REVIEW ARTICLE

NOVEL APPROACHES IN COLON TARGETED DRUG DELIVERY SYSTEMS

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Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. Colonic drug delivery has gained valued attention not just for the targeted delivery and effective therapy of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. A successful and precise colon drug delivery system requires a drug to be protected from the upper gastrointestinal tract and an abrupt release into the optimum site of the colon i.e. proximal colon. This review is an attempt to revise the basic concepts and aspects of colon targeted drug delivery systems and also encompasses an overview of diseases of the colon viz. inflammatory bowel disease (IBD), Ulcerative colitis, Crohn’s disease and colon cancer. Among the different approaches available to achieve targeted drug release to the colon, the use of especially biodegradable polymers holds great promise. The various primary and novel approaches for effective targeting in the colon have also been discussed briefly.

Key words: Colon, Gastrointestinal tract, Crohn’s disease, biodegradable polymers.

INTRODUCTION
Over decades, colon targeted drug delivery systems have been gaining significant attention not just for providing more effective therapy to colon related disease, but also as a potential approach for systemic delivery of therapeutic proteins and peptide drugs (Chourasia and Jain, 2003). It has serious drawbacks in conditions where localized delivery of the drug in the colon is required or in the condition where a drug needs to be protected from hostile environment of the upper region of the gastrointestinal tract (Wasnik and Parmar, 2011). Colon specific drug delivery system should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in the stomach as well as in the small intestine, but the drug only released and absorbed once the system reaches to the colon (Tiwari et al 2010). Colonic delivery offers numerous therapeutic advantages like drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes, are minimally affected in the colon (Gupta et al 2010). In addition of providing more effective therapy for the colon related diseases such as irritable bowel disease including ulcerative colitis and crohn’s disease, amoebiosis, colonic cancer, colon-specific delivery has potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs (Kshirsagar et al 2009), in comparison to other forms of sustained or controlled drug delivery systems (Dahiya and Gupta, 2011; Tripathi et al 2011). Colon is also a potential site for treatment of disease sensitive to circadian rhythms such as asthma, angina, arthritis etc. (Aurora et al 2006). In general, four primary approaches have been proposed for colon-specific delivery namely prodrugs, pH-dependent, time dependent and microflora-activated systems (Yang et al 2002). Most
recently, new colon specific delivery systems are developed. These are pressure controlled colon delivery capsule, CODESTM, osmotically controlled drug delivery system, pulsincap system, time clock system etc. There are some of the diseases and drugs which are generally used for the colon targeting sites as shown in Table 1.

### Table 1. Colon targeting sites, diseases and drugs

<table>
<thead>
<tr>
<th>Targeted sites</th>
<th>Diseases</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical action</td>
<td>Inflammatory bowel syndrome, Crohn’s disease,</td>
<td>Hydrocortisone, Budesonide,</td>
</tr>
<tr>
<td></td>
<td>Chronic pancreatic cancer</td>
<td>Prednisolone, Sulfasalazine</td>
</tr>
<tr>
<td>Local action</td>
<td>Pancreatectomy, cystic fibrosis, colorectal cancer</td>
<td>Digestive enzyme supplements,</td>
</tr>
<tr>
<td>Systemic action</td>
<td>To prevent gastric irritation and first pass</td>
<td>NSAIDS, Steroids</td>
</tr>
<tr>
<td></td>
<td>metabolism</td>
<td></td>
</tr>
</tbody>
</table>

**Rational for the development of oral colon targeted drug delivery**

Rational behind development of oral colon targeted drug delivery is the treatment of local pathologies; chronotherapy (asthma, hypertension, cardiac arrhythmias, arthritis or inflammation); greater responsiveness to the absorption enhancers; less enzymatic activity; site for delivery of delicate drugs (proteins and peptides) and oral delivery of vaccines as it is rich in lymphoid tissue (Patel et al 2008).

**Colonic diseases**

*Inflammatory bowel disease*

Inflammatory bowel disease (IBD) is often localized to specific sites in the gastrointestinal tract (GIT) and comprised of two specific conditions namely ulcerative colitis (UC) and crohn’s disease (CD).

*Ulcerative colitis (UC):*

It is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders such as acute flare-up, diarrhoea, bleeding ulcer, pus discharge etc. It may also be called as colitis or proctitis (Xu et al 2004; Rudolph et al 2001; Kotz, 2005). It is thought to result from a dysregulated mucosal response in the intestinal wall facilitated by defects in the protective barrier function of the intestinal epithelium and the mucosal immune system.

*Crohn’s disease (CD):*

It differs from ulcerative colitis because it causes deeper inflammation within the intestinal wall. There is discontinuous distribution of lesions and may involve any part of GIT from oral cavity to colon. It is an idiopathic, relapsing chronic inflammatory disease also called as regional enteritis (Sathiya sekaran and Shivbalan, 2006; Prushothaman et al 2010).

*Inflammatory bowel syndrome*

It is characterized by a variable combination of unexplained chronic and recurrent symptoms attributed to intestine, abdominal pain, disturbed defecation (urgency, straining, incomplete evacuation, altered stool form and frequency) and bloatedness (Singh et al 2003).

*Colorectal cancer*

It results from an accumulation of mutation in tumor suppressor genes and oncogenes. Colorectal cancer is the second leading cause of cancer death in the United States and progresses through a series of clinical and histopathological stages ranging from single crypt lesions through small benign tumors (adenomatous polyps) (Michor et al 2005).

**Approaches used for site specific drug delivery to colon**

*Primary approaches for CDDS*

*Microbial triggered colon targeted drug delivery system:*

The human colon is a dynamic and ecologically diverse environment containing over 400 distinct species of bacteria with a population of $10^{11}$ to $10^{12}$ CFU/ml with Bacteroides, Bifidobacterium, Eubacterium, Lactobacillus etc, greatly outnumbering other species (over 60% of total cultivable flora) (Yang, 2008). There are number of factors affecting the GIT microflora such as host factors including species, strain and individual differences, redox potential, bile salt, antibodies, age factor, GIT disorder, environmental factors such as diet, drug and bacterial factors such as bacterial metabolites, pH (Vandamme et al 2002).

*Prodrug approach:*

The specific delivery of drug to the colon by prodrug, polymeric prodrug and polymeric system has evoked a great interest in recent
times (Shantha et al 1995). Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery of drugs, prodrugs are designed to minimal absorption and hydrolysis in the tracts of the upper GIT and undergo enzymatic hydrolysis in the colon, thereby releasing the active drug (Philip and Philip, 2010). The prodrugs for colon-specific drug delivery and their performance are summarized in Table 2.

Table 2. Prodrugs for colon-specific drug delivery with their in vitro/in vivo performance

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Drug investigated</th>
<th>Linkage hydrolyzed</th>
<th>In vitro / In vivo model used</th>
<th>Performance of the prodrug conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azo conjugates Sulphapyridine (SP)</td>
<td>5-ASA</td>
<td>Azo linkage</td>
<td>Human</td>
<td>Site specific with a lot of side effects associated with SP</td>
</tr>
<tr>
<td></td>
<td>5-ASA</td>
<td>Azo linkage</td>
<td>Human</td>
<td>The prodrug was site specific with lesser side effects</td>
</tr>
<tr>
<td>Amino acid conjugates</td>
<td>Salicylic acid</td>
<td>Amide linkage</td>
<td>In vitro</td>
<td>Primary location of the hydrolysis of the prodrug was colon and the prodrug was not absorbed from the upper GIT</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>Dexamethasone/ prednisolone</td>
<td>Glycosidic linkage</td>
<td>Rat</td>
<td>Dexamethasone prodrug was site specific and 60% of oral dose reached the cecum. Only 15% of prednisolone prodrug reached the cecum</td>
</tr>
<tr>
<td>Glucuronide conjugates</td>
<td>Budesonide</td>
<td>Glucuronide linkage</td>
<td>Rat</td>
<td>Found to be superior than budesonide itself for treatment of colitis</td>
</tr>
<tr>
<td>Glucuronic acid</td>
<td>Dexamethasone</td>
<td>Glucuronide linkage</td>
<td>Rat</td>
<td>A 30 fold increase in glucuronidase activity was found between distal small intestine and cecum of the normal rat</td>
</tr>
<tr>
<td>Dextran conjugates</td>
<td>Naproxen</td>
<td>Ester linkage</td>
<td>Rabbits</td>
<td>Drug regeneration took place in GIT. The relative bioavailability of conjugates as compare to naproxen taken orally was 62%</td>
</tr>
</tbody>
</table>

Polysaccharides based approach:
The rationale for the development of a polysaccharide based colon delivery system is the presence of large amounts of polysaccharidases in the human colon as it is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. β-D-glucosidase, β-D-galactosidase, amylase, pectinase, xylanase, β-D-xylosidase, dextranase etc (Sinha and Kumria, 2003; 2001; Pawar et al 2011). The bacterial enzymes of colon degrades the carrier polymer and release the contents for localized and systemic absorption through colon (Kumar et al 2009; Singh, 2007). The list of microbially degradable materials is given in the Table 3.

Table 3. Microbially degradable materials used for colonic delivery

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disaccharides</td>
<td>Lactose, Maltose</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Celllobiose, Cyclodextrin, Lactulose</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Alginites, Amylose, Arabinogalactan, Cellulose, Chitosan, Dextran, Galactomannan, Inulin, Karaya gum, Pectin, Starch, Xylan, Xanthan and Tragacanth gum</td>
</tr>
</tbody>
</table>

pH sensitive polymer drug delivery to colon:
pH sensitive drug delivery systems (PSDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance. PSDDS wherein the drug release is controlled primarily by the delivery system. In stimuli induced PSDDS, the release is primarily controlled by the stimuli, such as the pH present in the intestinal tract. The pH range of fluids in various segments of gastrointestinal tract may provide environmental stimuli for responsive drug release (Balamuralidhara et al 2011). Radio-
telemetry shows the highest pH levels (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4±0.6. The pH in the mid colon is 6.6±0.8 and in the left colon 7.0±0.7. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

**Polymers used**
Most commonly pH dependent coating polymers are used such as copolymers of acrylic and methacrylic acid esters which contain low levels of quaternary ammonium groups - Eudragit RS (RS 100), Eudragit RL (RL 100), Eudragit L 100, Eudragit L 100-55 and Eudragit S 100, which dissolves at pH ranges from 5.5-7.0 and hence none of these polymers are suitable to be used alone for coating of dosage forms that would start releasing the drug at pH 6.5 although this has been generally accepted as the desired pH for colon targeted delivery (Khan et al 1999; Liu et al 2010).

**Table 4. Marketed products of pH dependent system**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine</td>
<td>Asacol</td>
<td>Eudragit S coated tablet</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Salofac</td>
<td>Eudragit L coated tablet</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Claversal</td>
<td>Eudragit L coated tablet</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Entocort</td>
<td>Eudragit L coated beads</td>
</tr>
</tbody>
</table>

**Delayed time controlled release system:**
There has always been a controversy about the usefulness of pH dependent polymers for colon targeted delivery due to high pH variability of GI tract. To overcome this problem, time controlled systems are used along with pH dependent systems (Patel et al 2009). Time controlled delivery has been achieved by applying coats onto the drug containing cores which delay the release through different mechanisms or alternatively based on capsule-shaped and osmotic devices (Sangalli et al 2004). Enteric coated time- release press coated (ETP) tablet are composed of three components i.e. a drug containing core tablets (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy- propyl cellulose layer, time release function) and an enteric coating layer (acid resistance function). After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occur (Philip and Philip, 2010).

**New drug approaches for colon targeting**

**Pressure controlled drug delivery system:**
GIT pressure is another mechanism that is utilized to initiate the release of the drug in the distal part of the gut. The muscular contraction of the gut wall generates this pressure which is responsible for the grinding and propulsion of the intestinal contents. The pressure generated varies in the intensity and duration throughout the GI tract while the colon is considered to have higher luminal pressure due to the process that occurs during stool formation. Capsule shells fabricated from a water insoluble polymer such as ethyl cellulose have been used for this purpose (Muraoka et al 1998). The delivery ability of a pressure-controlled colon delivery capsule (PCDC) containing caffeine as a test drug was evaluated after oral administration to healthy human volunteers. These kinds of PCDCs having different thickness of a water insoluble polymer membrane were prepared by coating the inner surface of the gelatin capsule with ethyl cellulose (EC). Biomagnetic measurement system (BMS) are also used to estimate the GI transit characteristics of this system in healthy volunteers. It is found that the capsule reaches at the ascending colon 4 and 5 h after oral administration in two subjects while a model drug - caffeine, was first detected in the saliva of the same two subjects 6 and 5 h following oral administration, respectively (Hu et al 2000). PCDCs were prepared from capsular shaped suppositories, which were spray coated with ethanolic EC and using fluorescein (FL) as model drug and by employing a pharmaceutical coating machine, Hicoater-mini® (Hu et al 1998). All examples stated indicate that PCDCs were able to deliver the drug efficiently to the colon.

**Osmotically regulated drug delivery system:**
A significant milestone in oral NDDS is the development of the osmotic drug delivery system, an innovative and highly versatile drug delivery system. Osmotic drug delivery system (ODDS) differ from diffusion-based system in that the delivery of active agent (s) is driven by an osmotic gradient rather than the concentration of drug in the device (Wang et al
Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. They are also known as gastrointestinal therapeutic system. Alza corporation of the USA was first to develop an oral osmotic pump and still they are leading in this field with the technology named OROS (Malaterre et al 2009). The mechanism of drug release from controlled porosity osmotic pump (CPOP) is represented in Figure 1. Principal oral osmotically driven technologies and designs are summarized in Table 5. Some marketed products of different osmotic systems are given in Table 6 (Gupta et al 2010).

![Figure 1. CPOP tablet before and after dissolution studies (Ajay Babu et al 2010)](image)

**Table 5. Principal oral osmotically driven technologies and designs**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Developer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unitary-core Osmotic pumps</td>
<td>Alza Corp., USA</td>
<td>Single-drug composition compressed as a core surrounded by a semipermeable membrane with a drilled orifice EOP containing agents modifying the drug kinetics, such as</td>
</tr>
<tr>
<td>(i) Osmotic pumps</td>
<td>ADD Technology, CH</td>
<td>(i) a polymer or wax (ii) salts e.g. sodium chloride for salbutamol EOP with highly porous membrane allowing high-drug loading (&gt;75%)</td>
</tr>
<tr>
<td>(a) elementary osmotic</td>
<td>Sun Pharma, India</td>
<td>EOP with incorporated agent for modifying the drug thermodynamic properties (e.g. solubility) such as</td>
</tr>
<tr>
<td>pumps (EOP)</td>
<td>Alza Corp., USA</td>
<td>(i) crystal-habit modifying agents e.g. polymers (ii) complexing agent e.g. β-cyclodextrin (iii) surfactants e.g. sodium laurylsulphate</td>
</tr>
<tr>
<td>‘Standard EOP’</td>
<td>Watson pharm./Andrx.USP</td>
<td>(iv) pH-modifying agent e.g. acid or basic agent EOP surrounded by</td>
</tr>
<tr>
<td>Single composition</td>
<td>Novartis Pharma, CH</td>
<td>(i) an immediate release drug layer (DOEOP) (ii) entering coating (OROS-CT™) EOP containing sodium bicarbonate to promote the drug release</td>
</tr>
<tr>
<td>osmotic tablet (SCOT)</td>
<td>Ranbaxy, India</td>
<td></td>
</tr>
<tr>
<td>Self-emulsified EOP</td>
<td>Shire, USA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alza Corp., USA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supernus Pharm, India</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alza Corp., USA</td>
<td></td>
</tr>
<tr>
<td>Over-coated EOP</td>
<td>Osmodica, Arg.</td>
<td></td>
</tr>
<tr>
<td>Effervescent EOP</td>
<td>Alza Corp., USA</td>
<td></td>
</tr>
<tr>
<td>(b) controlled-porosity</td>
<td>Merck &amp; Co., USA</td>
<td></td>
</tr>
<tr>
<td>osmotic pump (CPOP)</td>
<td>Alza Corp., USA</td>
<td></td>
</tr>
<tr>
<td>‘Standard’ CPOP</td>
<td>Merck &amp; Co., USA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Merck &amp; Co., USA</td>
<td></td>
</tr>
</tbody>
</table>

Table-core surrounded by a membrane that allows the diffusion of the drug CPOP containing agents to modify the drug thermodynamics i.e.
Self-emulsified CPOP

(ii) Multilayer osmotic pumps
Push-pull osmotic pump (PPOP)

Alza Corp., USA

Bi- or tri-layer tablet core composed by a drug layer to disperse the drug and a push-layer which generates a hydrodynamic pressure pushing the drug in one or more passageways PPOP improve to deliver high dose with both a sub-coating of the semi-permeable membrane to avoid drug adhesion

Push-stick osmotic pump (PSOP)

Over-coated PPOP

Muco-adhesive osmotic system (MOTS)

(iii) Capsule-based osmotic pumps
CHRONSET™

Alza Corp, USA

PPOP coated with enteric coating, delivering the drug without (OROS-CT™) or with a special onset (COER-24™)

OSMET™

Pfizer, USA

System specially designed to deliver a bolus (>80% drug within 15 min) for intestinal or colonic absorption of protein or muco-adhesive particles

Asymmetric-membrane osmotic pump
Liquid osmotic system (L-OROS™)

Product name | Active | Design | Dose |
---|---|---|---|
Acutrim | Phenylpropanolamine | Elementary pump | 75 mg |
Alpress LP | Prazosin | Push-Pull | 2.5-5 mg |
Covera HS | Verapamil | Push-Pull with time delay | 180, 240 mg |
Ditropan CR | Oxybutinin chloride | Push-Pull | 5, 10 mg |
Dynacire CR | Isradipine | Elementary pump | 5, 10 mg |
Efidac 24 | Pseudoephedrine | Elementary pump | 60 mg IR, 180 mg CR |
Glucotrol | glipizide | Push-Pull | 5, 10 mg |
Volmax | Salbutamol | Elementary pump | 4, 8 mg |

Table 6. Marketed products of different osmotic systems

Novel colon targeted delivery system (CODESTM): CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. It 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. The system consists of traditional tablet core containing lactulose, which is over coated with acid soluble material, Eudragit E and then subsequently overcoated with an enteric material, Eudragit L (Katsumas et al 2004).

In this technology, the enteric coating protects the tablet whilst 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 reaches at the colon, the lactulose within the tablet core ferments into short chain fatty acids which cause the Eudragit E coating to dissolve. This ultimately leads to the release of the contents of the tablet core in the colon (Fig. 2).

**CONCLUSION**

Since two decades, considerable amount of research work has been carried out in the area of colon targeting. CDDS offers potential therapeutic benefits to patients in terms of both local and systemic treatment. Although the surface area in colon is low compared to small intestine, this is compensated by the markedly slower rate of transit. Various approaches described above are quite promising and further improvements are required to achieve the high bioavailability and safe delivery of drugs to the colon.

**REFERENCES**


