Emerging Techniques and Challenges in Colon Drug Delivery Systems

Gurmeet Singh, Dinesh Kumar, Mankaran Singh, Deepak Sharma and Sukhibir Kaur

ABSTRACT

Colon specific drug delivery has achieved utmost importance because the colon is an area that is vulnerable to a number of diseases including ulcerative colitis, crohn’s disease, irritable bowel syndrome and carcinomas. And, preservation of formulation in upper GIT to colon is still important step. Treatment of these diseases with a colon-specific drug delivery system provides an interesting alternative over systemic drug administration because of lower dosing and fewer systemic side effects. Different challenges are associated with this delivery system like long transit time, enzymatic interference, intersubject variation of microflora etc. A variety of under clinical and commercially available approaches were designed for remediation of colonic ailments. Different dosage forms like tablets, capsules, pellets, multiparticulates, microspheres, liposome, nanoparticulates etc. were used for colon targeting. The present review article mainly focused on different approaches, mainly on formulation, carrier system and/or coating system, bioactive stability, patient compliance and evaluation of colon specific drug delivery system.

Keywords: Colon, pH, Microflora, Polymers, Approaches.

INTRODUCTION

The oral route is considered to be most convenient for the administration of drugs to patients. Oral delivery of drugs to the colon is valuable in the treatment of colon diseases (ulcerative colitis, crohn’s disease, carcinomas and infections) whereby high drug concentration can be achieved while minimizing side effect that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery (Kaushik et al., 2009).

As colon is the distal segment of the large intestine, hence targeting the drug to the colon is very problematic, so the rectal route can also be used for the colon delivery but it has some limitations of limited transit of the drug in the intestinal passage. Moreover the rectal route is not easy and unacceptable by the patient. So the oral route is most preferred. Colon targeted drug delivery is an example of controlled drug delivery system.
This system focused mainly on site specificity via release of bioactive drug in colon and absorption from the same. Colon targeted drug delivery differs from ordinary enteric coating (that are designed to merely avoid drug release in the stomach) in that the tablet or capsule is specially formulated to channel greater quantity of drug release to the colonic compartment, thus preventing or reducing drug release until the dosage form reaches the colon. Although the large intestine is difficult to access through per oral delivery it is still favored as the appropriate site to tackle local colon related diseases (Obitte et al., 2010).

Colon as a site offers distinct advantages on account of:
- Near neutral pH
- Much longer transit time
- Reduced digestive enzymatic activity
- Greater responsiveness to absorption enhancers

The colon is a site where both local and systemic drug delivery can take place. It is also preferred as an absorption site for oral administration of peptides drugs, because of the comparatively less hostile environment and low proteolytic enzyme activities in the colon (Devi et al, 2010). A variety of drugs can be used to counteract colon diseases endowing different site actions (as shown in the Table 1) (Reddy et al., 1999).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Target Sites</th>
<th>Disease Conditions</th>
<th>Drug and their active ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Topical action</td>
<td>Inflammatory Bowel Diseases, Irritable bowel disease and Crohn’s disease. Chronic pancreatitis</td>
<td>Hydrocortisone, Prednisolone, Sulfasalazine, Olsalazine, Mesalazine</td>
</tr>
<tr>
<td>2</td>
<td>Systemic action</td>
<td>To prevent gastric irritation To prevent first pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines</td>
<td>NSAIDS Steroids Insulin Typhoid</td>
</tr>
<tr>
<td>3</td>
<td>Local action</td>
<td>Pancreactomy and cystic fibrosis, Colorectal cancer</td>
<td>Digestive enzyme supplements 5-Flourouracil.</td>
</tr>
</tbody>
</table>

Table 1: Targeting diseases, drugs and sites for colon

Colonic micro flora & their enzymes

Drug release in various parts of GIT depends upon the presence of intestinal enzymes, gut juices and gut microflora. These enzymes are used to degrade coatings/matrices as well as to

Colon as a site offers distinct advantages on account of:
- Near neutral pH
- Much longer transit time
- Reduced digestive enzymatic activity
- Greater responsiveness to absorption enhancers

The colon is a site where both local and systemic drug delivery can take place. It is also preferred as an absorption site for oral administration of peptides drugs, because of the comparatively less hostile environment and low proteolytic enzyme activities in the colon (Devi et al, 2010). A variety of drugs can be used to counteract colon diseases endowing different site actions (as shown in the Table 1) (Reddy et al., 1999).

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

Colon act as Black-box of the body and site specificity is difficult task. Various factors to be considered for designing colon specific drug delivery.

Anatomy and physiology of the colon

Colon is divided into the cecum, ascending colon, transverse colon, rectum and anal canal (as shown in the Fig. 1). The cecum has a dilated portion, which is blinded interiorly and is continuous with the ascending colon superiorly. Ascending colon passes upwards from the cecum to the level of the liver where it bends acutely to the left at the right colic flexure to become transverse colon. The transverse colon, that extends across the abdominal cavity, in front of the duodenum and the stomach to the area of the spleen. The descending colon passes down the left side of the abdominal cavity then bends towards the midline. Pelvic colon describes an S-shaped curve in the pelvic, then continuous downwards to become the rectum (Ross and Wilson, 2010).

Colon consists of layer of tissues, i.e. the longitudinal muscle fiber, sub mucous layer, mucous membrane lining. Arterial Blood supply in the colon is mainly by superior and inferior mesenteric arteries and venous drainage is mainly by the superior and mesenteric vein (Wasnik and Parmar, 2011).

Physiologically, the human colon can be divided into three functional areas,
- The transverse colon, the motor patterns of which may hold material in the proximal colon or propel it distally but that may also be an important site for the absorption of water and the rectum,
- Proximal colon acts as a reservoir for fecal material and allows defecation to be delayed until socially convenient.
- The cecum and proximal colon, which act as a fermentation chamber (Kothawade et al., 2011).
break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug) resulting in the drug release from the formulation. Almost 400 distinct bacterial species have been found, out of which 20% to 30% are of the genus Bactericidae. The upper region of GIT consists of very small number of bacteria and predominantly gram-positive facultative bacteria. The concentration of bacteria in the human colon is around 1000 CFU/ml. The most important anaerobic bacteria’s are Bactericidae, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium, and Clostridium (Guarner and Malagelada, 2003).

pH in the colon

The pH is different in the GI tract starting from oral cavity to the large intestine (as shown in the Table 3) (Kumar et al., 2009 & Patel et al., 2011). The pH changes appear in stomach, small and large intestine, because of presence of different factors such as diet, food intake, intestinal motility and disease states. This variability in the GIT pH makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand these changes. The colonic drug delivery uses this variation in pH along the GIT to target the drug. The pH gradient in GIT range from 1.2 in the stomach, 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. The right, mid, and left colon have pH values approximately 6.4, 6.6 and 7.0 respectively. The pH of the colon is often lower than the pH of the small intestine, which is as high as 8 or 9.20. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids produced by bacterial fermentation of polysaccharides. This fall in pH has to be targeted to deliver the drug to the small intestine by the way of pH-sensitive enteric coatings (Kothawade et al., 2011).

Table 3: Average pH in the GIT.

<table>
<thead>
<tr>
<th>Portion of GI Tract</th>
<th>pH Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>6.2-7.4</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>5.0-6.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>Fasted condition: 1.5-2.0  Feed condition: 3.0-5.0</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Jejunum: 5.0-6.5  Ileum: 6.0-7.5</td>
</tr>
<tr>
<td>Large intestine</td>
<td>Right colon: 6.4  Mid colon and left colon: 6.0-7.5</td>
</tr>
</tbody>
</table>

Motility

Studies of colonic motility, in vivo, usually on measurement of changes in muscle electrical activity that may determine contractions. Manometer measure changes in colonic pressure caused by contractions and/or strain gauge measure contractions more directly. All approaches provide useful information but when used separately may not give a complete picture of colonic motor events. Electrical activity may not produce measurable contraction and manometric techniques can only detect contractions that occlude the lumen sufficiently to register as an increase in pressure. In vitro measurements using strips or segments of colon may suggest mechanisms and patterns of electrical and motor activity, but their role must be assessed in vivo in an intact colon with enteric and autonomic nervous system (ANS) and central nervous system (CNS) connection maintained. Since in vivo studies in human involve intubations and often bowel cleansing (sometimes with cathartics that may sensitize the colon), it is difficult to assess whether the same patterns would be seen without the invasive tubes and with a colon full of chemically and mechanically stimulating content (Wasnik and Parmar, 2011).

DIFFERENT APPROACHES USED FOR COLON TARGETING

- Prodrug approaches
- Probiotic approaches
- Hydrogel approaches
- pH-Dependent system
- Time dependent
- Microbially triggered system
- CODES technologies
- Osmotic controlled drug delivery system
- PULSINCAP System
- Port system
- Time clock system
- Chronotropic system
- COLAL-PRED system
- Pressure controlled drug delivery
- Multiparticulate approaches
- Pulsatile colon delivery
- Nanoparticulate system

Prodrug approach

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires biotransformation in vivo to release the active drug from the carrier. The enzymes like azoreductase, galactosidase, xylosidase, nitroreductase, glycosidase and deaminase are mainly targeted for colonic drug delivery (Kothawade et al., 2011 & Modasiya et al., 2011 & Patel et al., 2011). Prodrug targeted drug delivery system include three components: a drug, a carrier, targeting moiety. This approach shows promising results in the colon drug delivery system as it minimize absorption of active drug from the upper GI tract (Challa et al., 2011). A variety of carriers and materials used in the formulation of colon drug delivery system are Azo bond conjugates, amino acid (polypeptide) conjugates, cyclodextrin conjugates, dextrin conjugates, polymeric conjugates, glycoside conjugates, glucuronide conjugates and sulphate conjugates (Vemula and Veerareddy, 2009). Vemula and Veerareddy prepared cyclodextrin prodrugs by conjugating 5-ASA on to the hydroxyl groups of α-, β-, γ-cyclodextrins through an ester linkage and investigated the release in cecum and colon. In animal studies, they administered the same conjugate to rats and found that the conjugate passed through stomach and small intestine without degradation or absorption and in the cecum and/or colon site-specific degradation of conjugate released 5-ASA. The same approach was assessed as Azo conjugation. In this, azo conjugates...
were prepared by conjugation of sulphapyridine and 5-amino salicylic acid(ASA) through an azo linkage and investigated the release in the colon, after oral administration in human then site specific with lot of side effects associate with sulphapyridine and delivers two molecules of 5-ASA was compared to Sulphasalazine respectively (Rangasamy, 2010). Taurine conjugation of 5-ASA was assessed and found beneficial (Wasnik and Parmar, 2011). But this delivery system has certain limitations like drug delivery is incomplete and irregular (Koteshwara et al., 2011).

**Probiotic approach**

The Probiotic approach is one of the latest approach for colon targeting. In this approach, three components are desirable namely probiotic strain, microbially digestable carrier and triggering temperature. Probiotic strains include inactive microflora like Bifidobacterium and Lactobacillus species. At body temperature, these strains triggered to be active and start digesting the carrier and ultimately release the drug at desired place. This approach gain success in colon drug delivery system because these conditions are only available in colon. Ghosh et al. performed this approach for diclofenac sodium using guar gum as the carrier in matrix tablets. They gained success as the formulation containing probiotics show better release of drug than drug alone in carrier (Ghosh et al., 2010).

**Hydrogel approach**

Hydrogels incorporating drugs was also found to be used as oral colon drug delivery devices. Many studies show that this system has significant potential. Various type of hydrogel based CDDS were reported by different researchers. These are of three types, namely azo cross-linked, alcohol cross-linked and aldehyde cross-linked hydrogels. Azo hydrogels produced colon specificity by mutual involvement of pH sensitive monomers and azo cross-linking agents. This synthetic approach for colon targeting can be obtained by cross-linking polymerization of N-substituted (meth)acrylamides, N-tert-buty lacrylamide and acrylic acid with 4,4’-di (methacryloylamino) azobenzene (Kothawade et al., 2011) and N- N’-methylene bisacrylamide (Bajpai and Sonkusley, 2002). The hydrogels were also prepared by polymer–polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH2 groups. (Kothawade et al., 2011) Glutaraldehyde was found to be model candidate from aldehyde family to be used as cross-linker for various polymer system. Glutaraldehyde cross-linked dextran capsules of Hydrocortisone were prepared by Bronzed et al., 1998. Also Glutaraldehyde cross-linked guar gum hydrogel discs of ibuprofen were prepared by Adit et al., 2006. They used different concentration of glutaraldehyde and chose optimum for controlled swelling of guar gum. These cross-linked fabricated hydrogel systems was proved to be beneficial for colon specific drug delivery system. Poly vinyl alcohol has its own cross-linking property which was proved in many experiments. In the studies of Orient et al, he mentioned that PVA was used to cross link succinyl, adipoyl and sebacoyl chloride to get hydrogel foaming polymers (Vemula and Veerareddy, 2009).

**pH-dependent**

During fasting the pH range of the stomach is in between 1-2 but on eating its increases. The pH of proximal small intestine is about 6.5 and in the cecum are about 6.4. However, pH values as low as 5.7 has been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and in the descending colon 7.0 (Koteshwara et al., 2011). Colon targeted drug delivery systems based on meth acrylic resins has described for insulin, prednisolone, quinolones, cyclosporine, salsalazine, beclomethasone dipropionate and naproxane (Modasiya and Patel, 2011). The principle in this method is the coating of the tablets/pellets etc with various pH sensitive polymers (Eudragit L-100, Eudragit S-100, Eudragit L-30D, Eudragit L-100-55, Eudragit FS 30D, Poly Vinyl Acetate Phthalate, Hydroxy Propyl Methyl Cellulose Phthalate 50, Hydroxy Propyl Methyl Cellulose Phthalate 55, Hydroxy Propyl Ethyl Cellulose Phthalate, Cellulose Acetate Phthalate, Cellulose Acetate Trimellitate) which will produce delayed release and also give protection from gastric fluids (Vemula and Veerareddy, 2009). These different polymers having different threshold pH and according to that release the drug at same pH (as shown in the Table 4). Mostly the Eudragit L and S are used for the preparation of colon drug delivery, these dissolved at the pH of 6 and 7 respectively (Koteshwara et al., 2011). The decrease in the pH from the end of the small intestine to the colon have many problems like increases lag times at the ileocecal junction or fast elimination through the ascending colon, which can affects poor site specificity of the single unit formulation (Philip and Philip, 2010). Several factors affects the formulation, such as combinations of different polymers, pH of the media, coating level of the tablets and presence of plasticizers, influence the dissolution rate of Eudragit® (Challa et al., 2011).

| Table 4: Table showing different pH sensitive polymers and their threshold pH release. |
|---|---|---|---|
| S. No. | Polymer | Threshold pH | Reference |
| 1 | Eudragit S-100 | 7 | Akhtar et al., 2005 |
| 2 | Eudragit L-100 | 6 | Huang et al., 2008 |
| 3 | Eudragit FS 30D | >7 | Girhepunje et al., 2010 |
| 4 | Eudragit RS 100 | <6 | Jain and Singh, 2010 |
| 5 | Eudragit L 30D | 5.6 | Sinha and Kumria, 2003 |
| 6 | Eudragit L100-55 | 5.5 | Semde et al., 2000 |
| 7 | Hydroxy propyl methyl cellulose phthalate | >5.5 | Osorio et al., 2011 |
| 8 | Shellac | 7 | Singh, 2007 |
| 9 | Hydroxy propyl ethyl cellulose phthalate | 5.2 | Semde et al., 2000 |
| 10 | Hydroxypropylmethyloxycelulose acetate succinate (HPMCAS) | >5.5 | Singh, 2007 |
| 11 | LF Grade | >5.5 | MFC Grade |
| 12 | MF Grade | >6.0 | HFC Grade |
| 13 | HF Grade | >6.8 | |
The coating specify the release of bioactives, depending on the type of coating material and size of dosage form like granules and tablets (Asghar et al., 2006). Eudragit S coated 5-aminosalicylic acid (5-ASA) anti-inflammatory drug have been used to target the large intestine. Eudragit L coated 5-ASA have been used to target on the colon to cure ulcerative colitis or Crohn’s disease (Koteshwara et al., 2011). Film coated tablets of 5-ASA were prepared and coated with Eudragit RS, pectin, polygalacturonic acid, or its potassium and sodium salts. Negligible drug release occur during first five hours were the coated tablet in stomach and small intestine (Wasnik and Parmar, 2011). A comparative study of the enteric-coated polymers like Eudragit, Cellulose acetate phthalate with Shellac and Ethyl cellulose as carrier for colon specific drug delivery was also established (Vemula and Veeraredddy, 2009). Polymers alone and in combination showed their potential with different drugs (as shown in the Table 5).

The polypeptide hormone vasopressin and insulin have been administered to rats orally in Eudragit S coated Single unit capsules. Eudragit S-coated insulin capsules have also been administered orally to hyperglycemic beagle dogs. In the latter study, it was concluded that plasma glucose levels were lowered gradually and reproducibly but that delivery by means of the oral route was not bioequivalent to delivery by means of parenteral route (SC) (Rajguru et al., 2011).

Table 5: pH dependent polymers used for various drugs.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Polymer Used</th>
<th>Drug used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eudragit L100 and S100</td>
<td>Mesalamine,</td>
<td>Khan et al., 1999</td>
</tr>
<tr>
<td>2</td>
<td>Eudragit L100 and S100</td>
<td>Flurbiprofen</td>
<td>Najmuddin et al., 2010</td>
</tr>
<tr>
<td>3</td>
<td>Eudragit L100 and S100</td>
<td>Diclofenac sodium and 5-ASA</td>
<td>Cheng et al., 2004</td>
</tr>
<tr>
<td>4</td>
<td>Eudragit S, Eudragit FS, And Eudragit P413SF</td>
<td>Prednisolone</td>
<td>Basit and Bloor, 2003</td>
</tr>
<tr>
<td>5</td>
<td>Eudragit L30D-55 and Eudragit FS 30D</td>
<td>Paracetamol</td>
<td>Davis et al., 1991</td>
</tr>
<tr>
<td>6</td>
<td>Eudragit RS 100</td>
<td>5-Fluorouracil</td>
<td>Gupta et al., 2010</td>
</tr>
<tr>
<td>7</td>
<td>Eudragit RS 100</td>
<td>Paracetamol</td>
<td>Mishra et al., 2011</td>
</tr>
<tr>
<td>8</td>
<td>Eudragit L100</td>
<td>Ibuprofen</td>
<td>Patel et al., 2011</td>
</tr>
<tr>
<td>9</td>
<td>Eudragit RS 100</td>
<td>Dicyclomine</td>
<td>Jain and Singh, 2010</td>
</tr>
<tr>
<td>10</td>
<td>Eudragit S 100 and Eudragit L100</td>
<td>Indomethacin</td>
<td>Akhgar et al., 2005</td>
</tr>
</tbody>
</table>

Time dependent approach

In this approach, the basic principle is the release of the drug after a predetermined lag time from dosage form at the site of action at right time and in right amount (Wasnik and Parmar, 2011). Both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine, that can be unaffected by particle size, density or composition of the meals, because the time taken to leave the formulation to the stomach was not predicted (Rajguru et al., 2011). Ideally, formulation was to be designed that are not affected by the individual difference in gastric emptying time, pH of the stomach, small intestine or presence of anaerobic bacteria in the colon at the site of delivery (Sharma and Jain, 2010). In this formulation is comprised of three parts first a center core containing a drug and swelling excipients, secondly an inner semi-permeable polymer membrane containing a plasticizer which allow water influx but prevents the outward diffusion of drug and finally an outer enteric-coating which dissolves above pH 5.5 (Kumar et al., 2011). 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. Colon drug delivery system of diclofenac sodium (DS) was developed using time dependent approach. In this, diclofenac sodium tablets were coated with ethyl cellulose in ethanol solution cooling diethyl phthalate as a plasticizer and PEG 400 as channeling agent. The lag time of DS release was primarily controlled by thickness of ethylcellulose coating layer. By increasing the thickness of the coating layer, longer the lag time of DS release (Wasnik and Parmar, 2011).

Hydroxy Propyl Methyl Cellulose (HPMC) compression coated tablets of 5-fluorouracil were studied for colon drug delivery that based on time-dependent approach. In this, the core tablet was prepared by wet granulation method and then coated with 50% of HPMC / lactose coat powder by compression-coating method. Drug release characteristics were evaluated in distilled water by using a Chinese pharmacopoeia rotatable basket method (Wasnik and Parmar, 2011).

Time dependent polymers are mostly cellulose based and showed their potential in different studies incorporating drugs in them (as shown in the Table 6). However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability (Challa et al., 2011).

Table 6: Time dependent polymers used for various drugs.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Polymers Used</th>
<th>Drug Used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydroxy propyl methyl cellulose</td>
<td>Pseudoephedrine HCl</td>
<td>Halsas et al., 2001</td>
</tr>
<tr>
<td>2</td>
<td>Hydroxyethyl cellulose, Ethyl</td>
<td>Theophylline</td>
<td>Rao and Diwan, 1998</td>
</tr>
<tr>
<td>3</td>
<td>Cellulose, Microcrystalline cellulose Lactose/behinic acid</td>
<td>Indomethacin</td>
<td>Nykanen et al., 1999</td>
</tr>
<tr>
<td>4</td>
<td>Hydroxy propyl methyl cellulose</td>
<td>NS</td>
<td>Rao and Diwan, 1998</td>
</tr>
<tr>
<td>5</td>
<td>Hydroxy propyl methyl cellulose acetate succinate</td>
<td>Diltiazem HCl</td>
<td>Fukui et al., 2001</td>
</tr>
</tbody>
</table>

Microbial triggered approach

The basic principle involved in this method is degradation of coated polymers on the drug delivery system by microflora present in colon and release of drug in colonic region (Sinha and Kumaria, 2003). The microflora of the colon is in the range of 1011-1012 CFU/ml consisting mainly of anaerobic bacteria, e.g. Bacteroides Bifidobacterium, Euabacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc (Vassallo et al., 1992). This approach is different from probiotic
approach because in probiotic approach, we are providing microflora from external source which assist the interior flora. Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as excipients in drug formulations or are constituents of the human diet and are therefore generally regarded as safe. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems (as shown in the Table 7), such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amyllose, sodium alginante and locust bean gum (Hovgaard et al., 1996 & Sinha et al., 2001).

Table 7: Microbial Triggered based polymer for various drugs.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Polymers Used</th>
<th>Drug Used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chitosan</td>
<td>Diclofenac Sodium</td>
<td>Lorenzo-Lamosa et al., 1993</td>
</tr>
<tr>
<td>2</td>
<td>Chitosan</td>
<td>Budesonide</td>
<td>Liu et al., 2007</td>
</tr>
<tr>
<td>3</td>
<td>Pectin</td>
<td>Indomethacin</td>
<td>Rubinstein et al., 1993</td>
</tr>
<tr>
<td>4</td>
<td>Guargum</td>
<td>5-Fluorouracil</td>
<td>Kaushik et al., 2009</td>
</tr>
<tr>
<td>5</td>
<td>Guargum</td>
<td>Dextemethasone</td>
<td>Beirner, 1999</td>
</tr>
<tr>
<td>6</td>
<td>Chondrotin</td>
<td>Indomethacin</td>
<td>Heidenh et al., 1999</td>
</tr>
<tr>
<td></td>
<td>Sulphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Amylose</td>
<td>5-Acetyl Salicylic Acid</td>
<td>Cole et al., 2002</td>
</tr>
<tr>
<td>8</td>
<td>Sesbania gum</td>
<td>Metronidazole</td>
<td>Patel et al., 2011</td>
</tr>
<tr>
<td>9</td>
<td>Guargum</td>
<td>5- Amino Salicylic acid</td>
<td>Rajakukhmi, 2011 and</td>
</tr>
</tbody>
</table>

CODESTM

This technology was introduced to avoid viscerocolonic problems associated with time or pH. CODESTM is a combinational approach of microbially triggered and pH dependent CDDS. It has been developed for the site specific release in the colon by utilization of a unique triggered mechanism involving lactulose. In this system, lactulose is incorporated in the core, followed by coat of Eudragit E which is acid soluble in nature and then subsequently overcoated with an enteric material, Eudragit L. Outermost coat of Eudragit L protect the ultimate tablet to be dissolved in gastric fluids and former Eudragit protects the preparation as it passes through the alkaline pH of the small intestine. Microbial triggered degradation of lactulose starts when the tablet arrives in the colon. When polysaccharides (lactulose) dissociated into monosaccharides (organic acids) the pH surrounding the system get lower down makes favorable dissolution of the acid soluble coating and subsequent drug release (Kothawade et al., 2011).

Osmotic controlled drug delivery (ORDS-CT)

A novel CDDS was introduced by Alza Corporation, to target the drug locally to the colon, which is known as OROS-CT. The OROS-CT system include either single osmotic unit or upto 6 push pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. In this system a semi permeable membrane surrounds both osmotic push layer and drug layer. Next to the drug layer orifice is drilled through the membrane. The push-pull unit was dissolved after the OROS-CT is swallowed in the gelatin capsule. Because of the enteric coating of the impermeable drug, there is no drug release in the stomach due to push-pull unit prevents the absorption of drug in the acidic environment. As the push pull unit enters to small intestine, the coating of the drug was dissolved at the higher pH like greater than 7, the osmotic push compartment swell due to the absorption of the water into the unit, and creates a gel in the drug compartment. That gel was released by swelling of the osmotic push unit, by controlling of the rate of water through the semi permeable membrane. This push-pull system was designed for treating ulcerative colitis with a 3-4 h post gastric delay, to prevent drug delivery in the small intestine. OROS-CT units can deliver the drug into the colon for a short period of four hours and to maintain a constant release rate for up to 24 hours. That was the new idea to deliver the drug in colon, and many stability studies, in-vitro/in-vivo evaluation can performed in CDDS (Rangasamy, 2010).

PULSINCAP System

This technique was introduced by R.R.Scherer International Corporation, Michigan, US, to target a water insoluble capsules. This formulation possess seal coat with swellable hydrogel plug to enclosing the drug reservoir into the capsule body. At particular lag time, capsule was come to in contact with dissolution fluid, swelling take place and drug release rapidly. The different grade and viscosity of polymers was used to design the hydrogel plug, that includes polymethyl methacrylate, hydroxyl propyl methyl cellulose, poly vinyl acetate and poly ethylene oxide. The lag time of the Pulsincap capsule was controlled by the length and point of insertion of the plug, that was studied in human volunteers (Rangasamy, 2010).

PORT system

This technique was introduced by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of insoluble plug of drug and osmotically active agent coated with a semi permeable membrane of the capsule. System used to delivered methylphenidate to school age children and shows good in-vivo and in-vitro correlation in humans for the treatment of attention deficit hyper activity disorder (ADHD) (Kothawade et al., 2011).

Time clock system

In this technique, an aqueous dispersion is used for coating of the solid dosage form. In this coating is a hydrophobic surfactant layer to which a water soluble polymer is added to improve adhesion to the core. The rehydration of the system results when it comes in contact with dissolution fluid, and redisperses also. In this system, the lag time could be controlled by proportional varying the thickness of the coating material. The effect on the lag time may be different in high calorie and low calorie meal, that was studied by using gamma scintigraphy. The mean lag time of the drug release was 5.5 and 5.7 hours respectively (Rangasamy, 2010).

Chronotropic system

In this technology a drug release after a particular lag time that is surrounding with a soluble barrier layer, which consists of
a core containing drug reservoir coated by a hydrophilic polymer HPMC. The coating of additional enteric coating film outside that layer to overcome the gastric emptying variability and lag time of the drug was controlled by coating thickness and viscosity grade of the HPMC (Rangasamy, 2010).

**COLAL-PRED system**

COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis (US). It has arisen from combining Alizyme’s proprietary colonic drug delivery system, COLAL, with an approved generic steroid (Prednisolone sodium metasulfobenzoate). It is an effective anti-inflammatory treatment for UC without the typical side effects of steroids. There are currently no competitor products, either on the market or under development, with the same profile of product. A ‘Safe steroid’ product with the profile of COLAL-PRED would represent a significant advance in the management of UC. COLAL-PRED has a coating that is broken down only in the colon, by locally occurring bacteria. This leads to topical delivery of prednisolone to the colon without significant systemic exposure so minimizing steroid related side effects (Kothawade et al., 2011).

**Pressure controlled drug delivery system**

Peristaltic movements of intestines along with gastric contractile activity are responsible for the propulsion of intestinal contents. These peristaltic movements constitute elevated luminal pressure conditions in the colon. The design of pressure controlled drug delivery system is based upon above mechanism. Intensity and duration of this pressure varies with the muscular contractions in the visceral organs (Sharma and Jain, 2010 & Kumar et al., 2011). It consists of a capsule shaped suppositories coated with the water insoluble polymer like ethyl cellulose (EC). Once taken orally, they behave like balloon of ethyl cellulose because the base of the capsule was liquefy at the body temperature (Koteshwar et al., 2011 & Kothawade et al., 2011). The thickness of the ethyl cellulose membrane play a very vital role in the disintegration of the capsule. The size and density of the capsule may also affects the system. The preferred thickness of the capsule wall is about 35-60 µm. The viscosity of the luminal content is higher in the colon than the small intestine, because of re-absorption of water from the colon, so that drug dissolution in the colon could present a problem for colon-specific oral drug delivery system. When the pressure controlled capsule was administered to human volunteer, the lag time of three to five hours in relation of drug absorption were noted. And, found that disintegration of capsule achieved as the luminal pressure hikes. (Challa et al., 2011 & Patel et al., 2011 & Rajguru et al., 2010).

**Multiparticulate approach**

Multi particulate approach tried for colon delivery include formulations in the form of pellets, granules and microparticles. Researchers developed biodegradable colon targeted multi particulate system by using guar gum. In that study, the drug loaded pellets were coated with aqueous guar gum slurry and after in vitro evaluation the drug release after 4.5 h lag time in presence of enzyme and lag time increases in absence of enzyme which indicates the enzyme triggered system for colonic release. Multi particulate system has also be used for colon targeting (Hardy et al., 1991 & Mohapatra et al., 2011).

**Pulsatile colon delivery**

Pulsatile drug delivery systems (PDDS) can be classified in site-specific and time-controlled systems (as shown in the Fig. 2). Drug release from site-specific systems depends on the environment in the gastrointestinal tract, e.g., on pH, presence of enzymes, and the pressure in the gastrointestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers (Gothoskar et al., 2004 & Shivakumar et al., 2003).

![Fig. 2: Types of Pulsatile Drug Delivery System](image)

**Nanoparticulate system**

Nanoparticle size 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 (Kreuter, 1991). Nanoparticles have also been investigated for the delivery of protein and peptide drugs (Couvreur and Pursieux, 1993). The use of nanoparticles for bioadhesion purposes have also been investigated. Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of non-specific 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 (Krishnaiah et al., 2003).

**CONCLUSION**

The most critical challenge in oral colon specific drug delivery approach is to preserve the formulation during its passage through the stomach and about six meters of the small intestine. After seeking the limitations of different approaches, researchers invented various novel approaches which act as remedy for the previous ones. Now several approaches have been investigated to
achieve site specificity to colon. The selection of suitable carrier and/or coating system is a critical parameter in the fabrication of colon specific drug delivery. Novel approaches like Probiotic assisted, CODES™, Nanoparticulate system etc. showed significant potential in this area. Also, other having vivid types of advantages in them. These recent advances in CDDS have promoted targeting of drugs and peptides in the treatment and management of major diseases and infections of the colon.

REFERENCES


