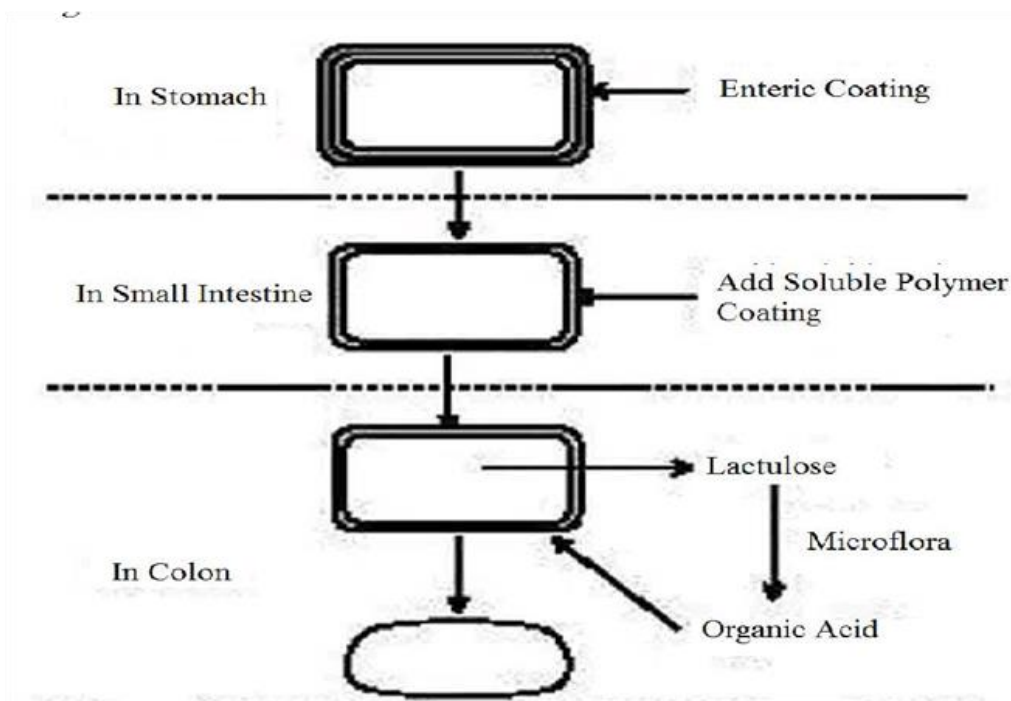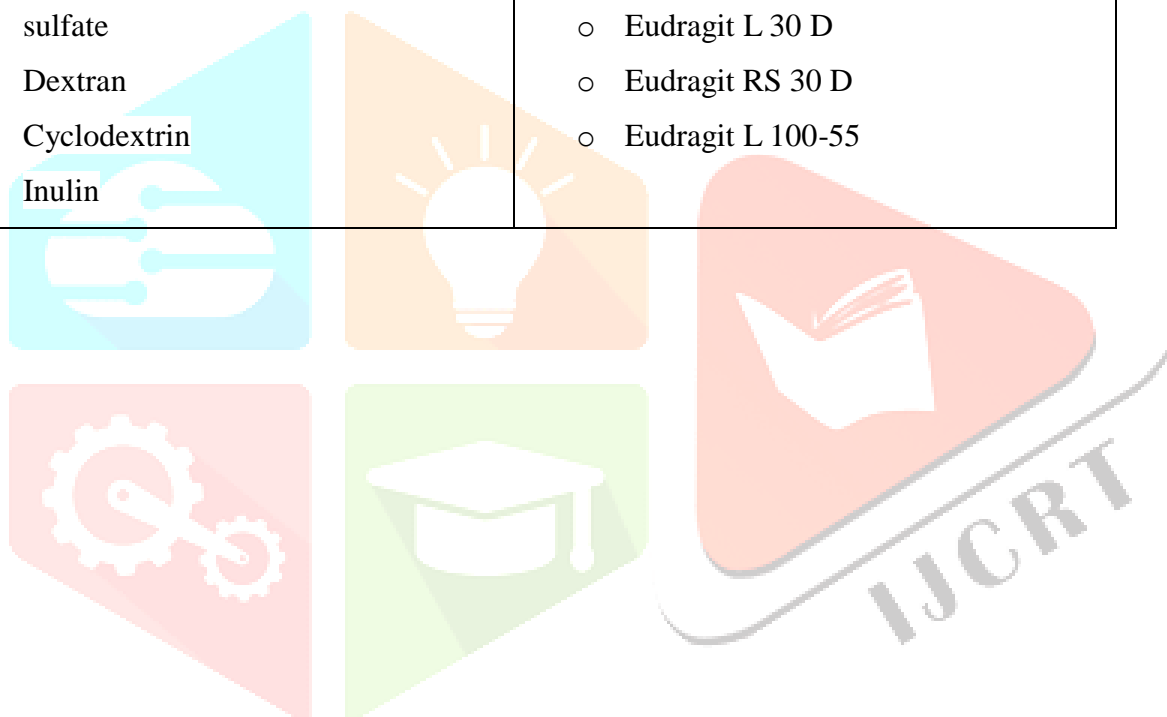
Fig No: 5 Schematics of conceptual design of codes

- **Multiparticulate Drug Delivery Systems**

The goal of creating multiparticulate dosage forms is to create a dependable formulation that has all the benefits of single unit formulations while being free of the risk of changing the drug release profile and formulation behaviour due to variation between units, changes in gastro-luminal pH, and changes in the population of enzymes. Multiparticulate systems, which disperse over the length of the gut to cause less irritation, enjoy a slower transit through the colon, and provide a more repeatable drug release, are usually thought to work better in vivo than single unit systems. Similar to single unit dose forms, the presence of certain bacterial populations in the colon and a growing pH gradient have been widely investigated as triggering mechanisms to begin colon specific drug release. (Dugad et al., n.d.; Fatima et al., 2006) Pellets are another another multi-particulate preparation. Between 500 and 1500 m in diameter, spherical or pseudo-spherical in form, and with a smooth surface, pellets have a respectably high density and respectable flow rate. (Iswandana et al., n.d.)

- **A list of several natural and synthetic polymers for colon-targeted medication delivery systems**(Neha, 2013)

NATURAL POLYMER	SYNTHETIC POLYMER
o Xanthan gum	o Polyvinyl acetate phthalate
o Amylose	o Hydroxypropyl ethylcellulose
o Locust bean gum	o phthalate 50
o Alginates	o Hydroxypropyl ethylcellulose
o Shellac	o phthalate 55
o Pectin	o Cellulose acetate trimelliate
o Chitosan	o Cellulose acetate phthalate
o Guar gum	o Eudragit L 100
o Chondroitin	o Eudragit S 100
o sulfate	o Eudragit L 30 D
o Dextran	o Eudragit RS 30 D
o Cyclodextrin	o Eudragit L 100-55
o Inulin	

- **A list of several natural and synthetic polymers for colon-targeted medication delivery systems**(Neha, 2013)

1) Amritpal, S., Ankush, S., & Pooja, A. (n.d.). *NOVEL APPROACHES FOR COLON TARGETED DRUG DELIVERY SYSTEM*. *3*(2), 844–853. www.ijrdpl.com

2) Bansal, V., Malviya, R., Malaviya, T., & Kumar Sharma, P. (2014). Novel Prospective in Colon Specific Drug Delivery System. *Polim. Med*, *44*, 109–118.

3) Bhowmik, D. (2013). Review on, colon specific drug delivery Strategies and in-vitro in-vivo evaluation. In *Elixir Pharmacy* (Vol. 57). https://www.researchgate.net/publication/276267923

4) Choudhary, L., Jain, A., & Agarwal, D. (2020). Asian Journal of Pharmaceutical Research and Development Colon-Targeted Oral Drug Delivery Systems: A Review A B S T R A C T. *Asian Journal of Pharmaceutical Research and Development*, *8*(4), 186–190. https://doi.org/10.22270/ajprd.v8i4.689

5) D, K. P., & H, G. H. (n.d.). *CONVENTIONAL AND NOVEL APPROACHES FOR COLON SPECIFIC DRUG DELIVERY: A REVIEW*. http://e-jst.teiath.gr33

6) Dong, R., Wang, M., & Dong, F. (2015). The New Progress and Outlook of Oral Colon-specific Drug Delivery System for Treating Cancer. *International Journal of Advance in Medical Science*, *3*(1), 25–32. https://doi.org/10.12783/ams.2015.0301.03

7) Dugad, A., Nalawade, P., Thakhre, R., & Kakade, S. (n.d.). Colon Targeted Drug Delivery System-A Review. In *Curr. Pharm. Res* (Vol. 2018, Issue 1). www.jcpronline.in/

8) Fatima, L., Asghar, A., & Chandran, S. (2006). Multiparticulate Formulation .. Approach to Colon Specific Drug Delivery: Current Perspectives. In *J Pharm Pharmaceut Sci (www. cspsCanada.org)* (Vol. 9, Issue 3).

9) Gaur, A., Mittal, A., Ghosh, D., & Sahoo, J. (2019). CHALLENGES IN DEVELOPMENT OF COLON DRUG DELIVERY SYSTEM WITH RESPECT TO DISSOLUTION STUDIES. *Mittal et al. World Journal of Pharmacy and Pharmaceutical Sciences*, *8*. https://doi.org/10.20959/wjpps20196-14051

10) Gupta, A., Mittal, A., & Kumar Gupta, A. (2010). Colon Targeted Drug Delivery Systems-A Review. In *International Journal of Pharmaceutical and Clinical Research* (Vol. 2, Issue 4). www.ijpcr.com

11) Iswandana, R., Sari Setio Putri, K., Amalia Putri, F., Gunawan, M., & Arum Larasati, S. (n.d.). ARTICLE HISTORY Challenge and Development Strategy for Colon-Targeted Drug Delivery System. In *Pharmaceutical Sciences and Research* (Vol. 9, Issue 1). PSR.

12) Jain, A., Gupta, Y., & Jain, S. K. (2007).): ???-??? In *J Pharm Pharmaceut Sci (www. cspsCanada.org)* (Vol. 10, Issue 1).

13) Jain, S. K., & Chourasia, M. K. (2003). Pharmaceutical approaches to colon targeted drug delivery systems. In *J Pharm Pharmaceut Sci (www.ualberta.ca/~csps)* (Vol. 6, Issue 1). www.ualberta.ca/~csps

14) Kaur, A., Kaur, A., Kaur, V. P., Kaur, M., & Murthy, R. S. R. (2014). *Polymeric Drug Delivery Approaches for Colon Targeting: A Review*.

15) Kumar Sharma, J., Madhav, N. V. S., Ojha, A., & Singh, P. (2011). DIFFEREET APPROACHES TO COLOO SPECIFIC DRUG DELIVERY: A REVIEW. In *Pharmacologyonline* (Vol. 2).

16) Lee, S. H., Bajracharya, R., Min, J. Y., Han, J. W., Park, B. J., & Han, H. K. (2020). Strategic approaches for colon targeted drug delivery: An overview of recent advancements. In *Pharmaceutics* (Vol. 12, Issue 1). MDPI AG. https://doi.org/10.3390/pharmaceutics12010068

17) Malik K, & Goswami. (2012). *THE PHARMA INNOVATION A Review on Colon Targeting Drug Delivery System: Novel Approaches, Anatomy and Evaluation*. *1*(9). www.thepharmajournal.com

18) Neha, S. (2013). *Polymers for Colon Targeted Drug Delivery: A Review*. http://www.ijddr.in

19) Pdvvpf, H. S. (n.d.). Colon Targeted Drug Delivery System: A Review. In *Review Article* (Vol. 2). www.ijpda.com

20) Periyasamy, K., & Pandey, V. P. (2013). Novel approaches for colon specific drug delivery system-a review. In *International Journal of Pharmacy and Pharmaceutical Sciences* (Vol. 5, Issue 3, pp. 118–122). https://doi.org/10.30750/ijpbr.1.3.12

21) Philip, A. K., & Philip, B. (2010). Colon targeted drug delivery systems: A review on primary and novel approaches. In *Oman Medical Journal* (Vol. 25, Issue 2, pp. 70–78). Oman Medical Specialty Board. https://doi.org/10.5001/omj.2010.24

22) Raghuvanshi, N. S., Goswami, L., & Kothiyal, P. (n.d.). *VARIOUS APPROACHES FOR TARGETING COLON: A REVIEW*. www.japtronline.com

23) Roy, A., Bahadur, S., Bhairam, M., Patel, M. K., & Kukreja, S. (2012). Colon targeted drug delivery: Approaches and newer technology. *Article in Research Journal of Pharmacy and Technology*, *5*(9). www.rjptonline.org

24) Singh, G., Kumar, D., Singh, M., Sharma, D., & Kaur, S. (n.d.). Emerging Techniques and Challenges in Colon Drug Delivery Systems. *Journal of Applied Pharmaceutical Science*, *2012*(03), 139–147.

25) Singh, K. I., Singh, J., Sharma, D., & Sharma, A. (2012). COLON SPECIFIC DRUG DELIVERY SYSTEM: REVIEW ON NOVEL APPROACHES. *IJPSR*, *3*(3), 3. www.ijpsr.com

26) Sunday, O. S. (2017). COLON SPECIFIC DRUG DELIVERY SYSTEMS: CURRENT TRENDS AND APPROACHES. *Universal Journal of Pharmaceutical Research*, *2*(4), 53–57. https://doi.org/10.22270/ujpr.v2i4.RW3

27) Tiwari, G., Tiwari, R., Wal, P., Wal, A., & Rai, A. K. (2010). Primary and novel approaches for colon targeted drug delivery – A review. *International Journal of Drug Delivery*, *2*(1), 1–11. https://doi.org/10.5138/ijdd.2010.0975.0215.02006

28) Trivedi, H. D. (2017). "COLON TARGETED DELIVERY SYSTEM (CODESTM): PROPITIOUS APPROACH IN TARGETING COLON". *World Journal of Pharmacy and Pharmaceutical Sciences*, 768–789. https://doi.org/10.20959/wjpps20174-8951

29) Verma, S. (2018). Colon targeted polymers. In *Article in Journal of Pharmacy Research* (Vol. 12). https://www.researchgate.net/publication/327177431