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COLON TARGETED DRUG DELIVERY: CURRENT AND NOVEL PERSPECTIVES

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ABSTRACT

In general, we know that small intestine is mostly the site for drug absorption but in some cases the drug needs to be targeted to some other sites for absorption due to various factors like any disease condition, degradation related situations, for sustained release of drugs etc. Colon targeted drug delivery is a relatively new concept for the absorption of drugs as it offers near neutral pH. Also it offers long residence time, thereby increasing the drug absorption. The nature of food and enzymes does not affect the drug absorption. Colon has proved to be a site for the absorption of poorly soluble drugs. For the successful targeting of drugs to colon the dosage form should be designed such that it prevents the drug release in upper GIT and releasing it in the colonic region. This review article comprises of the various aspects of colon targeting which we should know before experimenting the technique and their IVIVC using recent evaluation models through x-ray imaging and gamma-scintigrapy.

INTRODUCTION: The human GI tract is the union of stomach, small intestine and large intestine. Colon is the part of large intestine which starts from the ileocaecal junction to the anus. Colon, rectum and anal canal are the main parts of large intestine. Colon itself is composed of units named caecum, ascending colon, transverse colon, rectum and anal canal. The ascending and descending colon have peritoneal folds which are also called as mesenteries. The histological profile of colon is the longitudinal muscle fibre, submucosal layer, mucous lining one over another.

Superior and inferior mesenteric arteries are there for the supply of blood to the colon. The image depicting the colon anatomy is below. A big amount of micro flora is found in colon which plays a very important role in the metabolic process undergoing in the intestinal region. The microorganisms find colon as a suitable place for their growth. Colon is a storage site of fecal contents and it also has a very high absorption capacity. Oral route of dosage form administration is the convenient and most commonly used route for colonic drug delivery due to various advantages it offers in contrast to other routes of drug administration [1]. Rectal route of drug administration is also found to be shortest route for targeting drug to colon.

Although approaching the proximal part of colon is not easy via rectal route of administration. Rectal administration of drug offers less compliance and is also uncomfortable for patients [2]. Colonic diseases such as ulcerative colitis, crohn's disease, colon cancer, amebiosis require local therapy and also the systemic delivery of proteins and peptides is achieved by development of locally acting colon targeted drug delivery system as shown in the **figure 1**. The proteins and peptides drugs gets inactivated and destroyed in the acidic environment of stomach and in the presence of pancreatic enzyme [3].

Lymphoid tissue is largely present in colonic region and thus the mast cell of colonic mucosa produces large amount of antibodies on uptake of antigen, and this results in efficient vaccine delivery [4]. Colon has a near neutral pH, longer transit time, proteolytic enzyme activity. The properties of drug, type of delivery system, interaction of drug with healthy or diseased gut are some of the important factors to be considered for successful colonic drug delivery [3]. Primary approaches used for colon specific drug delivery are pH controlled, time controlled release systems, microbially triggered delivery which include prodrug approach , azo polymeric approach, polysaccharide approach. Novel approaches for colonic drug delivery include pressure controlled drug delivery, CODES, OROS-CT osmotic controlled drug delivery, hydrogels based systems, pressure controlled systems, nanoparticle etc [5].

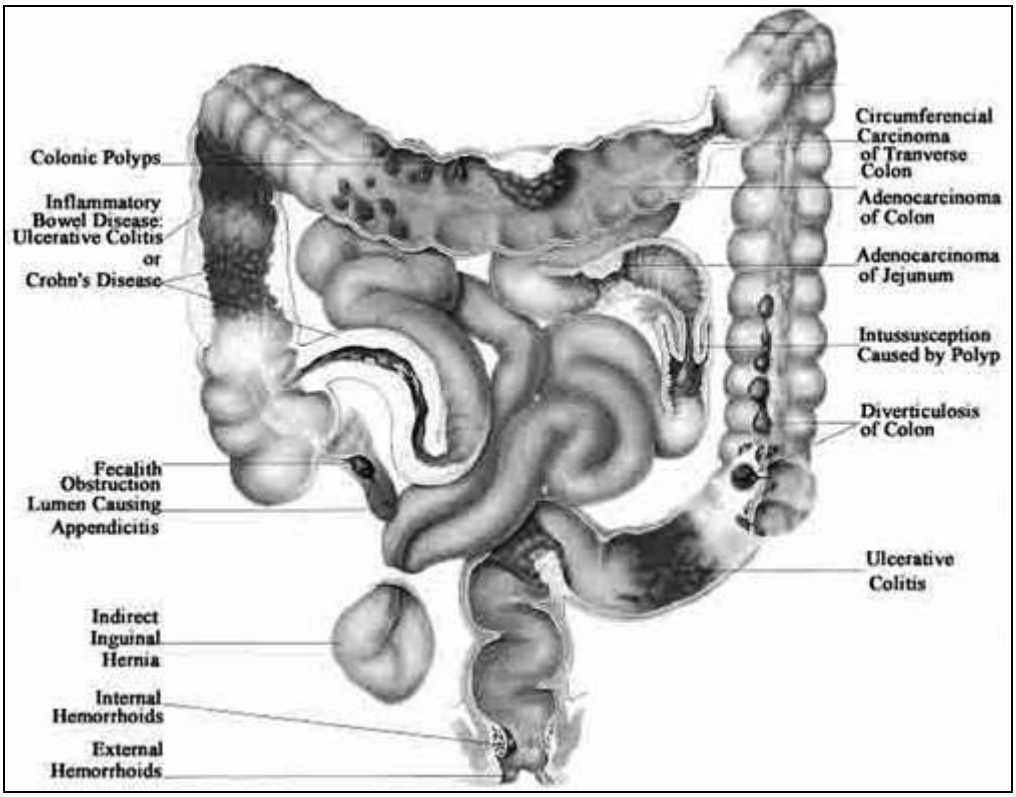

FIGURE 1: ANATOMICAL VIEW OF COLONIC DISEASES

Colon Targeting Drugs's Necessity:

- For the treatment of various colonic diseases like ulcerative colitis, crohn's disease, colon cancer, irritable bowel syndrome, and infections [3].
- For the treatment of nicotine addiction [6, 7].
- Diseases sensitive to circadian rhythms such as asthma, angina and arithritis are treated efficiently by colon targeting of drugs.
- Delivery to colon is also required for drugs that are found to be absorbable in colon like steroids thereby increasing efficiency and reducing the required effective dose [8].
- The suitable site for the absorption of peptides and protein drugs is believed to be colon due to less intensity of digestive and proteolytic enzymes [9].
- Systemic drug delivery to colon results in administration of reduced dose and reduced undesired side effects due to high doses [10].
- This site is used for delivery of drugs that undergo degradation in gastric acidic environment or irritate gastric mucosa.
- Required for minimizing first pass metabolism of drugs [4].

Limitations and challenges in Colon Targeted Drug Delivery:

- The colon is difficult to access due to its location at the distal portion of alimentary canal.
- The reliability and delivery efficiency is also doubtful due to presence of wide range of pH values and different enzymes present in the GI tract which is encountered by the drugs before reaching the target site [8].
- Colonic contents are considerably viscous because of high water absorption capacity of the colon thereby decreasing the availability of most drugs to absorbtive membrane [2].
- Dissolution could be problematic for poorly water soluble drugs because of less free fluid and more viscosity in the colon than in small intestine [3].
- Drug transport across the mucosa into the systemic circulation is restricted due to lower surface area and relative tightness of tight junctions in the colon [8].

Factors to be considered for Colonic Drug Delivery:

- The physicochemical and biopharmaceutical properties of drugs like solubility, permeability, stability at the intended site of administration should be taken into consideration [11] as mentioned in **table 1**.
- The colon specific drug delivery system should be able to control drug release and absorption in the stomach and upper part of GIT and allowing drug release only in colon [12].
- The drug needs to be in solution form before it arrives in the colon, where the fluild content is low and viscosity is higher than in upper GIT, and making it a limiting factor for poorly soluble drugs [8].
- The drug should be released at controlled rate and the released drug should be absorbed from intestinal lumen without any significant degradation [13].
- Developing an appropriate dissolution method for *in vitro* evaluation of colon targeted system is difficult because of changes in ph across the GIT [4].
- Various factors such as formulation factors, retention time, retrograde spreading etc influence the concentration of drug reaching the colon [14].
- Drug carrier has also a significant role in colon targeted drug delivery.
- The chemical nature, partition coefficient, stability of drug are some of the factors to be considered for the selection of carrier [15].
- Colon targeted drug delivery systems are supposed to be delayed release formulations which should be designed either to provide a 'burst release' or sustained release of drug in the colon [16].

TABLE 1: CRITERIA FOR SELECTION OF DRUGS FOR COLON TARGETED DELIVERY SYSTEM[17, 18, 19]

CRITERIA	PHARMACOLOGAL CLASS	DRUGS
localized action in colon	Anti-inflammatory drugs	Oxyprenolol, Nifedipine, Metoprolol
Colonic Cancer	Antineoplastic drugs	Pseudoephedrine, Glucagon
Extensive First- pass metabolism	Corticosteroids	Nicotine
Targeting of drugs	Antiarthritic and antiasthmatic drugs	Prednisolone, Hydrocortisone
Poorly absorbed drugs from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbides, Theophylline
Drugs that degrade in upper GIT	Peptides and proteins	Doxorubicin, Insulin 5-Flourouracil

Colon Targeted Drug Delivery Approaches:

A. **Primary Approaches**:

pH Controlled release: In pH controlled release systems, the different pH of human GIT is exploited by coating the dosage form with pH dependent polymers which remains as such in the upper GIT and degrade in the large intestine where the pH is high i.e., 7-8. This approach can be used in any dosage form such as tablets, capsules, pellets etc [20-23]. On coating the dosage forms with pH sensitive polymers, the active drug is protected from gastric fluid and also a delayed

release is obtained. By gathering the maximum information of polymers and their solubility at different pH, delivery systems are designed to target drug to desired location [20]. Methacrylic acid and methyl methacrylate are the most commonly used polymers for colonic drug delivery. On the in vitro evaluation of Eudragit S and Eudragit FS, it was found that the latter proves to be more appropriate for ileocolonic drug delivery [21].Combination of different polymers, coating level, pH of media are some factors that affect the dissolution rate of Eudragit [22]. The pH controlled systems are commercially available for some drugs like mesalazine (5 ASA) (Asacol and Salafalk), budesonide (Budenofalk and Entrocort) for the treatment of ulcerative colitis and crohn's disease respectively [2] as mentioned below in **table 2 & 3** depicting enteric coating polymers along with their threshold pH.

TABLE 2: THRESHOLD pH OF MOST COMMONLY USED ENTERIC POLYMERS [24-26]

ENTERIC POLYMERS	THRESHOLD pH
Polyvinyl acetate phthalate(PVAP)	4.5-5.0
Cellulose acetate phthalate (CAP)	5.0
Shellac	7.0
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L 100-55	5.5
Eudragit L 30 D	5.6
Hydroxypropyl methylcellulose Phthalate (HPMCP)	>5.5
Hydroxypropyl ethylcellulose phthalate	5.2
Cellulose acetate trimelliate	5.5
Hydroxypropyl methylcellulose acetate succinate	>6.0
Eudragit FS 30 D	6.8

TABLE 3: MARKETED pH DEPENDENT SYSTEMS

DRUG USED DISEASE	POLYMER USED	DOSAGE FORM	DISEASE
Tegaserod maleate	Eudragit L 100, Eudragit S 100	Tablet	IrritableBowel Syndrome [27]
Prednisolone	Eudragit L 100, Eudragit S 100	Tablet	Ulcerative collitis[28]

Time Controlled Release System: The time controlled systems works on the principle of drug release after a predetermined lag time at the desired site of action and time of release [29]. A considerable lag time of five hours is considered adequate for colon targeting. The coated polymer or mixture of polymers and their thickness influences the time required for dosage form to release drug in colon [1]. As the gastric emptying time of dosage forms differ from person to person, the colon arrival time of dosage form can't be predicted accurately [30]. However, these systems are useful in the therapy of diseases based on circadian rhythms [31-34]. A time controlled system in the form of capsules and bilayer tablets is described. Here the balance between the thickness of water insoluble membrane and the amount of swellable excipient controls the release time of drug from dosage form. The swellable excipients may be L-HPC, sodium starch glycolate etc [35].

The disadvantages of this system are:

1. Gastric emptying time shows intersubject and intrasubject variation leading to unpredictable colon arrival time of drug [21, 31].
2. The peristaltic movements or contractions in the stomach result in altered gastrointestinal transit of the drug [21].
3. Altered transit is also observed in conditions of IBD, diarrhea, ulcerative colitis [36].

Thus the integration of pH and time release systems in a dosage form may improve the targeted drug delivery to colon and also the transit time of dosage forms in small intestine is less variable i.e about 3±1 hr [37]. Different polymers used for developing time dependent systems are Hydroxyl Propyl Methyl Cellulose, Hydroxy Ethyl Cellulose, Ethyl Cellulose, Microcrystaline Cellulose, Hydroxy Propyl Methyl Cellulose Acetate Succinate, Lactose/ Behinic acid [1] etc. representing below in **table 4**.

TABLE 4: MARKETED TIME DEPENDENT SYSTEMS

DRUG	POLYMER USED	DOSAGE FORM	LAG TIME
Diltiazem hydrochloride	Hydroxypropylmethylecellulose acetate succinate (HPAMCAS)	Press coated tablets	Lag time can be upto 2-9h in pH 6.8 [38]
Mesalamine	HPMCK-100M, HPMCK-4M, HPMC E15, HPMC E15.	Tablets	Lag time of 10h [39]

Microbially Triggered Approach: The principle involved in this system is the degradation of the polymers coated on the dosage form by the microflora of the colon releasing the drug load there [40]. Colon has a range of complex microflora which fulfills its energy requirements by fermenting the substrate e.g. Polysaccharides present in the intestinal region [41, 44]. These microflora produces wide variety of enzymes which are able to metabolize substrates like carbohydrates and proteins that escape digestion in upper GIT [48, 42, 43]. The majority of polymers are used in pharmaceutical composition and generally regarded as safe excipients [2].

Polymer pectin was needed in large quantity when used alone to control the release of drug from the dosage form. But when pectin was mixed with chitosan and hydroxyl propyl methyl cellulose in adequate quantity, it proved to be very efficient to prevent the drug release in stomach and releasing it in the colon [44]. Sulphasalazine , a prodrug of mesalazine was the first bacteria sensitive system developed to deliver drug to the colon [45]. The microbially degradable polymers includes Chitosan, Pectins, Guar Gum, Dextrans, Inulin, Lactulose, Amylose, Cyclodextrins, Alginates, Locust bean gum, Chondroitin sulphate, Boswellia gum etc. Microbially triggered approach include the following three approaches mentioned below.

a. **Prodrug approach:** Prodrug is defined as the pharmacologically inactive derivative of a parent drug which requires spontaneous or enzymatic transformation *in vivo* in order to release the active agent. In this approach there exist a covalent linkage between the drug and its carrier which remains as such in the upper GIT and breakdown in the colon releasing the drug. A number of linkages of drug with hydrophobic moieties like amino acids, glucoronic acid glucose, galactose, cellulose etc have been prepared which are susceptible to hydrolysis in the colon [5]. The major limitation for prodrug approach is that for its design and development the functional group present on the drug moiety plays a very significant role for chemical linkage [46]. An example of prodrug is 5-ASA, which was conjugated with glycine by amide linkage which was found stable in upper GIT and hydrolysed by ceacal contents to release 5-ASA [35].

b. **Azo- Polymeric Prodrugs:** Newer techniques involve the use of different polymers as carrier of drugs for their colonic delivery. Polymeric prodrug with azo linkage between polymer and drug moiety are designed by using sub synthetic polymers [47]. Polymers cross linked with azo aromatic group when coated on drug protected it from degradation in upper GIT and released in the colon where the azo bonds were reduced. An example of azo polymer based drug delivery system is segmented polyurethane was coated over the pellets of budesonide and when evaluated *in vivo* and *in vitro* resulted in the colonic delivery of drug [48].

c. **Polysaccharide based approach:** Naturally occurring polysaccharides are widely in use for drug targeting because of their abundance, easy availability, and also they are inexpensive [49].They are highly stable, safe, nontoxic, hydrophilic, gel forming and biodegradable importantly as shown in **table 5**.

TABLE 5: MARKETED MICROBIALLY CONTROLLED SYSTEMS

DRUG USED	POLYMER USED	DOSAGE FORM	DISEASE
Valdecoxib	Guar Gum and Sodium Starch Glycholate	Tablet	IInflammatory bowel disease [51]
5- fluorouracil	Pectin	Tablet	Colon cancer [52]
Metronidazole	Sesbania Gum	Matrix Tablet	Intestinal Amoebiasis [53]

A number of natural polysaccharides are investigated which include Chitosan, Pectin, Chondroitin sulphate, Alginates etc. obtained from plants, animals, algae or microbes as depicted below in **table 6**. Colonic microflora is able to break down these polysaccharides into simpler ones [50]. Chitosan is used mainly in the form of capsule forming material for the colonic delivery.

TABLE 6: NOVEL FORMS OF NATURAL POLYSACCHARIDES USED [54]

DRUG	POLYSACCHARIDE	DOSAGE FORM
Diclofenac Sodium	Chitosan	Microspheres
Insulin	Chitosan	Capsules
Indomethacin	Pectin	Matrix Tablet
Dexomethasone	Guar Gum	Matrix Tablet
Indomethacin	Chondroitin Sulphate	Matrix Tablet
5-ASA	Alginates	Swellable Beads
Theophylline	Locust- BeanGum	Film
Theophylline	Dextran Fatty Acid Esters	Film

Radioactive Tracer	Starch	Enteric coated capsules
Paracetamol	Amidated Pectin	Matrix Tablet
Ropivacaine	Amidated Pectin	Matrix Tablet

Pressure Controlled Release: Inside the GIT, contractile and peristaltic movements takes place for the propulsion of intestinal contents. In the large intestine, forcible peristaltic movements called as mass peristalsis occurs which move the intestinal contents from one place to another [55]. These peristaltic waves are of short duration and also they occur only 3 to 4 times a day. In this kind of system the drug is released after the disintegration of water insoluble polymer capsule by the luminal pressure of colon viewed in **table 7**.

The thickness of the membrane is the important factor for the disintegration of the dosage form. The luminal pressure in the colon is higher due to peristaltic motion which in turn is because of viscosity of luminal contents. Takaya et al. (1995) designed the pressure controlled colon specific capsules using ethyl cellulose which is water insoluble [56]. This system also depends on the capsule size. When the pressure controlled capsules were administered to human, a lag time of 3 to 5 hours for drug absorption was noted[42].The capsule shells are made of ethyl cellulose and by controlling the thickness of the shell the collapse time can be controlled. The adequate thickness of capsule wall is about 35-60 micrometers [4].

TABLE 7: MARKETED PRESSURE CONTROLLED RELEASE SYSTEM

DRUG USED	POLYMER USED	DOSAGE FORM	DISEASE
Caffeine as test drug	Ethyl Cellulose	Capsule	Healthy male human volunteer
Glycyrrhizin	PEG, labrasole	Capsule	To improve its bioavailability [57]

B. Novel Approaches

Hydrogels Based Approach: Hydrogels may be defined as the 3-D polymer network which is hydrophilic in nature and because of which it is able to swell in water or other biological fluids. It has the ability to retain a significant amount of fluid in the swollen state [58]. The property of water absorption of hydrogels is due to the presence of hydrophilic groups such as OH-, -CONH-, -COOH etc. [59].The hydrogels are used as delivery systems because of their ability to allow the passage of drug across its structure. The mechanism of drug release in this kind of systems is diffusion because hydrogels have good permeability for water soluble drugs [60]. Hydrogels can be formulated in a number of physical forms like microparticles, coating, films, nanoparticles.

The commonly used hydrophilic polymers for hydrogels are PEG, PVA, PAA, Polymethacrylic acid, Polyacrylamide [61]. These polymers can absorb water from a fraction to several thousand of their own weight [62]. Diffusion controlled release is the considered the primary method of drug release from dosage form [63, 64]. The mesh size of hydrogels range from 5-100 nm which is much larger than the most drugs. In some cases diffusion of drugs is faster than the hydrogel distension, then swelling is considered the limiting factor for drug release and these systems are called as Swelling controlled systems [65]. Chemically controlled release is also identified where chemical reaction occurs within the gel matrix which controls the release mentioned in table 8. These can be further divided on the basis of the type of chemical reaction occurring during drug release [66].Various stimuli sensitive hydrogels like pH, temperature sensitive hydrogels are prepared to target drugs or proteins to colon and other therapeutic agents to tumors [67].

TABLE 8: MARKETED HYDROGEL BASED SYSTEM.

DRUG USED	POLYMER USED	APPROACH USED	METHOD OF PREPARATION
Satranidazole	Chitosan	pH senstive	Cross linking method[68]
5-fluorouracil	Hydroxyethylmethacrylate, Methacryloyloxy azobenzene (MAB)	Degradation by azoreductase	Polymerisation [69]

CODES-Novel Colon Targeted Delivery System: CODES was designed to overcome the problems associated with pH and time dependent systems [70,71]. In this system both the pH and microbially triggered approach are utilized to control the drug release at desired location. Lactulose is used as a trigger for site specific drug release in colon. The system consists of aconventional tablet core containing lactulose. It is then coated with an acid soluble material, Eudragit E and then further coated with an enteric substance;

Eudragit L. This enteric coating of Eudragit L prevents the drug release in the upper GIT. Acid soluble material protects the drug core from the alkalinity of small intestine [72]. On reaching the colon the system is attacked by bacteria which degrade the polysaccharide lactulose into organic acid thereby lowering the pH of surrounding leading to the dissolution of acid soluble coat and thus drug release [73]. An example of the marketed preparation based on CODES technique is given in **table 9**.

TABLE 9: MARKETED CODES BASED SYSTEM

DRUG USED	POLYMER USED	DOSAGE FORM	DISEASE
Mebeverine Hydrochloride	Eudragit E100	Tablets	spasmolytic drug[74]

OROS -CT: This OROS-CT system can be a single osmotic unit or 5-6 push-pull units incorporated in a hard gelatin capsule. When the OROS-CT is swallowed, the outer gelatin capsule dissolves. Due to the presence of enteric coating drug is protected in the acidic environment of stomach from being dissolved there. As this system enters the small intestine, the coat dissolves leading to the entry of water in the osmotic region making it to swell. Swelling forces the drug out of the orifice at a rate by which water enters the system[5]. In the treatment of ulcerative colitis, such system is designed in a way to get 3-4 hr post gastric delay to prevent drug release in small intestine [75].

Nanoparticles for Colon Targeted Drug Delivery: Nanoparticles are now a days become novel area for colon specific drug delivery as depicted in table 10. These are novel approaches used to target drugs. These are small colloidal particles of size about 200 nm made up of biodegradable and non- biodegradable polymers. The drug moiety can be dissolved, entrapped, or encapsulated in the nanoparticle matrix [76].They are better than conventional dosage forms in many aspects .They results in more efficacy, reduced toxicity, better biodistribution and improved patient compliance [77]. They results in controlled release due to biodegradability, pH, ion, temperature sensitivity [78].

TABLE 10: NOVEL NANOPARTICLES BASED SYSTEMS.

DRUG USED	POLYMER USED	METHOD OF PREPARATION	DISEASE
5- Fluorouracil	Soyalecithin, Dynasan114 and dynasin 118	Solid-Lipid Nanoparticles	Colon cancer [79]
Tripeptide,Lys-Pro-Val	Alginate and chitosan	Double-emulsion/solvent evaporation	Inflammatory bowel disease

TARGIT Technology: This technology is developed for the targeted delivery of drugs in colonic region. It is mainly used in the delivery of therapeutic agents to the lower GIT for local treatment of disorders. In this technique pH sensitive coating is done on the moulded starch capsules. The *in vivo* studies confirmed that about 90% of the TARGIT Capsules delivered their contents to the target site [87].

Gas Empowered Drug Delivery System (GEDD): It is also a novel drug delivery system to colon which is designed to target the proteins and peptides to the intestinal region by using mucoadhesive polymer polyethylene oxide and TMC as penetration enhancer using co_2. By the presence of mucoadhesive polymer the drug remains adhered to the mucous layer and the permeation enhancer is used to open the tight junctions to promote paracellular pathway for drug absorption. In this system the co_2 gas is used as driving force to push the drug substance to the absorbing membrane and also it covers the dosage form completely to protect it from enzymatic and proteolytic degradation. CO_2 also functions as permeation enhancer by opening the tight junctions mechanically. This system is successful in delivering the drug to the intestine because of the use of CAP(cellulose acetate phthalate) which protects the dosage form from the acidic pH of stomach [80].

Microspheres: Microspheres are used now a days for the delivery of proteins and peptides .They provide stability to the compounds which are prone to degradation *in vivo*. The microspheres shield the drug from the acidic environment of stomach and target the drug to the desired site, and also improve drug absorption from paracellular route [81, 82]. The mechanisms of drug release from microspheres can be diffusion, degradation, hydrolysis or erosion [83]. The drug encapsulated in microspheres have shown increased stability, reduced toxicity and also targeted delivery to the site of action. Some of the examples where microspheres are prepared for colon targeting are given below in **table 11**.

TABLE 11: MICROSPHERES BASED COLON TARGETED SYSTEM

DRUG	POLYMER USED	METHOD OF PREPARATION	DISEASE
Theophylline	Ca-pectinate, Eudragit S100	Ionotropic gelation method	Anti-asthmatic activity [84]
Indomethacine	Eudragit L-100, Eudragit S-100	Solvent evaporation method	Rheumatoid disorders [85]
Aceclofenac	Guar gum	Emulsification methood	Rheumatoid arithritis [86]

COLAL-PRED system: This system is designed by Alizyme for the treatment of ulcerative colitis. It is the combination of Alizyme's colonic delivery system, COLAL, and an approved generic steroid, Prednisolon sodium metasulfobenzoate. It provides the effective treatment of ulcerative colitis without the side effects of steroids. There is no competitor of this product yet in the market. Its colon targeting is done by coating it with such substances which get degraded by the colonic bacteria [75].

Evaluation techniques of Colon Targeted preparations:

1. *In vivo* evaluation

a) **X-ray imaging**: - The dogs were used for the in vivo evaluation of dosage form by x-ray method. 50 ml of radiodiagnostic agent, omnipaque was given to the dogs. Then after specific time intervals post administration of omnipaque x-ray imaging was done. This was done to get reference dog GIT x-ray images for comparison. During x-ray imaging the animals are subjected to fast overnight with full access to water and a radiograph is made before the administration of the substance under test. Then the units are administered along with 50ml of water. The radiograph of animals were taken at 0h, 0.5h, 2.5h, 4h, 5h, 6h, 7h, 8h after the ingestion of substance under test[87].

b) **Gamma scintigraphy**: It is the technique used for determination of the *in-vivo* behavior of different colon targeted systems. It is a non invasive imaging technique. This is done by incorporating small amount of gamma- emitting radionuclides in the dosage forms, which describes the GIT transit patterns and the time and place of disintegration is also depicted [88].

a. *In vivo* imaging on rabbits: 12 male albino rabbits of 1 year age were taken for the study of the in-vivo transit of dosage form. The rabbits were divided into 2 groups and were fasted for 12 hrs before the study. The polymer coated radiolabelled pellets containing drug were administered to the animals of group 1 in suspension form and the uncoated pellets were administered to the group 2 animals along with sufficient amount of drinking water. Then the animals were monitored under gamma camera. 140 keV gamma rays emitted by ^{99m}Tc were imaged. The generated gamma rays were recorded using computer system and then those images were analyzed for the distribution pattern of dosage form in the GIT. During the intervals between gamma scanning animal were allowed to move but any kind of food or water uptake was prohibited until the stomach was free from the formulation [89]. It was seen that the coated pellets showed adequate controlled release pattern and then the scintigraphy study of coated and uncoated pellets were compared. The scintigraphy study indicated that the coated formulations remained intact in the colon for 10hrs period. After reaching colon the pellets were disintegrated and drug was released [90].

c) **High frequency capsule**: Colonoscopy and intubation are the techniques mostly used for the analysis of dosage form inside the body. High frequency capsules are the smooth plastic capsules taken orally. These contain small latex balloon, drug and radiotracer substance. The drug and radiotracer are released by an impulse, and the release is analyzed inside the different parts of GIT. By this technique the absorption properties of drugs in the colon are monitored [91].

2. ***In vitro evaluation***: *In vitro* evaluation techniques involves the simulation of the in vivo conditions of the GIT, like pH, volume, bacteria, enzymes food particles etc under the laboratory conditions. The conventional

basket method is usually used for performing the in vitro dissolution studies of a dosage form. The dissolution studies are carried out in different buffer solutions to mimic the GIT environment and to know the behavior of dosage form under different pH conditions. The in vitro tests for enteric coated systems is done by keeping them in simulated stomach pH conditions (0.1 N HCl) for 2 hrs (mean gastric emptying time) and then in the simulated intestinal pH conditions for next 3 hrs (mean small intestine transit time). The site and amount of degradation and dissolution of the dosage form is thus predicted during the *in vitro* studies [92].

CONCLUSION: Till now we have studied about the basic features of colon targeting, different approaches used for colon targeting . Now as we have mentioned earlier that many approaches can be used for colon targeting of drugs but each approach has its own advantages and disadvantages which decides their application in different disease conditions. With the day by day advancements going on in this field many new approaches are designed and developed to overcome the problems encountered during drug targeting. New polymers are used to improve the targeting while minimizing the failure chances and improving the patient compliance. The colon targeted systems like nanoparticles, microspheres, liposomes have proved to be a new successful technique for the delivery of vaccines, peptidal drugs, proteins etc.

Colon targeting is now a days focusing a lot of attention of research fellows as this has proved to be effective for both local and systemic drug delivery and treatment of many diseases also. The in vitro evaluation studies used by far doesn't provide the exact in vitro in-vivo correlation due to several reasons. In the whole it can be concluded that the colon targeted drug delivery system has proved to be effective for the delivery of proteins and peptides also and this is becoming a new route and method of drug administration.

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