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Review Article

ORAL COLON TARGETED DRUG DELIVERY SYSTEM: A REVIEW ON CURRENT AND NOVEL PERSPECTIVES

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ABSTRACT
Small intestine is mostly the site for drug absorption but in some cases the drug needs to be targeted to colon due to some factors like local colonic disease, degradation related conditions, delayed release of drugs, systemic delivery of protein and peptide drugs etc. Colon targeted drug delivery is important and relatively new concept for the absorption of drugs because it offers almost neutral pH and long residence time, thereby increasing 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 discusses in brief about introduction of colon along with the novel and emerging technologies for colon targeting of drug molecule. Treatment of these diseases with colon-specific drug delivery system provides an interesting alternative over systemic drug administration because of lower dosing and fewer systemic side effects.
KEYWORDS: Colon targeting, Microbial degradation, Prodrug, Time dependency, Colon.

INTRODUCTION

To the date, oral delivery is still the most favorable route of drug administration, especially for chronic therapies where repeated administration of drugs is required. Oral administration offers less pain, good patient convenience and reduced risk of cross infection and needle stick injuries[1]. Thus, formulations of oral drug delivery continue to dominate more than half of the drug delivery market share[2]. Despite these advantages, the oral route is not applicable to the administration of protein and polypeptide drugs, due to their high susceptibility to digestive enzymes in the gastrointestinal tract (GIT), and poor absorption. As a result, new strategies of drug delivery have been developed to overcome obstacles encountered by oral delivery. Among these strategies, oral colon-specific delivery has been extensively studied from the last two decades[1].

The colonic region of the GIT is one area that would benefit from the development and use of such modified release technologies. Although it has simple functions in the form of water and electrolyte absorption, the colon is vulnerable to a number of disorders including ulcerative colitis, crohn's disease, helminthes, irritable bowel syndrome and carcinomas[2]. Targeted drug delivery to the colon, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the GIT but releases in the colon following oral administration. Specifically delivering drug to the colon, a lot of benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases[3].

In addition to local therapy, the colon can also be utilized as a portal for the entry of drugs like proteins and peptides into the systemic circulation. Successful colonic drug delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut[2].The representatives of colon specific diseases are inflammatory bowel disease (IBD), including ulcerative colitis and crohn's disease, helminthes, irritable bowel syndromes (IBS) and colorectal carcinoma[3]. Most of the conventional drug delivery systems for treating the colon disorders are failing as the drugs do not reach the site of action in appropriate concentrations. Thus, an effective and safe therapy of these colonic disorders, using site specific drug delivery system is a challenging task to the pharmaceutical technologists[4]. The therapeutic advantages of targeting drug to the diseased organ include

- Delivery of drug in its intact form as close as possible to the target site.
- The ability to cut down the conventional dose.
- Reduced incidence of adverse side effects.
- Low hostile environment, the colonic transit time is long (20-30 h). The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make the colon a promising site for the delivery of most of drugs for systemic absorption.[4]

Factors to be considered in the design of colon specific drug delivery system

Anatomy and physiology of GIT

The GIT, also called the alimentary canal, is a muscular digestive tube that winds through the body. The GIT is a selective barrier between the environment and the systemic circulation, which functions to digest dietary food, to absorb nutrients, electrolytes and fluid, and to prevent the absorption of potentially harmful substances[1]. The small intestine is the longest part of the GIT there most enzymatic digestion and virtually all absorption occurs. The large intestine is the last major subdivisions of the GIT. Major regions of the large intestine are the cecum, colon, rectum and anal canal[5].

pH in the colon

The pH of the GIT is subjected to both inter and intra subject variations.[6] Table 1 gives an overview of the pH of The GIT.

Gastro intestine transit

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small

intestinal transit time[4].

The transit times of small dosage forms in GIT are given in table 2.

Colonic bacteria

Almost 400 distinct bacterial species have been found throughout the length of GIT, out of which 20% to 30% are of the genus Bactericides. The upper region of GIT consists of very small number of bacteria and predominantly gram-positive facultative bacteria. The most important anaerobic bacteria's are Bactericides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium, and Clostridium[7]

The bacterial count (CFU/mL) in different regions of the GIT is,

Stomach: 0-10^3 CFU/ml

Small intestine: 10^3 -10^4 CFU/ml

Colon: 10^{11} -10^{12} CFU/ml[8]

Requirement of colon targeted drug delivery

Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. A number of diseases of the colon, e.g. colorectal cancer, helminthes, ulcerative colitis or Crohn's Disease, might also be capable of being treated more effectively if drugs were targeted to the colon.[9]

Advantages of colon targeting drug delivery system over conventional drug delivery[9,10]

Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs.
- Bypass initial first pass metabolism.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.

Limitations of colon targeting drug delivery system[10]

- Multiple manufacturing steps
- Incomplete release of drug
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.

Drug candidate for colonic drug delivery

Drugs which show poor absorption from the stomach or intestine including peptide drugs are most suitable for colon specific drug delivery systems. The criteria for selection of drugs for colon specific drug delivery systems are shown in Table 3. Selection of carrier for particular drug candidate depends on the physicochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of the absorption enhancer chosen influence the carrier selection[6].

Approaches for targeting drugs to the colon via oral route

An oral colonic delivery system should retard drug release in the stomach and small intestine but allow complete release in the colon. The system designed for the delivery of drug in the colon may be single or multiple unit dosage[2].

Single unit colon targeted drug delivery systems may suffer from unintentional disintegration of the formulation due to manufacturing deficiency[4].

Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microspheres and nanoparticles. The use of multiparticulate drug delivery systems than single unit dosage forms for colon targeting showed Proper colon targeting of drug and also for longer period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GIT easily. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GIT and also ensure more uniform drug absorption[2,4].

In general there are five approaches for colon targeted delivery namely[4],

1. pH dependent system
2. Time dependent systems
3. pressure dependent systems
4. Microbially triggered approach
   - Prodrugs
   - Azo polymeric prodrug
   - Polysaccharides based approach
5. Novel approach
   - Hydrogels based approach
   - CODES-Novel Colon Targeted Delivery System
   - OROS system
   - Nanoparticles
   - TARGIT Technology:
   - Gas Empowered Drug Delivery System
   - Microspheres

pH dependent system

The basic principle in this method is the coating of the dosage form with various pH sensitive polymers (given in Table 4), which will protect from gastric acid and produce delayed release of drug. The selected polymers to colon targeting should be able to withstand the pH of the stomach and small intestine[2]. Methacrylic acid esters are most commonly used polymers for colon targeting because they are soluble at above pH 6. The ideal polymer should be able to withstand the lower pH of the stomach and of the proximal part of the small intestine but able to dissolve at neutral and nearly alkaline pH of the terminal ileum and preferably at ileocecal junction. Eudragit L and Eudragit S are widely used in the colon targeting because Eudragit L is soluble at pH 6 and above and Eudragit S is soluble at pH 7 and above and the combination of these polymers give the desirable release rates[5].

Time Dependent Systems[2,5,7,9,12]

It is also known as pulsatile release or delayed release system. The basic principle involved in this system the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at predetermined time. In this system formulation is comprised of three parts first a center core containing a drug and swelling excipients, second an inner semi permeable polymer membrane containing a plasticizer which allow water influx but prevents the outward diffusion of drug and last an outer enteric-coating which dissolves above pH 5.5. In this method the solid dosage form coated with different sets of polymers and the thickness of the outer layer determines the time required disperse in aqueous environment. Time dependent polymers are mostly cellulosic based (as shown in the Table 5). However, the disadvantages of this system are:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
- Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis.

One of the earliest systems to utilize this principle was the pulcincap device. The system consists of an impermeable capsule filled with drug and stopperd at one end with a hydrogel plug. On contract with gastrointestinal fluids, the plug hydrates and swells and after a set lag time, ejects from the capsule body, thereby allowing drug release to occur. The lag time is controlled by the size and composition of the plug.

Pressure Dependent Drug Delivery Systems[2,9,12]

Gastrointestinal pressure has also been utilized to trigger drug release in the distal gut. This pressure, which is generated via muscular contractions of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the GIT, with the colon considered to have a higher luminal pressure due to the processes that occur during stool formulation. Systems have therefore been developed to resist the pressure of the upper GIT but rupture in response to the raised pressure of the colon. Capsule shells fabricated from the water-insoluble polymer ethyl cellulose have been used for this purpose. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall.

Microbial triggered approach

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by release of drug load in colonic region. The resident gastrointestinal bacteria provide a further means of effecting drug release in the colon. These bacteria predominantly colonize the distal regions of the GIT where the bacterial count in the colon is 10^{11} CFU/mL, as compared with 10^{4} CFU/mL in the in the upper small intestine[2]. Moreover 400 different species are present. In this method drugs and/or dosage forms are coated with the biodegradable polymers (Table 1.3) i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating[5]. Colonic bacteria are predominately anaerobic in nature and produce enzymes that are capable of metabolizing endogenous and exogenous substrates, such as carbohydrates and proteins that escape digestion in the upper GIT[7].

Prodrug approach: A prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release active drug at the target site[8]. This approach involves covalent linkage between the drug and its carrier so that upon oral administration the moiety remains intact in the upper part of the GIT and after reached in the colon, enzymatic cleavage will regenerate the drug. An example for such a prodrug is Sulfasalazine[9].

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 [13]. 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 [14].

Polysaccharide based approach: Naturally occurring polysaccharides are widely in use for drug targeting because of their abundance, easy availability, and also they are inexpensive. They are highly stable, safe, nontoxic, hydrophilic, gel forming and biodegradable[11]. (Table 6).

Novel approaches

Now a days the basic colon targeted approaches are applied to formulate novel drug delivery systems like Multiparticulate systems (pellets etc.), Microspheres, Nanoparticles, Microencapsulated particles, etc[5].

Hydrogels based approach: Hydrogels are three dimensional polymer networks which are hydrophilic in nature so it is swellable in water and body fluids. Hydrogels are used in drug delivery systems because it allows the passage of drug through its structure. The mechanism of drug release is diffusion mediated because hydrogels have good permeability for water soluble drugs. Hydrogels can be formulated in a number of physical forms like microparticles, coating, films, nanoparticles. The commonly used hydrophilic polymers for hydrogels based drug delivery system are PEG, PVA, PAA, polymethacrylic acid and polyacrylamide. These polymers can absorb water from a fraction to several thousand of their own weight [15]. Diffusion controlled release is the considered the primary method of drug release from dosage form [16].Various stimuli sensitive hydrogels like pH, temperature sensitive hydrogels are prepared to target drugs or proteins to colon and other therapeutic agents to tumors[17].

CODES-novel colon targeted delivery system: CODES is the newly designed technique that overcomes the problems related to pH and time dependent systems[18]. In this system

both the pH and microbially triggered approaches are utilized to target the drug at desired location. Lactulose is used as a polymer for target the drug in to the colon. The system consists of a core material of lactulose and drug matrix. It is then coated with enteric polymers like Eudragit which prevents the drug release in the upper GIT[19].

OROS colon targeted system: OROS colon targeted system is a single osmotic unit incorporated in a hard gelatin capsule. When the OROS colon targeted system is swallowed, the outer gelatin capsule dissolves in the acidic media. Due to the presence of an enteric coating, drug is protected in the acidic environment of stomach. When this system enters the small intestine, the coating material is dissolves leading to the entry of body fluid 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 and thus drug is targeted to the colon[20].

Nanoparticles for colon targeted drug delivery: In recent days nanoparticles are become novel area for colon specific drug delivery to target the drug. Nanoparticles are small colloidal particles of size about 200 nm made from biodegradable and non-biodegradable polymers. The drug moiety can be dissolved, entrapped, or encapsulated in the nanoparticle matrix.They are better than conventional dosage forms in many aspects .They results in more efficacy, reduced toxicity, better biodistribution and improved patient compliance[11].

TARGIT technology: This technology is formulated to target the drugs in colonic area. It is mainly used to target the drugs to the lower GIT for local treatment of GI disease. In this technique pH sensitive coating is done on the starch capsules[21].

Gas empowered drug delivery system: It is also a novel drug delivery system mainly designed to targeting the proteins and peptides drug in to the upper GIT using mucoadhesive polymer polyethylene oxide and 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 cellulose acetate phthalate which protects the dosage form from the acidic pH of stomach[22].

Microspheres: Microspheres are used for the delivery of proteins and peptides to the colonic region. They provide stability to the acid labile drugs. The drug matrixes to form microspheres have shown increased stability, reduced toxicity and also targeted delivery to the site of action. The microspheres also improve drug absorption from paracellular route. The mechanisms of drug release from microspheres can be diffusion, degradation, hydrolysis or erosion[11].

Evaluation techniques of Colon Targeted preparations

***In vivo* evaluation**

X-ray imaging: The animals were used for the *in vivo* evaluation of dosage form by x-ray method. Few ml of radiodiagnostic agent was given to the animals. Then after specific time intervals post administration of radiodiagnostic agent x-ray imaging was done. This was done to get reference animal 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 was taken at different time interval after the ingestion of substance under test[21].

Gamma scintigraphy: It is the technique used for determination of the *in-vivo* behavior of different colon targeted systems. 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 predicted[22].

Colonoscopy by 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[23].

***In vitro* evaluation**

In vitro evaluation techniques involve the simulation of the *in vivo* conditions of the GIT, like pH, volume, bacteria, enzymes 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[23].

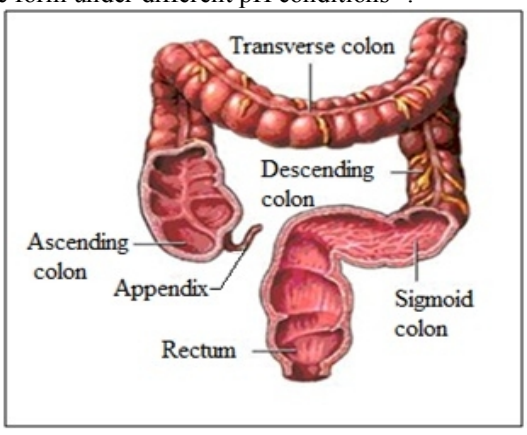

Figure 1: Structure of Colon.

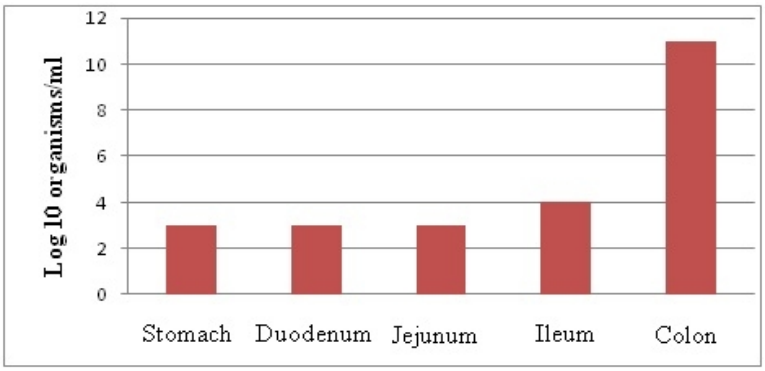

Figure 2: Bacterial strength in GIT.

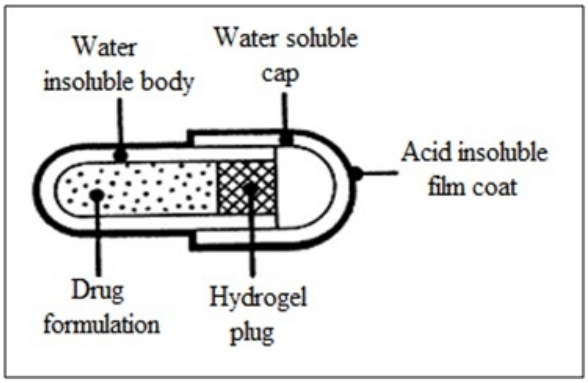

Figure 3: Design of Pulsincap system

Table 1: Average pH of GIT[6]

Location	pH
Oral cavity	6.2- 7.4
Oesophagus	5.0- 6.0
Stomach	Fasted condition: 1.5-2.0, Fed conditions: 3.0-5.0
Small intestine	Jejunum: 5.0-6.5 Ileum: 6.0- 7.5
Large intestine	Right colon: 6.4 Mild colon and left colon: 6.0- 7.6

Table 2: The transit time of dosage forms in GIT[4]

Organ	Transit Time (h)
Stomach	<1(fasting) and, >2 (fed)
Small intestine	3- 4
Large intestine	20- 30

TABLE 3: Criteria for selection of drugs for colon specific drug delivery systems[6]

Criteria	Nonpeptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Diclofenac, Metaprolol	Amylin, Calcitonin
Drugs poorly absorbed from upper GIT	Ibuprofen, Theophylline, Isosorbides	Cyclosporine, Desmopressin
Drugs for colon cancer	Pseudoephedrine	Glucagon, Epoetin
Drugs that degrade in stomach and small intestine	Bromophenaramine, 5-Flourouracil	Gonadorelin, Insulin
Drugs that undergo extensive first pass metabolism	Nimustine, Bleomycin	Sermorelin, Saloatonin
Drugs for targeting	5-Aminosalicylic- acid, Prednisolone	Vasopressin, urotoilitin

TABLE 4: Threshold ph of most commonly used enteric polymers[11]

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 5: Materials used in Formulation of Colon Targeted Drug Delivery System[5]

Prodrug conjugates	Azo bond conjugates, Glycoside conjugates, Glucuronide conjugates, Polymeric conjugates, Cyclodextrin conjugates, Dextran conjugates
PH-Sensitive Polymers	Eudragit L-100, Eudragit S-100, Poly vinyl acetate phthalate, Hydroxy propyl methyl cellulose phthalate, Hydroxy propyl ethyl cellulose phthalate, Cellulose acetate phthalate, Cellulose acetat trimellate
Materials used In Time-Dependent System	Hydroxy propyl methyl cellulose, Hydroxy ethyl cellulose, Ethyl cellulose, Microcrystalline cellulose, Lactose/Behinic acid
Microbial degradable polymers	Chitosan, Pectins, Guar gum, Dextrans, Inulin, Amylose, Cyclodextrins, Alginates

TABLE 6: Characteristics of various biodegradable polysaccharides for colon targeted drug delivery[6]

Polymer	Chemical name	Pharmaceutical uses	Bacterial species that degrade polysaccharide
Amylose	1, 4 D- glucose	Unbranched constituent of starch, used as tablet excipients	Bactericides Bifidobacterium
Chitosan Deacetylated	1, 4- N- acetyl –Dglucosamine	Deacetylated chitin, used as a absorption enhancing agent	Bactericides
Cyclodextrins	1, 4 D- glucose Cyclic structures of 6,7or 8 units	used as a solubilising and absorption enhancing agent	Bactericides
Pectin	1,4 D- galacturonic acid and 1,2 D-rhamnose	Commonly used as thickening agent	Bifidobacterium, Eubacterium,
Dextran	1, 6 D- glucose 1,3 D- glucose	Plasmaexpanders	Bactericides
Guar gum	1, 6 D-galactose 1,4 D- mannose	Galactomanan, used as a thickening agent	Bacteroides, Ruminococus
Xylan	1,4 D- xylose with 1,3 L- arabinose	Abundant hemi cellulose of plant cell wall, used as a thickening agent	Bacteroides, Bifidobacterium

TABLE 7: Novel forms of natural polysaccharides used[11]

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
Paracetamol	Amidated Pectin	Matrix Tablet
Ropivacaine	Amidated Pectin	Matrix Tablet

CONCLUSION

We have discussed about the basic features of colon targeting, different traditional and novel approaches used for colon targeting. Many techniques can be used for colon targeting of drugs but each technique has its own advantages and disadvantages which decides their application in the treatment of different disease conditions. The research going on in this field many new approaches are designed and developed to overcome the problems during drug targeting. Newly developed polymers are used to improve the targeting by minimizing the side effect and improving the patient compliance. The colon targeted systems like nanoparticles and microspheres have proved to be new successful techniques for the delivery of vaccines, peptide and proteins. In the recent time colon targeting is focusing a lot of attention of research scientists because this has proved to be effective for both local and systemic drug delivery and this is becoming a new route and method of drug administration.

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