AN APPROACH TOWARDS REVIEW ON COLON TARGETED DRUG DELIVERY SYSTEM

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Keywords:
Colon targeted delivery system, microbial flora, pH dependent, novel approaches

ABSTRACT
Numerous routes of drug administration have been proposed and explored for the effective delivery of the drug to the target site. Colon is a site where both systemic and local drug are used for situated diseases. Local delivery allows the topical treatment of inflammatory bowel disease, Crohn’s disease, ulcerative colitis, etc. Various drugs are been used for targeting systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. Colon target aimed mainly because of microbial flora, less enzymatic activity, longer transit time so it is suitable to delivering especially the protein and peptide molecules. Different primary and novel approaches are designed based on time-dependency (lag time), prodrug approaches, microbial degradation, pH-sensitivity to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes for colon targeting. Novel colon targeted delivery system like osmotic controlled drug delivery system, Pulsincap system, time clock system, chronotropic system. The effectiveness of drug delivery system is evaluated using different in vitro and in vivo release studies and using recent evaluation models through x-ray imaging and gamma-scintigraphy studies.
1. INTRODUCTION
The per-oral dosage form is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach and intestinal fluid hence absorb from these regions of gastro intestinal tract GIT. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT.

Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs.

The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon.

Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and/or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries.

Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. A colonic targeted approach found to be effected in minimizing uncertain side effects.

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as (ulcerative colitis, crohn’s disease) amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine and bioactive agent should not be degraded and to allow drug release only in the colon.

2. MATERIALS AND METHODS
The search was conducted electronically in Wiley online library, pubmed, google scholar from 1995 to 2014. The key words were colon targeted delivery system, novel approaches, microbial flora, pH dependent. The articles written in English were included in the review. A total of 1289 references were identified, after this 657 article were screened and 335 full text articles were studied for eligibility. Among which 72 articles were included matching the inclusion criteria. Finally 263 articles were excluded from this review process.
3. **Objective for Colon Targeted Drug Delivery**

To ensure direct treatment at the disease site, minimize 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. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn’s Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism.

4. **Advantages of colon specific drug delivery system**

1. Minimizes the side effects in the treatment of colon diseases.
2. Prevents gastric irritation resulting due to the administration of non-steroidal anti inflammatory drug NSAIDs.
3. Minimizes first pass metabolism.
4. Increases patient compliance.
5. Maximum bioavailability at small doses.
6. High retention time thus increasing the bioavailability of poorly absorbable drugs.
7. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
8. Decreased frequency of administration, hence decreased cost of therapy.
9. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn’s disease, etc.

5. **Factors to be considered in the design of Colon-Specific Drug Delivery System**

5.1 **Anatomy and Physiology of the Colon**

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long. The colon is upper 1.52 meter of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 5-8 cms in diameter (Table 1). The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal (Figure 1). The physiology of the proximal and distal
colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

![FIGURE 1: ANATOMY OF COLON](image)

**TABLE 1: ANATOMICAL AND PHYSIOLOGICAL FEATURES OF SMALL INTESTINE AND COLON**

<table>
<thead>
<tr>
<th>Region of Gastrointestinal Tract</th>
<th>Transit Time (Hrs)</th>
<th>Length (cm)</th>
<th>pH</th>
<th>Internal diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>---</td>
<td>&lt;1 (Fasting)</td>
<td>1.5-3 (fasted)</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 (Fed)</td>
<td>2-5 (fed)</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td></td>
<td></td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>3-4</td>
<td>20-30</td>
<td>6.1(fasted)</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.4(fed)</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td></td>
<td>150-200</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td></td>
<td>200-350</td>
<td>7-8</td>
<td></td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
<td></td>
<td>6-7</td>
<td>5.5-7</td>
</tr>
<tr>
<td>Ascending colon</td>
<td></td>
<td>20</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Transverse colon</td>
<td></td>
<td>45</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Descending colon</td>
<td></td>
<td>30</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td></td>
<td>40</td>
<td>7-8</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td>12</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Anal canal</td>
<td></td>
<td>3</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

**5.2 pH in the Colon**

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery. There is a pH gradient in the gastrointestinal tract with value ranging from pH 1.2 in the stomach through pH 6.6 in the proximal small intestine to a peak of about pH 7.5 in the distal small intestine (Table 1). The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.
5.3 Transit of material in the colon

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. The transit times of small oral dosage forms in GIT are given in (Table 1).

The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors such as diet, dietary fiber content, mobility, stress, disease and drugs. In healthy young and adult males, dosage forms such as capsules and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur. Diseases affecting colonic transit have important implications for drug delivery: diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant.

5.4 Colonic Micro Flora and their enzymes

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut micro flora residing in high number in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus Bacteroides\textsuperscript{13,14}. The upper region of the GIT has very small number of bacteria and predominantly consists of Gram-positive facultative bacteria.

The concentration of bacteria in the human colon is 10^{11} - 10^{12} CFU/ml. The most important anaerobic bacteria are \textit{Bacteroides, Bifidobacterium, Eubacterium, Peptostreptococcus, peptococcus, Ruminococcus} and \textit{clostridiums}\textsuperscript{15}. Summary of the most important metabolic reaction carried out by intestinal bacteria are given in (Table 3).

| TABLE 3: DRUG METABOLIZING ENZYMES IN THE COLON THAT CATALYZE REACTIONS |
|--------------------------|-----------------|----------------------------------|
| Enzymes                  | Microorganism   | Metabolic reaction catalyzed     |
| Nitroreductase           | \textit{E. coli}, Bacteroides | Reduce aromatic and heterocyclic nitro compounds |
| Azoreductase             | \textit{Clostridia, Lactobacilli, E. coli} | Reductive cleavage of azo compounds |
| Esterase and amidases    | \textit{E. coli, P. vulgaris, B. subtilis, B. mycoides} | Cleavage of esters or amidases of carboxylic acids |
| Glycosidase              | \textit{Clostridia, Eubacterium} | Cleavage of β-glycosidase of alcohols and phenols |
| Glucuronidase            | \textit{E. coli, A. aerogenes} | Cleavage of β-glucuronidases of alcohols and phenols |
5.5 Colonic Microflora

The human alimentary canal is highly populated with bacteria and other microflora at both ends, the oral cavity and the colon/rectum. In between these two sites, the GIT is very sparsely populated with microorganisms. Microorganisms of the oral cavity do not normally affect oral drug delivery systems and as such will not be considered here further. However, gut microflora of the colon have a number of implications in health and the treatment of disease such as irritable bowel disease IBD. This section presents some background information on gut microflora as it relates to colonic-based delivery system. Concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalyzing a wide range of metabolic events. Many colon-specific drug delivery systems rely on enzymes unique to gut microflora to release active agents in the colon. However, only two or three enzyme systems have been exploited in this area: azoreductases and glycosidases (including glucuronidase). A large number of polysaccharides are actively hydrolyzed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. In addition, ethereal sulfate prodrugs or carboxylated prodrugs may be metabolized in the colon to the parent drug leading to local delivery in the colon. There is certainly room for innovative approaches to carry and release drugs in the colon based on the metabolic capabilities of the colon microflora. Azoreductases produced by colon play a central role in a number of delivery systems, mostly in catalyzing the release of 5-Amino salicylic acid (5-ASA) from a variety of prodrugs. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for beta-glycosidases activity are lactobacilli, bacteroides and bifidobacteria. As with azo-reductase activity, the level of bacterial glycosidase activity in the gastrointestinal tract is associated with the concentration of bacteria in a given region.

6 Criteria for selection of drug for Colonic Drug Delivery

6.1 Drug candidate

Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used in treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery.

6.2 Drug carrier

The selection of carrier for particular drug candidate depends on the physiochemical 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 drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule\(^{18}\). The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems\(^{19}\).

7 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.
- Lower surface area and relative tightness of the tight junctions in the colon due to continuous blankets can restrict drug transport across the mucosa in to the systemic circulation\(^{20}\).
- 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\(^{21}\).
- Colonic contents are considerably viscous because of high water absorption capacity of the colon thereby decreasing the availability of most drugs to absorptive membrane\(^{22}\).
- Dissolution is minimal for poorly water soluble drugs because of less fluidity and more viscous contents in the colon than in small intestine\(^{23}\).
- 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\(^{21}\).

8 Factors affecting Colon Absorption\(^{24}\)

1. Physical properties of drug such as drug pKa and degree of ionization.
2. Colonic residence time as commanded by GIT motility.
3. Degradation by bacterial enzymes and metabolic products.
4. Local physiological action of drug.
5. Selective and non-selective binding to mucus.
6. Disease state.

9 PRIMARY APPROACHES FOR COLON TARGETED DRUG DELIVERY (CTDD) SYSTEM

9.1 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., pH 7-8. This approach can be used in any dosage form such as tablets, capsules, pellets etc. 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. 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. Combination of different polymers, coating level, pH of media are some factors that affect the dissolution rate of Eudragit. 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. Depicting enteric coating polymers along with their threshold pH as mentioned in (Table 4).

**FIGURE 2**: pH Controlled release enteric coated tablet for CDDS.

**TABLE 4**: THRESHOLD pH OF MOST COMMONLY USED ENTERIC POLYMERS

<table>
<thead>
<tr>
<th>ENTERIC POLYMERS</th>
<th>THRESHOLD pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate trimelliate</td>
<td>5.5</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose Phthalate (HPMCP)</td>
<td>≥5.5</td>
</tr>
<tr>
<td>Shellac</td>
<td>7.0</td>
</tr>
<tr>
<td>Eudragit® FS 30D</td>
<td>6.8</td>
</tr>
<tr>
<td>Eudragit L 100</td>
<td>6.0</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>7.0</td>
</tr>
<tr>
<td>Eudragit L 100-55</td>
<td>5.5</td>
</tr>
<tr>
<td>Eudragit L 30 D</td>
<td>5.6</td>
</tr>
<tr>
<td>Hydroxypropyl ethylcellulose phthalate</td>
<td>5.2</td>
</tr>
<tr>
<td>Polyvinyl acetate phthalate(PVAP)</td>
<td>4.5-5.0</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose acetate succinate</td>
<td>≥6.0</td>
</tr>
<tr>
<td>Cellulose acetate phthalate (CAP)</td>
<td>5.0</td>
</tr>
</tbody>
</table>
9.2 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\(^\text{29}\). 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. 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 \(^\text{30}\). However, these systems are useful in the therapy of diseases based on circadian rhythms \(^\text{31-34}\). 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 \(^\text{35}\).

The disadvantages of this system are:

1. Gastric emptying time shows intersubject and intrasubject variation leading to unpredictable colon arrival time of drug \(^\text{21,31}\).
2. The peristaltic movements in the stomach result in altered gastrointestinal transit of drug \(^\text{21}\).
3. Altered transit is also observed in conditions of IBD, diarrhea, ulcerative colitis \(^\text{36}\).

### TABLE 5: SUMMERY OF THE DOSAGE FORM USED FOR CDD SYSTEMS

<table>
<thead>
<tr>
<th>DOSAGE FORM</th>
<th>POLYMER USED</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Press coated tablets</td>
<td>Hydroxypropylmethylcellulose acetate succinate (HPAMCAS)</td>
<td>Diltiazem hydrochloride</td>
</tr>
<tr>
<td>Tablets</td>
<td>HPMCK-100M, HPMCK-4M, HPMC E15, HPMC E15</td>
<td>Mesalamine</td>
</tr>
<tr>
<td>Tablet</td>
<td>Guar Gum and Sodium Starch Glycolate</td>
<td>Valdecoxib</td>
</tr>
<tr>
<td>Tablet</td>
<td>Pectin</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>Matrix Tablet</td>
<td>Sesbania Gum</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Chitosan</td>
<td>Diclofenic Sodium</td>
</tr>
<tr>
<td>Capsules</td>
<td>Chitosan</td>
<td>Insulin</td>
</tr>
<tr>
<td>Matrix Tablet</td>
<td>Pectin</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Matrix Tablet</td>
<td>Guar Gum</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Matrix Tablet</td>
<td>Chondroitin Sulphate</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Swellable Beads</td>
<td>Alginate</td>
<td>5-ASA</td>
</tr>
<tr>
<td>Film</td>
<td>Locust- BeanGum</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Film</td>
<td>Dextran Fatty Acid Esters</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Enteric coated capsules</td>
<td>Starch</td>
<td>Radioactive Tracer</td>
</tr>
<tr>
<td>Matrix Tablet</td>
<td>Amudated Pectin</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Matrix Tablet</td>
<td>Amudated Pectin</td>
<td>Ropivacaine</td>
</tr>
<tr>
<td>Capsule</td>
<td>Ethyl Cellulose</td>
<td>Caffeine as test drug</td>
</tr>
<tr>
<td>Capsule</td>
<td>PEG, labrasole</td>
<td>Glycyrrhizin</td>
</tr>
<tr>
<td>Capsule</td>
<td>Ethyl Cellulose</td>
<td>Caffeine as test drug</td>
</tr>
<tr>
<td>Hydrogel-pH sensitive- Cross linking method</td>
<td>Chitosan</td>
<td>Satrandaazole</td>
</tr>
<tr>
<td>Hydrogel- Polymisation Degradation by azoreductase</td>
<td>Hydroxyethylmethacrylate, Methacryloyloxy azobenzene (MAB)</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>Tablets</td>
<td>Eudragit E100</td>
<td>Mebeverine Hydrochloride</td>
</tr>
<tr>
<td>Solid-Lipid Nanoparticles</td>
<td>Soyalecithin, Dynasan114 and dynasin 118</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Double-emulsion/solvent evaporation</td>
<td>Alginate and chitosan</td>
<td>Tripeptide, Lys-Pro-Val</td>
</tr>
<tr>
<td>Microspheres-Ionotropic gelation method</td>
<td>Ca-pectinate, Eudragit S100</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Microspheres -Solvent evaporation method</td>
<td>Eudragit L-100, Eudragit S-100</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Microspheres Emulsification method</td>
<td>Guar gum</td>
<td>Aceclofenac</td>
</tr>
</tbody>
</table>
9.3 Pulsincap

The first formulation introduced based on this principle was Pulsincap® (Figure 3) developed by R.R.Scherer International Corporation, Michigan, US. It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell. The length of the plug and its point of insertion into the capsule controlled the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants.

The plug material consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (eg, pectin).

![FIGURE 3: DESIGN OF PULSINCAP SYSTEM](image)

9.4 Chronotropic System

The Chronotropic system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The system is suitable for both tablets and capsules.
9.5 PORT System
The Port system (Figure 4) was developed by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of a gelatin capsule coated with a semi permeable membrane. Inside the capsule an insoluble plug (lipidic) consisting of osmotic active agent and the drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans. The system proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children.

FIGURE 4: PORT SYSTEM

9.6 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. Colon has a range of complex microflora which fulfills its energy requirements by fermenting the substrate e.g. Polysaccharides present in the intestinal region. These microflora produces wide variety of enzymes which are able to metabolize substrates like carbohydrates and proteins that escape digestion in upper GIT. The majority of polymers are used in pharmaceutical composition and generally regarded as safe excipients. 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. Sulphasalazine, a prodrug of mesalazine was the first bacteria sensitive system.
developed to deliver drug to the colon. The microbially degradable polymers includes Chitosan, Pectins, Guar Gum, Dextran, Inulin, Lactulose, Amylose, Cyclodextrins, Alginates, Locust bean gum, Chondroitin sulphate, Boswellia gum etc. Microbially triggered approach includes the following three approaches mentioned below.

9.7 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, glucoronid acid glucose, galactose, cellulose etc have been prepared which are susceptible to hydrolysis in the colon. 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. 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.

9.8 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. 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.

9.9 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 importantly as shown in (Table 5).
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. Chitosan is used mainly in the form of capsule forming material for the colonic delivery.
9.10 Pressure Controlled Release: The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. Takaya et al., (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of water insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The preferred thickness of the capsule wall is about 35-60 μm. The system also appeared to depend on capsule size and density. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

9.11 CODESTM- Colon Targeted Delivery System: CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon\textsuperscript{46}. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the
polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release\textsuperscript{47, 48, 25}. Design of CODESTM delivery system is given in (Figure 5).

![FIGURE 5: CODESTM- COLON TARGETED DELIVERY SYSTEM](image)

**10. NOVEL APPROACHES FOR CTDD SYSTEM**

**10.1 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\textsuperscript{49}. The property of water absorption of hydrogels is due to the presence of hydrophilic groups such as OH\textsuperscript{-}, -CONH\textsuperscript{-}, -COOH etc.\textsuperscript{50}. 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\textsuperscript{51}. Hydrogels can be formulated in a number of physical forms like microparticles, coated films and nanoparticles. The commonly used hydrophilic polymers for hydrogels are poly ethylene glycol (PEG), poly vinyl acetate (PVA), poly acetic acid (PAA), Polymethacrylic acid, Polyacrylamide\textsuperscript{52}. These polymers can absorb water from a fraction to several thousand of their own weight\textsuperscript{53}. Diffusion controlled release is the considered the primary method of drug release from dosage form\textsuperscript{54, 55}. 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\textsuperscript{56}. 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
Various stimuli sensitive hydrogels like pH, temperature sensitive hydrogels are prepared to target drugs or proteins to colon and other therapeutic agents to tumors.

10.2 Bioadhesive Systems

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for Bioadhesive systems. Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

10.3 Osmotic controlled drug delivery system (OROS-CT)

The OROS-CT (Alza corporation) (Figure 6) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves.

Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hours post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which...
promise to be a good tool for targeting drugs to the colon.[41-44] Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

![Diagram of Osmotic Controlled Drug Delivery System (OROS-CT)](image)

**FIGURE 6: OSMOTIC CONTROLLED DRUG DELIVERY SYSTEM (OROS-CT)**

### 10.4 Nanoparticles for Colon Targeted Drug Delivery

Nanoparticle sized colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability. Nanoparticles have also been investigated for the delivery of protein and peptide drugs. For colonic pathologies, it was shown that nanoparticles tend to accumulate at the site of inflammation in IBD. This is because in case of colitis, a strong cellular immune response occurs in the inflamed regions due to increased presence of neutrophils, Natural Killer cells, macrophages and so on. It has been reported that microspheres and nanoparticles could be efficiently taken up by these macrophages. This results in accumulation of the particulate carrier system resulting in prolonged residence time in the desired area. However, an important area of concern is to prevent loss of Nanoparticle in the early transit through GI tract in order to optimize therapeutic efficacy. Moreover, particle uptake by Payer’s patches and/or enzymatic degradation may cause the release of entrapped drug leading to systemic drug absorption and side effects. In order to overcome this problem, drug loaded nanoparticles were entrapped into pH sensitive microspheres, which serve to deliver the incorporated nanoparticle to their site of action, thereby preventing an early drug leakage. The use of nanoparticles for bioadhesion purposes has also been investigated. Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion can be induced by binding nanoparticles with different molecules. For covalent attachment, the nanoparticle surface has to show free functional groups, such as carboxylic or amine residues.
10.5 Microspheres
In the treatment of IBD, sustained release devices like pellets, capsules or tablets have less efficiency due to diarrhea, a symptom of IBD that enhances their elimination and reduces the total time available for drug release. Microspheres are used nowadays 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. The mechanisms of drug release from microspheres can be diffusion, degradation, hydrolysis or erosion. The drug encapsulated in microspheres have shown increased stability, reduced toxicity and also targeted delivery to the site of action.

10.6 TARGET 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 TARGET Capsules delivered their contents to the target site.

10.7 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 tri methyl chitosan (TMC) as penetration enhancer using carbon dioxide. 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 carbon dioxide 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 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. In the treatment of ulcerative colitis, such system is designed in a way to get 3-4 hour post gastric delay to prevent drug release in small intestine.

10.8 COLAL-PRED system
This system is designed by Alizyme for the treatment of ulcerative colitis. It is the combination of Alizyme’s colon 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.

10.9 Covalent linkage of the drug with a Carrier

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug. Formation of prodrugs has improved delivery properties over the parent drug molecule. The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon.

10.9.1 Azo Bond Conjugates

The intestinal microflora is characterized by a complex and relatively stable community of microorganism, many with physiological functions, which play vital roles in health and disease. In addition to protection of the patient against colonization of the intestinal tract by potentially pathogenic bacteria, the indigenous microflora are responsible for a wide variety of metabolic processes, including the reduction of nitro and azo groups in environmental and therapeutic compounds. Sulphasalazine was introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazosulphapyridine (SASP), where sulfapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact. There it is split at the azo bond by the colonic bacteria with the liberation of sulphapyridine (SP) and 5 ASA. However sulphapyridine is seems to be responsible for most of the side effects of sulphasalazine and hence various new approaches for the treatment of IBD have emerged.

10.9.2 Glycoside Conjugates

Steroid glycosides and the unique glycosidase activity of the colonic microflora from the basis of a new colon targeted drug delivery system. Drug glycosides are hydrophilic and thus, poorly absorbed from the small intestine. Once such a glycoside reaches the colon it can be cleaved by bacterial glycosidases, releasing the free drug to be absorbed by the colonic
mucosa. The major glycosidases identified in human feces are: 1) D-galactosidase, 2) D-glucosidase, 3) L-arabinofuranosidase, 4) D-xylopyranosidase

These enzymes are located at the brush border and hence access to the substrate is relatively easy. In the plant kingdom numerous compounds are found as glycosides. Certain drugs act as glycon and can be conjugated to different sugar moieties which results in the formation of glycosides. Due to the bulky and hydrophilic nature of these glycosides, they do not penetrate the biological membrane upon ingestion\textsuperscript{47}.

10.9.3 Glucuronide Conjugates

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower GIT, however, secrete glucuronidase and can deglucuronidate a variety of drugs in the intestine. Since the deglucuronidation process results in the release of active drug and enables its re-absorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery\textsuperscript{46,47}.

10.9.4 Cyclodextrin Conjugates

Cyclodextrins (CyDs) are cyclic oligosaccharides consisted of six to eight glucose units through 1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine; however, they are fermented by colonic microflora into small saccharides and thus absorbed in the large intestine. Because of their bioadaptability and multi functional characteristics, CyDs are capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. In an oral drug delivery system, the hydrophilic and ionizable CyDs can serve as potent drug carriers in the immediate release and delayed release formulations, respectively, while hydrophobic CyDs can retard the release rate of water-soluble drugs. Since, CyDs are able to extend the function of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable tool in the improvement of drug formulation. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site; conjugates of a drug with CyDs can be a versatile means of constructing a new class of colon targeting prodrugs\textsuperscript{1,47}. 
10.9.5 Polymeric Prodrugs
Azo-linked polymeric prodrugs of 5-ASA were prepared and evaluated in simulated human intestinal microbial ecosystem. Polyamides containing azo groups in the backbone were prepared and tested in vitro in a reductive buffer or in the bioreactor medium. It was demonstrated that for the hydrophobic polymer, reduction stops at the hydrazine stage whereas for hydrophilic analogue reduction occurred. Amount of the drug released depends on the nature of the polymer and can approach that of low molecular weight prodrug\textsuperscript{47}.

10.9.6 Amino-Acid Conjugates
Due to the hydrophilic nature of polar groups like NH\textsubscript{2} and COOH, that is present in the proteins and their basic units, they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA. The salicyluric acid was found to be metabolized to SA by the microorganisms of the intestinal flora of rabbit and dog. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. By increasing the hydrophilicity and chain length of the carrier amino acid and decreasing the membrane permeability of conjugates. This conjugate showed splendid results with minimal absorption and degradation in the upper GIT and proved suitable for colon targeted delivery of SA\textsuperscript{47,48}.

10.9.7 Dextran Conjugate
Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the Bacteroides, which are present in a concentration as high as 10\textsuperscript{11} per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon. In the colon, dextran’s glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (\textendash{}COOH).NASIDS were directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Glucocorticoids do not possess \textendash{}COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid-dextran conjugates\textsuperscript{67,68}. 
11. Evaluation

11.1 In-vitro Evaluation

11.1.1 In vitro Dissolution Test

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels.

Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunum region of the small intestine, and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. In-vitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time).

11.1.2 In vitro Enzymatic Test:

i. Incubate carrier drug system in fermenter containing suitable medium for bacteria (Streptococcus faecium or B.ovatus) amount of drug released at different time intervals determined.

ii. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

11.2 In-vivo Evaluation:

11.2.1 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. 64.

11.2.2 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 radionuclide in the dosage forms, which describes the GIT transit patterns and the time and place of disintegration is also depicted. 69. 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 99mTc 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. 70. 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. 71.

11.3 Clinical Evaluation

11.3.1 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. 72.

12. CONCLUSION

Since past decades, considerable amount of research work has been proposed in the area of colon targeting. There are specific advantages and limitation for the system as mentioned earlier for the targeting drugs, specifically to the diseased colon are minimizing incidence of systemic side effects, lower dose of drug, delivery of the drug only when it is required and
holding of the dosage form in its intact form as close as possible to the target site to give maximum concentration drug.

The novel approaches are more effective compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially activated system and others. Different polymers natural and synthetic are used to prepare CDDS by various approaches and are evaluated for their efficiency and safety.

As concern to the evaluation there is no such standardized dissolution method established for possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, but still x-ray studies and gamma sintagrophy is the effective tool till date to correlate in-vitro/in-vivo data.

REFERENCES


