1. INTRODUCTION

1.1 GENERAL

Oral drug delivery system is the most commonly used route for drug delivery due to its ease of administration, better patient compliance, and flexibility in design and development of formulation. The drug delivery to the colon has attracted a lot of attention of the scientist working on oral drug delivery system which is mainly due to the fact that colon is a site where both local and systemic drug delivery can take place (Bussemmer et al., 2001). In recent times, the colon-specific drug delivery systems are also gaining importance for the systemic delivery of proteins and peptide drugs. Due to negligible activity of brush border membrane peptidase activity and less activity of pancreatic enzymes, the colon is considered to be more suitable for delivery of protein and peptide in comparison to small intestine (Lee, 1991; Ikesue et al, 1991).

Besides this low hostile environment, the colonic transit time is long (20-30 h) and the colonic tissue is highly responsive to the action of absorption enhancers (Digenis and Sandefer, 1991; Taniguchi et al, 1980). The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make colon a promising site for the delivery of protein and peptides, oral vaccines, insulin, growth hormone, erythropoietin, interferons and interleukines (Saffran et al, 1988 and 1988a; Mackay and Tomilinson, 1993).

Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed (Wood et al, 1985) and enema solutions can only offer topical treatment to the sigmoid and descending colon (Hardy, 1989). Therefore, oral administration is preferred, but for this purpose, many physiological barriers have to be overcome. Absorption or degradation of the active ingredient in the upper part of the GIT
is the major obstacle and must be circumvented for successful colonic drug delivery.

1.2 COLON-SPECIFIC DRUG DELIVERY SYSTEMS (CDDS)

1.2.1 Factors to be considered in the design of CDDS

Anatomy and physiology of colon

The GIT is divided into stomach, small intestine and large intestine. The large intestine extending from the ileo-caecal junction to the anus is divided into three main parts. These are the colon, the rectum and the anal canal. The colon itself is made up of the caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon. The anatomical features are depicted in Figure 1.1 and Table 1.1. The wall of the colon is composed of four layers: the serosa (exterior coat), the muscularis externa, the submucosa and the mucosa. Lining the lumen of the colon, the mucosa is divided into epithelium, lamina propria and muscularis mucosae. The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon.

*Figure 1.1 Anatomy of human gastrointestinal tract (Friend & Tozer, 1992)*
Table 1.1 Anatomical and physiological features of small intestine and colon

<table>
<thead>
<tr>
<th>Region of gastrointestinal tract</th>
<th>Length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire gastrointestinal tract</td>
<td>500-700</td>
</tr>
<tr>
<td>Small intestine</td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>20-30</td>
</tr>
<tr>
<td>Jejunum</td>
<td>150-200</td>
</tr>
<tr>
<td>Ileum</td>
<td>200-350</td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
</tr>
<tr>
<td>Caecum</td>
<td>6-7</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>20</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>45</td>
</tr>
<tr>
<td>Descending colon</td>
<td>30</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>40</td>
</tr>
<tr>
<td>Rectum</td>
<td>12</td>
</tr>
<tr>
<td>Anal canal</td>
<td>3</td>
</tr>
</tbody>
</table>

Colonic Drainage

The rate of blood flow through the absorptive epithelium is likely to determine the rate of drug absorption from the lumen. Blood flow to the colon is less than to small intestine and the proximal colon receives a more prolific supply than the more distal regions (Edwards CA, 1993). The nature of the drainage from the colon determines the fate of a drug taken up from this region. The drainage from the upper colon appears distinct from that of the more distal regions of the large intestine, where the former is drained by both the hepatic portal veins and the lymphatics and the latter is drained predominantly by the lymphatics (Caldwell et al., 1982). The blood flow rate in humans is 1000-2000 times greater than the rate of lymphatic flow (Kararli TT, 1989) and blood circulation has consequently been considered more significant for drug distribution (Wang W, 1996). However, drugs entering the blood through the hepatic portal vein circulate directly to the liver, where they may undergo rapid biotransformation (hepatic first-pass metabolism) before they are able to act. Introduction of drugs in to the lymphatic, on the other hand, has been considered a means of improving oral bioavailability, because drugs could
potentially passage from the lymphatic in to the blood circulation before reaching to the liver (Ichihashi el al., 1991).

Colonic pH

The pH of the GIT is subjected to both inter- and intra-subject variations. Table 1.2 gives an overview of the pH of the GIT (Wilson and Washington, 1989).

Table 1.2 Average pH in the GIT

<table>
<thead>
<tr>
<th>Location</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>6.2 - 7.4</td>
</tr>
<tr>
<td>Esophagus</td>
<td>5.0 - 6.0</td>
</tr>
</tbody>
</table>
| Stomach          | Fasted condition: 1.5 - 2.0  
                   Fed condition: 3.0 - 5.0 |
| Small intestine  | Duodenum (fasted state): ~ 6.1  
                   Duodenum (fed state): ~ 5.4  
                   Ileum: ~ 7-8                  |
| Large intestine  | Right colon: 6.4 
                   Mild colon and left colon: 6.0 - 7.6  
                   Rectum: ~7                  |

Gastrointestinal transit

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. The transit times of small dosage forms in GIT are given in Table 1.3 which may be affected by intake of food or disease conditions.

Table 1.3 The transit time of dosage forms in GIT

<table>
<thead>
<tr>
<th>Organ</th>
<th>Transit time (h)</th>
</tr>
</thead>
</table>
| Stomach        | <1 (Fasting)     
                   >3 (Fed)         |
| Small intestine| 3 - 4            |
| Large intestine| 20 - 30          |
Volume of ascending colon

Up to 1,500 g of liquids and undigested materials (dietary fibers, resistant starch, partially degraded polysaccharides, proteins, mucins, exfoliated epithelial cells, etc.) enters colon per day, which act as the substrates for microflora fermentation. Water together with the products of the fermentation and other nutrients was efficiently absorbed in the colon, condensing the contents into feaces through the transit in the colon for eventual defecation. Therefore, it is very likely that the ascending colon contains the largest quantity of liquid. The moisture content of caecal contents is believed to be about 86%.

Colonic microflora

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 (Table 1.4). For example, it was reported that Bacteroides, Bifidobacterium and Eubacterium could constitute as much as over 60% of the total cultivable microflora. These bacteria produce a wide spectrum of enzymes that, being reductive and hydrolytic in nature, are actively involved in many processes in the colon, such as carbohydrate and protein fermentation, bile acid and steroid transformation, metabolism of xenobiotic substances, as well as the activation and destruction of potential mutagenic metabolites. The primary source of nutrition for these anaerobic bacteria is carbohydrates such as non-starch polysaccharides (i.e., dietary fibers) from the intestinal chime. Enzymes responsible for the degradation of polysaccharides include $\alpha$-Larabinofuranosidase, $\beta$-D-fucosidase, $\beta$-D-galactosidase, $\beta$-Dglucosidase, $\beta$-xylosidase, with the last three enzymes being the most active.
Table 1.4 The composition of the intestinal flora of four animal species and man [Gruber et al., 1987]

<table>
<thead>
<tr>
<th>Site &amp; test animal species</th>
<th>Stomach</th>
<th>Upper small intestine</th>
<th>Lower small intestine</th>
<th>Large Intestine</th>
<th>Rectum/Feces</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>(3)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>(9)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Rat</td>
<td>(8)</td>
<td>4.1</td>
<td>3.9</td>
<td>6.6</td>
<td>N</td>
</tr>
<tr>
<td>Mouse</td>
<td>(3)</td>
<td>3.1</td>
<td>2.9</td>
<td>8.3</td>
<td>N</td>
</tr>
<tr>
<td>Man</td>
<td>(30)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>(3)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>(9)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Rat</td>
<td>(8)</td>
<td>4.5</td>
<td>4.7</td>
<td>6.7</td>
<td>N</td>
</tr>
<tr>
<td>Mouse</td>
<td>(3)</td>
<td>4.2</td>
<td>4.5</td>
<td>7.7</td>
<td>N</td>
</tr>
<tr>
<td>Man</td>
<td>(30)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>(3)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>(9)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Rat</td>
<td>(8)</td>
<td>4.1</td>
<td>5.0</td>
<td>6.8</td>
<td>N</td>
</tr>
<tr>
<td>Mouse</td>
<td>(3)</td>
<td>3.6</td>
<td>4.8</td>
<td>7.5</td>
<td>N</td>
</tr>
<tr>
<td>Man</td>
<td>(30)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>(3)</td>
<td>3.4</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>(9)</td>
<td>3.2</td>
<td>4.3</td>
<td>4.0</td>
<td>N</td>
</tr>
<tr>
<td>Rat</td>
<td>(8)</td>
<td>5.5</td>
<td>6.0</td>
<td>7.6</td>
<td>N</td>
</tr>
<tr>
<td>Mouse</td>
<td>(3)</td>
<td>5.7</td>
<td>5.2</td>
<td>7.4</td>
<td>N</td>
</tr>
<tr>
<td>Man</td>
<td>(11)</td>
<td>7.0</td>
<td>7.0</td>
<td>6.5</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>(3)</td>
<td>2.3</td>
<td>2.3</td>
<td>4.0</td>
<td>N</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>(9)</td>
<td>2.9</td>
<td>3.1</td>
<td>3.9</td>
<td>N</td>
</tr>
<tr>
<td>Rat</td>
<td>(8)</td>
<td>5.9</td>
<td>6.6</td>
<td>7.8</td>
<td>N</td>
</tr>
<tr>
<td>Mouse</td>
<td>(3)</td>
<td>5.0</td>
<td>4.8</td>
<td>8.1</td>
<td>N</td>
</tr>
<tr>
<td>Man</td>
<td>(30)</td>
<td>6.0</td>
<td>3.5</td>
<td>4.0</td>
<td>N</td>
</tr>
</tbody>
</table>

Mean log. viable count of the stated organisms

1. The number tested is given in brackets.
2. The figures are the mean log. viable count per g wet weight of test material.
3. N = less than 10 organisms per g wet weight of test material.
Microbial Contribution to Carbohydrate Metabolism

Carbohydrates form the bulk of most human and animal diets and thus are critical nutrients for both host and microbiota. Mammals are well equipped to absorb simple sugars such as glucose and galactose in the proximal portion of their small intestine (Ferraris RP, 2001). They can hydrolyze certain disaccharides (e.g., sucrose, lactose, and maltose) to their constituent monosaccharides. They can also degrade starch to glucose monomers but are generally limited in their capacity to hydrolyze and utilize other polysaccharides. Therefore, a large quantity of undigested dietary carbohydrate passes into the distal portion of the gastrointestinal tract each day. This material includes polysaccharides (including cellulose, xylan, and pectin) as well as undigested starch (Figure 1.2). As per this figure, mammals absorb simple sugars, such as glucose and galactose, via active transport in the proximal regions of their small intestine. However, they have limited intrinsic capacity to digest dietary polysaccharides. Undigested polysaccharides such as cellulose, xylan, and undigested starch, as well as host-derived glycans (mucins and glycosphingolipids) pass into the distal regions of the small intestine (ileum) and colon where they are degraded by resident microbes. Bacteria ferment the resulting monosaccharides, and the byproducts of this fermentation (short chain fatty acids) are absorbed and utilized by the host (Wrong et al., 1981).

Figure 1.2 Overview of host and bacterial contributions to carbohydrate utilization in the intestine.
The polysaccharides can be divided into several groups based on their source: microbial, plants, algae and sewage weeds and animals (Table 1.5).

**Table 1.5** Several enzymes together with their potential cleavage sites in different polysaccharides (Park et al., 1993; Shalaby and Park 1994)

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Cleavage sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarase</td>
<td>Hydrolysis of 1,3-β-D-Galactosidic linkage in agarose</td>
</tr>
<tr>
<td>α-Amylase</td>
<td>Hydrolysis of 1,4-α-D-glucosidic linkages containing three or more 1,4-linked D-glucose units</td>
</tr>
<tr>
<td>β-Amylase</td>
<td>Hydrolysis of 1,4-α-linked D-glucosidic linkages from non reducing ends of chains</td>
</tr>
<tr>
<td>κ-Carageenase</td>
<td>Hydrolysis of more 1,4-β-linkages between D-galactose-4-sulfate and 3,6-anhydro-D-galactose in carrageenans</td>
</tr>
<tr>
<td>Cellulase</td>
<td>Endohydrolysis of 1-4-β-D glucosidic linkages in cellulose</td>
</tr>
<tr>
<td>Chitinase</td>
<td>Random hydrolysis of N-acetyl-β-D-glucosaminde 1,4 β-linkages in chitin and chitodextrin</td>
</tr>
<tr>
<td>Dextranase</td>
<td>Endohydrolysis of 1,6-α-D-glucosidic linkages in dextran</td>
</tr>
<tr>
<td>α-Galactosidase</td>
<td>Hydrolysis of terminal, non reducing α-D-galactosidase residues in α-D-galactosides</td>
</tr>
<tr>
<td>β-Galactosidase</td>
<td>Hydrolysis of Terminal, Non reducing β-D-Galactosidase Residues In β-D-Galactosides</td>
</tr>
<tr>
<td>α-Glucosidase</td>
<td>Hydrolysis of terminal, nonreducing 1,4-linked α-D-glucose residues</td>
</tr>
<tr>
<td>β-Glucosidase</td>
<td>Hydrolysis of terminal, nonreducing β-D-glucose residues</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Random hydrolysis of 1,4 linkages between N-acetyl-β-D-glucosamine and D-glucuronic acid residues in hyaluronate and random hydrolysis of 1,3-linkages between N-acetyl-β-D-glucosamine and N-acetyl-D-glucosamine residues in hyluronate</td>
</tr>
<tr>
<td>Inulinase</td>
<td>Endohydrolysis of 2,1-β-D fructosidic linkages in inulin</td>
</tr>
<tr>
<td>Isoamylase</td>
<td>Hydrolysis of 1,6-α-glucosidic branch linkages in glycogen, amylopectin, and their β-limit dextin</td>
</tr>
<tr>
<td>Lysosyme</td>
<td>Hydrolysis of 1,4 β-linkages between N-acetylmuramic acid and N-acetyl-D-glucosamine residues in peptidoglycan and between N-acetyl-D-glucosamine residues in cyclodextrin</td>
</tr>
<tr>
<td>Phosphorylase</td>
<td>Cleavage of α-D-glucose-L-phosphate from the non-reducing end of the amylose molecule.</td>
</tr>
</tbody>
</table>

Monosaccharides released from carbohydrate polymers are converted by bacterial cells to pyruvate via glycolysis, resulting in net production of adenosine triphosphate (ATP) (Figure 1.3).
Monosaccharides released from carbohydrate polymers are converted in the bacterial cytoplasm to pyruvate via glycolysis, which results in net production of ATP. In the highly anaerobic environment of the distal intestine, additional carbon and energy are extracted from pyruvate by microbial fermentation. The predominant end-products of fermentation are acetate, propionate, and butyrate. To recover some of the nutritional value of polysaccharides degraded by gut microbes, mammalian hosts absorb and utilize these short chain fatty acid species.
1.2.2 Drug Candidates for Colonic Drug Delivery

Table 1.6 Criteria for selection of drug for CDDS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Non-peptide drugs</th>
<th>Peptide drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used for local effects in colon against GIT diseases</td>
<td>Diclofenac, Metaprolol, Penaverium bromide, oxyprenolol, Nifedipine</td>
<td>Amylin, Calcitonin, Oligonucleotide, Antisense</td>
</tr>
<tr>
<td>Drugs poorly absorbed from upper GIT</td>
<td>Ibuprofen, Theophylline, Isosorbides</td>
<td>Cyclosporine, Desmopressin</td>
</tr>
<tr>
<td>Drug for colon cancer</td>
<td>Pseudoephedrine, 5-FU, Doxorubicine, Nimustine</td>
<td>Glucagon, Epoetin</td>
</tr>
<tr>
<td>Drugs that are degraded in stomach and small intestine</td>
<td>Bromopheniramine, 5-FU, Aspirin, Iron supplements</td>
<td>Gonadoreline, Insulin</td>
</tr>
<tr>
<td>Drugs that undergo extensive first pass metabolism</td>
<td>Nimustine, Bleomycine, Nicotine</td>
<td>Sermorelin, Saloatoin, Protireline</td>
</tr>
<tr>
<td>Drugs for targeting</td>
<td>5-ASA, Prednisolone, Metronidazole, Hydrocortisone</td>
<td>Vasopressin, Urotoilitin, Somatropin</td>
</tr>
<tr>
<td>Drugs produces intensive side effects when administered orally or IV</td>
<td>Dexamethasone, Prednisolone, Hydrocortisone, Nicotine</td>
<td>-</td>
</tr>
<tr>
<td>Drugs having good absorption properties from colon</td>
<td>Theophylline, Glibenclamide, Oxeprenolol, Ibuprofen, nitredipine, Nisoldipine, Nifedipine</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1.6 represents various criteria for selection of drugs for CDDS.
1.2.3 Strategies for CDDS

Approaches used for CDDS are:

A. Primary approaches for CDDS (Bussemer and Bodmeier, 2003)
   a - pH sensitive polymer coated drug delivery to colon
   b - Delayed (Time controlled release system) release drug delivery to colon
   c - Microbiially triggered drug delivery to colon
      i. Prodrug approach for drug delivery to colon
      ii. Azo-polymeric approach for drug delivery to colon
      iii. Polysaccharide based approach for drug delivery to colon

B. Novel approaches for CDDS (Hita, 1997)
   i. Pressure controlled drug delivery system (PCDCS)
   ii. CODESTM
   iii. Osmotic controlled drug delivery to colon (OROS-CT)

A. Primary Approaches for CDDS

a) pH sensitive polymer coated drug delivery to colon
Table 1.2 revealed that pH varies from 1 to 8 throughout GI transit and it declines significantly from the ileum to the colon (Jung et al., 1998; Chan et al., 1983; Basit and Bloor, 2003). Thus, pH-dependent polymers can be utilized for colon targeting based on these differences in pH levels. The polymers described as pH-dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH-dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve even in the lower small intestine, and the site-specificity of formulations can be poor (Chavan, 2001). The decline in pH from the end of the small intestine to the colon can also result in problems. Lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon can also result in poor site-specificity of enteric-coated single-unit formulations (Chan et al., 1983).
b) Delayed (Time controlled release system) release drug delivery to colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising. However due to potentially large variation of gastric emptying time of dosage forms in humans (Jung et al., 1998), in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonic availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5h (Vandelli et al., 1996).

Disadvantages of this system are:

(i) Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
(ii) Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug (Bussemer and Bodmeier, 2003).
(iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, (Cole et al., 2002), the carcinoid syndrome, diarrhea and the ulcerative colitis (Cummings and Englyst, 1987).

Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases.

c) Microbially triggered drug delivery to colon

The microflora of colon is in the range of $10^{11}-10^{12}$ CFU/mL (Cole et al., 2002), consisting mainly of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and trisaccharides, polysaccharides etc (Cui et al., 1994). For this fermentation the
microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminase, and urea dehydroxylase (Jung et al., 1998). Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches (Chavan, 2001). Biodegradable polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer backbone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer (Davis et al., 1986).

(i) Prodrug approach for drug delivery to colon

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 the prodrug are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the drug carrier. Limitations of prodrug approach is that it is not very versatile approach as it’s formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities and need a lot of evaluation before being used as carriers (Tozaki et al., 1997).

(ii) Azo-polymeric prodrugs

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Semi-synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety (Friend and Chang, 1984). These have been evaluated for CDDS, various azo
polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreductase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group has been found to protect drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced and the drug is to be released (Friend and Chang, 1985).

(iii) Polysaccharide based drug delivery systems

Use of naturally occurring polysaccharides is attracting lot of attention for drug targeting to the colon since these polymers of monosaccharides are found in abundance, have wide availability, are inexpensive and are available in a variety of a structures with varied properties (Friend et al., 1991). They can be easily modified chemically and biochemically and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginites) or microbial (dextran) origin. These are broken down by the colonic microflora to simple saccharides (Fukui et al., 2001). So these fall into the category of “generally regarded as safe” (GRAS). A number of polysaccharides based delivery systems have been outlined in Table 1.7.
Table 1.7 Characteristics of various biodegradable polysaccharides for colon specific drug delivery

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Chemical name</th>
<th>General properties</th>
<th>Bacterial species that degrade polysaccharide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylose</td>
<td>1,4 D – glucose</td>
<td>Used as tablet excipients</td>
<td>Bactericides, Bactericides</td>
</tr>
<tr>
<td>Arabinogalactose</td>
<td>1,4 and 1,3 galactose, 1,6 and 1,3 D – arabinose and D – galactose</td>
<td>Used as thickening agent</td>
<td>Bifidobacterium</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Deacetylated 1,4-N-acetyl – D- glucosamine</td>
<td>Used as an absorption enhancing agent</td>
<td>Bactericides</td>
</tr>
<tr>
<td>Cyclodextrin</td>
<td>1,4 D- glucose</td>
<td>Used as a solubilizing and absorption enhancer</td>
<td>Bactericides</td>
</tr>
<tr>
<td>Chondroitin sulphate</td>
<td>1,3 D- glucoronic acid and N-acetyl – D- glucosamine</td>
<td>Mucopolysaccharides contains various amounts esters of sulphate at 4 or 6 position</td>
<td>Bactericides</td>
</tr>
<tr>
<td>Pectin</td>
<td>1,4 D- galacturonic acid and 1,2 D- rhamnose with D- galactose and D- arabinose side chain</td>
<td>Partial methyl ester, commonly used as thickening agent</td>
<td>Bifidobacterium, Eubacterium</td>
</tr>
<tr>
<td>Dextran</td>
<td>1,6 D- glucose, 1,3 D- glucose</td>
<td>Plasma expanders</td>
<td>Bactericides</td>
</tr>
<tr>
<td>Guar gum</td>
<td>1,6 D- galactose, 1,4 D- mannose</td>
<td>Galactomanan, used as a thickening agent</td>
<td>Bacteroides, Ruminococus</td>
</tr>
<tr>
<td>Xylan</td>
<td>1,4 D- xylose with 1,3 L- arabinose side chain</td>
<td>Abundant hemi cellulose of plant cell wall</td>
<td>Bacteroides, Bifidobacterium</td>
</tr>
</tbody>
</table>

B. Novel approaches for CDDS

a) Pressure-controlled drug delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Researchers’ 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 a 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 (Fukui et al., 2000). The system also appeared to depend on capsule size and density. Because of re-absorption of water from
the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag time was three to five h in relation to drug absorption were noted when pressure-controlled capsules were administered to human (Gazzaniga, 1994).

b) Novel colon targeted delivery system (CODES™)

CODES™ is a unique CDDS technology that was designed to avoid the inherent problems associated with pH-or time-dependent systems. CODES™ is 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 form site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with an acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The promise 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 passage through the alkaline pH of the small intestine. Once the tablet arrives in the colon the bacteria will 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 (Hata, 1994). The schematic of conceptual design of CODES™ is shown in Figure 1.4.
The OROS-CT (Alza corporation) 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 single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule (Figure 1.5). 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 enter the small intestine, the coating dissolve 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 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon.

**Figure 1.4 Schematics of conceptual design of CODES™**

(c) Osmotic controlled drug delivery (ORDS-CT)
colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon. Various in vitro / in vivo evaluation techniques has been developed and proposed to test the performance and stability of CDDS (Hay et al., 1979).

![Cross-section of the OROS-CT colon targeted drug delivery system.](image)

**Figure 1.5** Cross-section of the OROS-CT colon targeted drug delivery system.

### 1.3 BASIS FOR SELECTION OF STRATEGIES FOR CDDS

**Table 1.8** Summary of colon specific drug delivery strategies

<table>
<thead>
<tr>
<th>Design strategy</th>
<th>Drug release triggering mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH-dependent systems</td>
<td>Combinations of polymer with pH-dependent solubility to take advantage of the pH changes along with the GI tract</td>
<td>Unpredictable site specificity of drug release because of inter-intra subject variation and similarity of pH between small intestine and colon</td>
</tr>
<tr>
<td>Time-dependent systems</td>
<td>The onset of drug release is aligned with positioning the delivery system in the colon by incorporating a time factor simulating the system transit in upper GI tract</td>
<td>High variation of gastric retention times makes this approach complicated in predicting the accurate location of drug release. Transit through the colon is more rapid in patients with colon disease than normal</td>
</tr>
<tr>
<td>Prodrugs</td>
<td>Cleavage of the linkage bond between drug and carrier via reduction and hydrolysis by enzymes from colon bacteria.</td>
<td>Product is able to achieve site specificity. However, it will be considered as a new chemical entity from regulatory perspective.</td>
</tr>
<tr>
<td>Microflora-activated systems</td>
<td>Primarily fermentation of non-starch polysaccharides by colon anaerobic bacteria.</td>
<td>This strategy is highly promising because non-starch polysaccharides can only be degraded in the colon.</td>
</tr>
</tbody>
</table>

Table 1.8 summarizes various design strategies for CDDS.
1.4 PROFILE OF POLYMERS

1.4.1 Okra Gum (Agarwal, 2001)

Biological source:

Okra gum is a high molecular weight natural polysaccharide obtained from the fruits of *Albemoschus esculentus (Hibiscus esculentus)*.

General applications:

Okra pods are commonly used in Asia as a vegetable, food ingredient, as well as a traditional medicine for the following:

- As diuretic agent for the treatment of dental diseases and to reduce/prevent gastric irritations.
- Okra powder (fruit) is one of the key ingredients in GASTREX® used to support digestion.
- Syrup from mucilaginous fruit used for sore throat.
- Decoction of young fruit useful for catarrh, urinary problems.
- Mucilage, found in okra, is responsible for washing away toxic substances and bad cholesterol, which loads the liver.
- It has purgative property that would be beneficial for bowel purification.
- Fiber okra is a valuable nutrient for intestine microorganisms which ensures proper intestine functionality.
- Okra ensures recovery from psychological and mental conditions, like anxiety, depression and general weakness.
- Okra is an effective remedy for ulcers and joint healthiness.
- Okra is additionally applied for pulmonary inflammations.
- According to Indian researches, okra is a complex replacement for human blood plasma.
- Okra can be beneficial in treating asthma due to its high vitamin C content.
Okra is highly popular for stimulating the nervous system, thus, being an aid in depressions, anxiety and weakness.

Pharmaceutical applications:

- As a binding/granulating/disintegrating agent in tablet dosage forms.
- As foam stabilizer, thickener and swelling agent in pharmaceutical industries.
- As matrix forming material for preparation of controlled release tablet dosage form.
- As plasma expander and emulsifying agent in disperse system.
- As suspending agent in pharmaceutical suspension.
1.4.2 Guar gum (Rowe et al., 2009)

Guar gum also called guaran is a galactomannan. It is primarily the ground endosperm of guar beans. The guar seeds are dehusked, milled and screened to obtain the guar gum. It is typically produced as a free-flowing, pale, off-white-colored, coarse to fine ground powder.

Chemical structure:

[Chemical structure diagram]

Chemically, guar gum is a polysaccharide composed of the sugars viz. galactose and mannose. The backbone is a linear chain of $\beta 1,4$-linked mannose residues to which galactose residues are $1,6$-linked at every second mannose, forming short side-branches.

General properties:

- In water it is nonionic and hydrocolloidal.
- It is not affected by ionic strength or pH.
- It remains stable in solution over pH range 5-7.
- Strong acids cause hydrolysis and loss of viscosity and alkalies in strong concentration also tend to reduce viscosity.
- It is insoluble in most hydrocarbon solvents.
- It shows high low-shear viscosity but is strongly shear-thinning.
- It is economical because it has almost eight times the water-thickening potency of cornstarch (only a very small quantity is needed for producing sufficient viscosity).
Industrial applications:

- Textile industry – sizing, finishing and printing.
- Paper industry – improved sheet formation, folding and denser surface for printing.
- Explosives industry – as waterproofing agent mixed with ammonium nitrate, nitroglycerin etc.
- Pharmaceutical industry – as binder or as disintegrant in tablet dosage form and as main ingredient in some bulk-forming laxatives.
- Cosmetics and toiletries industries – as thickener in toothpaste or conditioner in shampoos.
- Medical institutions, especially nursing homes; used to thicken liquids and foods for patients with dysphagia.

Nutritional and medicinal effects:
Guar gum is a water-soluble fiber that acts as a bulk forming laxative. It is claimed to be effective in promoting regular bowel movements and relieve constipation and chronic related functional bowel ailments, such as diverticulosis, Crohn's disease, colitis and irritable bowel syndrome, among others. The increased mass in the intestines stimulates the movement of waste and toxins from the system, which is particularly helpful for good colon health, because it speeds the removal of waste and bacteria from the bowel and colon.
1.5 PROFILE OF DRUGS

1.5.1 Theophylline (KD Tripathi, 1990; RS Satoshkar, 2001)

Empirical formula:
C_{7}H_{8}N_{4}O_{2}.H_{2}O

Structure:

3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione 1,3-Dimethylxanthine

Physicochemical Properties:

Appearance:
It occurs as a white, odourless, crystalline powder with a bitter taste

Molecular Weight:
198.2

Solubility:
It is slightly soluble in water and sparingly soluble in ethanol. It dissolves in solutions of alkali hydroxides, in ammonia and in mineral acids.

Melting point:
270-274 °C

Pka:
8.6
Storage:
Keep tightly closed. Store at controlled room temperature 15-30°C (59-86°F).

Pharmacology

*Mechanism of action:*
Theophylline has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation (i.e. bronchodilator) and suppression of the response of the airways to stimuli (i.e. non-bronchodilator prophylactic effects).

While the mechanisms of action of theophylline are not known with certainty, studies in animals suggest that bronchodilatation is mediated by the inhibition of two isoenzymes of phosphodiesterase (PDE III and to a lesser extent, PDE IV). While non-bronchodilator prophylactic actions are probably mediated through one or more different molecular mechanism that do not involve inhibition of PDE III or antagonism of adenosine receptors. Some of the adverse effects associated with theophylline appear to be mediated by inhibition of PDE III (e.g., hypotension, tachycardia, headache, and emesis) and adenosine receptor antagonism (e.g., alterations in cerebral blood flow).
Theophylline increases the force of contraction of diaphragmatic muscles. This action appears to be due to enhancement of calcium uptake through an adenosine-mediated channel.

Pharmacodynamics

*Asthma*
The various studies published on the efficacy and toxicity of theophylline have led to a carefully defined range of serum concentrations, between 10 and 20 p.g/mL, where there is an optimal likelihood of maximal safe effect. It is this optimal range for maximal safe effect that has been commonly termed the “therapeutic range.” The connotations of this term have sometimes been misinterpreted to suggest that there is no effect from theophylline at serum concentrations under 10µg/mL and no further potential for antiasthmatic effect
at serum concentrations over 20µg/mL. Even a cursory examination of the literature, however, would argue that this is not so. A measurable effect of theophylline is apparent at lower serum concentrations and higher serum concentrations almost certainly would provide more effect for some patients.

Pharmacokinetics (Anon, 1995; Ellis et al., 1976; Longman et al., 1976; Du Preez et al., 1999)

*Overview:*

Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. Theophylline does not undergo any appreciable pre-systemic elimination, distributes freely into fat-free tissues and is extensively metabolized in the liver.

*Absorption:*

Theophylline is rapidly and completely absorbed after oral administration in solution or immediate-release solid oral dosage form. After a single dose of 5 mg/kg in adults, a mean peak serum concentration of about 10µg/mL (range 5-15µg/mL) can be expected 1-2h after the dose. Co-administration of theophylline with food or antacids does not cause clinically significant changes in the absorption of theophylline from immediate-release dosage forms.

*Distribution:*

Once theophylline enters the systemic circulation, about 40% is bound to plasma protein, primarily albumin. Unbound theophylline distributes throughout body water, but distributes poorly into body fat. The apparent volume of distribution of theophylline is approximately 0.45L/kg (range 0.3-0.7L/kg) based on ideal body weight.

*Metabolism:*

Following oral dosing, theophylline does not undergo any measurable first-pass elimination. In adults and children beyond one year of age, approximately 90% of the dose is metabolized in the liver. Biotransformation takes place through demethylation to 1-methylxanthine and 3-methylxanthine and hydroxylation to one, 3-dimethyluric acid. 1-methylxanthine is further hydroxylated, by
xanthenes oxidase, to 1-methyluric acid. About 6% of a theophylline dose is N-methylated to caffeine.

**Excretion:**
In neonates, approximately 50% of the theophylline dose is excreted unchanged in the urine. Beyond the first three months of life, approximately 10% of the theophylline dose is excreted unchanged in the urine. The remainder is excreted in the urine mainly as 1, 3-dimethyluric acid (35-40%), 1-methyluric acid (20-25%) and 3-methylxanthine (15-20%). The elimination half-life is in the range of 54 to 76h in premature neonates (Du Preez et al, 1999), 2 to 7h in children (Anon, 1995; Ellis et al, 1976; Loughnan et al, 1976), and 6 to 12h in adults (Anon, 1995). Theophylline is mainly eliminated renaly (10-13%) as unchanged.

**Indication:**
Theophylline is indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases, e.g., emphysema and chronic bronchitis.

**Contraindication:**
This product is contraindicated in individuals who have shown hypersensitivity to its components. It is also contraindicated in patients with active peptic ulcer disease, and in individuals with underlying seizure disorders (unless receiving appropriate anti-convulsant medication).

**Precautions:**
Careful consideration of the various interacting drugs and physiologic conditions that can alter theophylline clearance and require dosage adjustment should occur prior to initiation of theophylline therapy, prior to increases in theophylline dose and during follow up.

**Adverse effect:**
Theophylline has a narrow margin of safety: Starts from the upper part of therapeutic concentration range. Adverse effects are primarily referable to GIT,
CNS, and CVS. They occur in a dose related manner and are listed as convulsion, shock, arrhythmias, increase muscle tone flashes of light seen, agitation flushing, restlessness, vomiting, palpitation, diuresis, dyspepsia, headache, nervousness, insomnia etc. Children are more liable to develop CNS toxicity.
1.5.2 Diclofenac Sodium (Nokhodchi et al., 1997)

Empirical formula:
C\textsubscript{14}H\textsubscript{10}Cl\textsubscript{2}NO\textsubscript{2}Na

Structure:

\[
\text{2-[(2,6-dichlorophenyl)amino] benzene acetic acid, monosodium salt}
\]

General properties:

\textit{Appearance:}
It occurs as a White Crystalline odorless Powder, Slightly Hygroscopic.

\textit{Molecular weight:}
318.14 g/mole

\textit{Solubility:}
It is sparingly soluble in water; soluble in alcohol; slightly soluble in acetone; freely soluble in methyl alcohol.

\textit{Melting Point:}
284°C (543.2°F)

\textit{pKa:}
4.0

\textit{Storage:}
Keep the container in dry and cool place.
Pharmacology:

**Mechanism of action:**

The exact mechanism of action is not entirely known, but it is thought that the primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis (Dutta et al., 2001).

Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side-effect of Diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have, therefore, a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin.

The action of one single dose is much longer (6 to 8h) than the very short half-life that the drug indicates. This could be partly because it persists for over 11h in synovial fluids (Fowler et al., 1986).

Diclofenac may also be a unique member of the NSAIDs. There is some evidence that Diclofenac inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that Diclofenac may inhibit phospholipase A₂ as part of its mechanism of action. These additional actions may explain the high potency of Diclofenac – it is the most potent NSAID on a broad basis (Dietrich et al., 1986).

There are marked differences among NSAIDs in their selective inhibition of the two subtypes of cyclo-oxygenase, COX-1 and COX-2. Much pharmaceutical drug design has attempted to focus on selective COX-2 inhibition as a way to minimize the gastrointestinal side-effects of NSAIDs like aspirin. In practice, use of some COX-2 inhibitors with their adverse effects has led to massive numbers of patient family lawsuits alleging wrongful death.
by heart attack, yet other significantly COX-selective NSAIDs such as Diclofenac have been well-tolerated by most of the population. Besides the well-known and often-cited COX-inhibition, a number of other molecular targets of Diclofenac that could contribute to its pain-relieving actions have recently been identified. These include:

- Blockage of voltage-dependent sodium channels (after activation of the channel, Diclofenac inhibits its reactivation also known as phase inhibition)
- Blockage of acid-sensing ion channels (ASICs)
- Positive allosteric modulation of KCNQ- and BK-potassium channels (Diclofenac opens these channels, leading to hyperpolarization of the cell membrane)

Pharmacodynamics:

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, Diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity.

Pharmacokinetics:

Diclofenac sodium delayed-release tablets are in a pharmaceutical formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH-environment in the duodenum. Its pattern of drug release and absorption is shown in Table 1.9.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>AUC (ng.h/mL)</th>
<th>C_{max} (ng/mL)</th>
<th>T_{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac sodium delayed-release tablets</td>
<td>50</td>
<td>1429 (38.4%)</td>
<td>1417 (22.4%)</td>
<td>2.22 (49.8%)</td>
</tr>
</tbody>
</table>
Absorption
Under fasting condition, Diclofenac is completely absorbed from the gastrointestinal tract. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Peak plasma levels are achieved in 2h in fasting normal volunteers, with a range from 1 to 4h. The area-under-the-plasma-concentration curve (AUC) is dose-proportional within the range of 25mg to 150mg. Peak plasma levels are less than dose-proportional and are approximately 1.0µg/mL, 1.5µg/mL, and 2.0µg/mL for 25mg, 50mg, and 75mg doses, respectively. It should be noted that the administration of several individual Diclofenac sodium tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is probably due to the staggered gastric emptying of tablets into the duodenum. After repeated oral administration of Diclofenac sodium 50mg b.i.d., Diclofenac did not accumulate in plasma. When Diclofenac sodium is taken with food, there is usually a delay in the onset of absorption of 1 to 4.5h, with delays as long as 10h in some patients and a reduction in peak plasma levels of approximately 40%. The extent of absorption of Diclofenac, however, is not significantly affected by food intake.

Distribution
Plasma concentrations of Diclofenac decline from peak levels in a bi-exponential fashion, with the terminal phase having a half-life of approximately 2h. Clearance and volume of distribution are about 350mL/min and 650mL/kg, respectively. More than 99% of Diclofenac is reversibly bound to human plasma albumin. As with other NSAIDs, Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of Diclofenac.
Metabolism and Elimination

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of unchanged Diclofenac account for 5% to 10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged un-conjugated drug is excreted. Conjugates of the principal metabolite account for 20% to 30% of the dose excreted in the urine and for 10% to 20% of the dose excreted in the bile. Conjugates of three other metabolites together account for 10% to 20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80h) accounts for only 1.4% of the oral dose. The degree of accumulation of Diclofenac metabolites is unknown. Some of the metabolites may have activity.

Indications and usage:

Diclofenac sodium delayed-release tablets are indicated for the acute and chronic treatment of signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Contraindications:

Diclofenac sodium is contraindicated in patients with known hypersensitivity to Diclofenac and Diclofenac-containing products. Diclofenac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to Diclofenac have been reported in such patients.

Adverse Reactions:

Adverse reaction information is derived from blinded, controlled and open-label clinical trials, as well as worldwide marketing experience. In the
description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks with Diclofenac sodium delayed-release tablets. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3% of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in 0.6% (95% confidence interval: 0.2% to 1%) of approximately 1800 patients during their first 3 months of Diclofenac treatment and in 1.6% (95% confidence interval: 0.8% to 2.4%) of approximately 800 patients followed for 1 year.

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%).

Meaningful (exceeding 3 times the Upper Limit of Normal) elevations of ALT (SGPT) or AST (SGOT) occurred at an overall rate of approximately 2% during the first 2 months of Diclofenac Sodium treatment. Unlike aspirin-related elevations, which occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations were seen in 1% of patients treated for 2 to 6 months.

The following adverse reactions were reported in patients treated with Diclofenac:

Body as a Whole: Abdominal pain or cramps, headache, fluid retention, abdominal distention.

Digestive: Diarrhea, indigestion, nausea, constipation, flatulence, liver test abnormalities, peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer.

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special Senses: Tinnitus.
Incidence Less Than 1% - Causal Relationship Probable:
Body as a whole: Malaise, swelling of lips and tongue, photosensitivity, anaphylaxis, anaphylactoid reactions.
Cardiovascular: Hypertension, congestive heart failure.
Digestive: Vomiting, jaundice, melena, esophageal lesions, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, hepatic necrosis, cirrhosis, hepatorenal syndrome, appetite change, pancreatitis with or without concomitant hepatitis, colitis.
Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura, allergic purpura.
Metabolic and Nutritional Disorders: Azotemia.
Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability, aseptic meningitis, convulsions.
Respiratory: Epistaxis, asthma, laryngeal edema.
Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, bullous eruption, erythema multiforme major, angioedema, Stevens-Johnson syndrome.
Special Senses: Blurred vision, taste disorder, reversible and irreversible hearing loss, scotoma.
Urogenital: Nephrotic syndrome, proteinuria, oliguria, interstitial nephritis, papillary necrosis, acute renal failure.

Incidence Less Than 1% - Causal Relationship Unknown:
Body as a Whole: Chest pain.
Cardiovascular: Palpitations, flushing, tachycardia, premature ventricular contractions, myocardial infarction, hypotension.
Digestive: Intestinal perforation.
Hemic and Lymphatic: Bruising.
Metabolic and Nutritional Disorders: Hypoglycemia, weight loss.
Nervous System: Parasthesia, memory disturbance, nightmares, tremor, tic, abnormal coordination, disorientation, psychotic reaction.
Respiratory: Dyspnea, hyperventilation, edema of pharynx.
Skin and Appendages: Excess perspiration, exfoliative dermatitis.
Special Senses: Vitreous floaters, night blindness, amblyopia.
Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.
1.6 PROFILE OF EXCIPIENTS

1.6.1 Microcrystalline cellulose (Rowe et al., 2009)

Synonyms:
Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Tabulose, Vivacel.

Empirical Formula:
(C₆H₁₀O₅)n

Molecular Weight:
(162.03)n

Structural Formula:

![Structural Formula of Microcrystalline Cellulose](image)

Description:
White-colored, odorless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications.

Functional Category:
It can acts as tablet and capsule as diluent, as suspending agent, as adsorbent, as tablet disintegrant.
Applications:
As a diluent in tablets (wet granulation and direct compression) and capsule formulation. In addition to its use as a diluent, it also has some lubricant and disintegrant property.

Solubility:
Slightly soluble in 5 % w/v NaOH solution, practically insoluble in water, dilute acids and most organic solvents.

Stability:
It is a stable, though hygroscopic material.

Storage conditions:
The bulk material should be stored in a well-closed container in a cool, dry, place.

Incompatibilities:
Incompatible with strong oxidizing agents.

Safety:
It is generally regarded as a nontoxic and nonirritant material.
1.6.2 Polyvinyl pyrrolidine (PVPK30) (Rowe et al., 2009)

Synonyms:
Plasdone K-30, Agrimer, Albigen A, Hemodesis, K30, Luviskol K30, Plasdone, Povidone, PVPP, PVP-K 30; PVP; Polyvinylpyrrolidone; Poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; Povidone K-30; 1-Ethenyl-2-pyrrolidinone polymers; 2-Pyrrolidinone, 1-ethenyl, homopolymer; 2-Pyrrolidinone, 1-vinyl-, polymers; N-Vinylpyrrolidinone polymer; N-Vinylbutyrolactam polymer; N-Vinylpyrrolidone polymer; Poly(n-vinlybutyrolactam); Poly(1-vinlypyrrolidinone); Poly(N-vinlypyrrolidinone); Vinylpyrrolidinone polymer; Vinylpyrrolidone polymer.

Empirical formula:
(C₆H₉NO)ₙ

Molecular Weight
111.143

Structure

![Structure of Polyvinylpyrrolidone](image)

Description:
PVP exists as powder or aqueous solution. It can dissolve in water and a variety of organic solvent. It has good hygroscopicity, film-forming capability, complexing ability and physiology compatibility.

Functional category:
Binder, dispersing, viscosity-enhancement reagent
Applications:

*Cosmetics:*  
PVP-K series can be used as film-forming agent, viscosity-enhancement agent, lubricator and adhesive. They are the key component of hair sprays, mousse, gels and lotions & solution, hair-dying reagent and shampoo in hair-care products. They can be used as assistant in skin-care products, eye makeup, lipstick, deodorant, sunscreen and dentifrice.

*Pharmaceuticals:*  
Povidone k30 is a new and excellent pharmaceutical excipient. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for enzyme and heat sensitive drug, coprecipitant for poorly soluble drugs, lubricator and antitoxic assistant for eye drug. PVP works as excipients in more than one hundreds drugs.

Storage: Keep in dry place at the room temperature.
1.6.3 Starch (Rowe et al., 2009)

It is a carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. Pure starch is a white, tasteless and odorless powder that is insoluble in cold water or alcohol.

Description:

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

Structure:

![Starch Structure Diagram]

Solubility:

Practically starch is insoluble in cold ethanol (96%) and cold water. Starch swells instantaneously in water by about 5–10% 37°C. Starch becomes soluble in hot water at temperatures above the gelatinization temperature. Starches are partially soluble in dimethylsulfoxide and dimethylformamide.

Acidity/alkalinity:

Aqueous dispersions of starch usually have a pH in the range 4.0–8.0. Starch does not exhibit a significant self-buffering capacity.

Stability and Storage Conditions

Dry starch is stable if protected from high humidity. Starch is considered to be chemically and microbiologically inert under
Physical properties:

While amylose was traditionally thought to be completely unbranched, it is now known that some of its molecules contain a few branch points. Starch molecules arrange themselves in the plant in semi-crystalline granules. Each plant species has a unique starch granular size: rice starch is relatively small (about 2μm) while potato starches have larger granules (up to 100μm). Starch becomes soluble in water when heated.

Digestive enzymes have problems digesting crystalline structures. Raw starch will digest poorly in the duodenum and small intestine, while bacterial degradation will take place mainly in the colon. When starch is cooked, the digestibility is increased. Hence, before humans started using fire, eating grains was not a very useful way to get energy.

Starch gelatinization during cake baking can be impaired by sugar competing for water, preventing gelatinization and improving texture.

Functional Category:

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

Use as food additive:

As an additive for food processing, food starches are typically used as thickeners and stabilizers in foods such as puddings, custards, soups, sauces, gravies, pie fillings, and salad dressings and to make noodles and pastas.

Resistant starch is starch that escapes digestion in the small intestine of healthy individuals. It is used as an insoluble dietary fiber in processed foods such as bread, pasta, cookies, crackers, pretzels and other low moisture foods. It is also utilized as a dietary supplement for its health benefits.

Applications in Pharmaceutical Formulation or Technology:

- Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent and disintegrant.
As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations.

Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix and to improve powder flow, especially when using dried starches. Starch quantities of 3–10% w/w can act as an antiadherent and lubricant in tableting and capsule filling.

In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% wt/wt (usually 5–10%, depending on the starch type) as a binder for wet granulation. However, starch that is not pregelatinized does not compress well and tends to increase tablet friability and capping if used in high concentrations. Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids.

Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerin.

Starch has been investigated as an excipient in novel drug delivery systems for nasal, and other site-specific delivery systems.

Starches are useful carriers for amorphous drug preparations, such as pellets with immediate or delayed drug release obtained, for example, by melt extrusion, and they can improve the bioavailability of poorly soluble drugs.

Starch, particularly rice starch, has also been used in the treatment of children’s diarrheal diseases. Specific starch varieties with high amylose content (resistant starches) are used as insoluble fiber in clinical nutrition, and also for colon-targeting applications.

Due to their very high gelatinization temperature, these starches are used in extrusion/spheronization processes.

Starches with high amylopectin content (waxy starches) are used as the starting material for the synthesis of hydroxyethyl starch, a plasma volume expander.
Safety:

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially nontoxic and nonirritant material. Starch is therefore widely used as an excipient in pharmaceutical formulations.
1.6.4 Magnesium stearate (Rowe et al., 2009)

Synonyms:
Metallic stearic, Magnesium salt.

Emperical Formula:
$C_{36}H_{70}MgO_4$

Molecular Weight:
591.3

Chemical Names:
Octadecanoic acid; Magnesium salt; magnesium Stearate.

Structure

\[ \text{Structure} \]

Description:
It is a fine, white, precipitated, or milled, impalpabale powder of low bulk density, having a faint characteristic odour and taste. The powder is greasy to touch and readily adheres to the skin.

Functional category:
Tablet and capsule lubricant

Solubility:
Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol(95%)

Storage:
Store in a cool, dry place in a well closed container.
Incompatibilities:
Incompatible with strong acids, alkalies, iron salts and with strong oxidizing material.

Applications in Pharmaceuticals Formulation or Technology:
Tablet and capsule lubricant, glidant and antiadherent in the concentration range of 0.25-2.0%.
1.7 Review of literature

1.7.1 Polymers

Okra gum

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<th>Performance</th>
<th>References</th>
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<tr>
<td>Sulphaguanidine</td>
<td>Matrix tablet prepared by wet granulation method</td>
<td>Gum was compared as binder with gelatin and maize starch at same concentrations and evaluated for physical properties of granules and tablets. Granules prepared with okra gum possessed good flow characteristics and exhibited higher binding capacity.</td>
<td>Ofoefule et al., 2001</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Ibuprofen Matrix tablets by wet granulation technique</td>
<td>Tablets were prepared using binders like okra gum, starch and PVP and were evaluated for weight variation, hardness, friability and disintegration time according to the USP XXVI requirements. However the physical properties of ibuprofen and calcium acetate tablets containing Okra gum showed sufficient hardness, slow disintegration and low friability. The results showed that the drug release from tablets containing Okra gum significantly decreased (p&lt;0.05) in comparison with other binders.</td>
<td>Naser Tavakoli et al., 2004</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Matrix tablets prepared by direct compression method</td>
<td>Matrices of okra gum, NaCMC were prepared and drug release was assessed for 6h. A time-independent kinetics with zero-order release from matrices was observed that indicates that okra gum is suitable for the sustained release of water soluble drugs.</td>
<td>Kalu et al., 2006</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Film coated tablets</td>
<td>Core tablets of paracetamol were obtained from a pharmacy shop in the locality and the physicochemical properties such as weight, hardness, friability, and disintegration time were evaluated. Aqueous coating suspensions of okra gum and hydroxypropylmethylcellulose (0.6%w/v) were prepared and used to coat the tablets in Hi-coater. The coated tablets had lower friability, increased disintegration time (24 min) compared to the core (3 min) and improved hardness, but there was no difference in the dissolution profile of the samples from the batches containing</td>
<td>Ikoni and Obiageli, 2010</td>
</tr>
</tbody>
</table>
Introduction

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<tr>
<th>Material</th>
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<tbody>
<tr>
<td>okra and hydroxypropylmethylcellulose</td>
<td>Dispersible tablets</td>
<td>It was our conclusion that okra gum is a promising natural, biodegradable, cheap and eco-friendly film former in aqueous tablet film coating operation, particularly when masking of taste or objectionable odor in a solid dosage formulation is desired.</td>
</tr>
<tr>
<td>Abelmoschus esculentus mucilage powder</td>
<td>Dispersible tablets</td>
<td>The mucilage extracted is devoid of toxicity. Tablets were prepared and evaluated for physical parameters. The formulated tablets had good appearance and better drug release properties. The study revealed that <em>Abelmoschus esculentus</em> mucilage powder was effective as disintegrant in low concentrations, 4%.</td>
</tr>
<tr>
<td>Metronidazole matrix tablets</td>
<td>Prepared by direct compression technique</td>
<td>Comparative effects of the Okra powder, corn starch B.P and MCC on physical characteristics of tablet were studied. Highest crushing strength – friability ratio were observed for Okra powder. Tablets containing Okra powder showed good dissolution profile with T&lt;sub&gt;50&lt;/sub&gt; and T&lt;sub&gt;90&lt;/sub&gt; values comparable to those of corn starch B.P and MCC. The result shows the potentials of Okra powder as tablet disintegrant and suggests that it could be further developed for commercial purposes.</td>
</tr>
<tr>
<td>Glibenclamide matrix tablets</td>
<td>Prepared by wet granulation technique</td>
<td>Matrix tablets were prepared using dried fruit mucilage of okra in various drug: mucilage ratios. The results shown that as the proportion of okra fruit mucilage increased, the overall time of release of the drug from the matrix tablet was also increased. Drug releases from matrix tablets were by drug dissolution, drug diffusion or a combination of both.</td>
</tr>
<tr>
<td>Thiamine hydrochloride matrix tablets</td>
<td>Prepared with gelatin, acacia and PVP</td>
<td>A comparative evaluation of okra gum as a binder in tablet formulation was performed with gelatin, acacia and PVP. The properties of granules and tablets were evaluated and found to have good flow properties. Okra gum gave the highest hardness/friability ratios. It also prolonged disintegration time and dissolution time and dissolution rate. Hence, okro gum may not be useful as a binder in conventional tablet formulation but could be used as hydrophilic polymer in sustained release tablet formulation.</td>
</tr>
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Ravi Kumar et al., 2009
Bakre and Jaiyeoba, 2009
Hindustan Abdul Ahad et al., 2010
Onunkwo, 2010
Guar gum

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<th>Drug</th>
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<tr>
<td>Dexamethasone/budesonide</td>
<td>Matrix tablets</td>
<td>Tablets containing 60.5% w/w of guar gum showed negligible drug release in upper GIT conditions. Presence of galactomannase accelerated drug release.</td>
<td>Wong et al., 1997</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Matrix tablet (Radio labeled)</td>
<td>Tablets were found to disintegrated completely in the colon and release 72-82% of the drug in the colon</td>
<td>Kenyon et al., 1997</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Matrix tablet</td>
<td>Only 21% of drug release was observed in upper GIT conditions. Presence of rat cecal contents increases drug release. As the concentration of rat caecal content was increased drug release increased further.</td>
<td>Rama Prasad et al., 1998</td>
</tr>
<tr>
<td>Technetium-99m-DTPA</td>
<td>Matrix tablet</td>
<td>Tablets containing 77% guar gum released only small amount of tracer in upper GIT and bulk of tracer was released in ascending colon.</td>
<td>Krishnaiah et al., 1998</td>
</tr>
<tr>
<td>5-ASA</td>
<td>Compression coat</td>
<td>A guar gum coat of 152 mg showed 95.51±1.50% of 5-ASA release in presence of rat caecal content after 26 h. a guar coating between 0.61 to 0.91 mm was found sufficient to deliver the drug selectively to the colon.</td>
<td>Krishnaiah et al., 1999</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>Matrix tablet</td>
<td>The tablets released 8-15% of the drug in the upper GIT. The matrix tablets containing 20% &amp; 30% of guar gum released another 83% &amp; 50% of drug in simulated colonic fluids, respectively.</td>
<td>Krishnaiah et al., 2001</td>
</tr>
<tr>
<td>Albendazole</td>
<td>Matrix tablet</td>
<td>The tablets were found degraded by colonic bacteria of rat caecal contents and released about 44% of drug in simulated colonic fluids after 24 h.</td>
<td>Krishnaiah et al., 2001</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Matrix, multilayer and compression coated tablets</td>
<td>Matrix tablets and multilayer tablets released 52% and 44% of drug, respectively, in the upper GIT compare to compression coated tablets which release LT 1% of drug in the same. When dissolution continued in simulated colonic fluids, the compression coated tablet released another 61% of drug after degradation by colonic bacteria at the end of 24h of dissolution study.</td>
<td>Krishnaiah et al., 2002</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Characteristics</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------------</td>
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<tr>
<td>5-FU</td>
<td>Compression tablet</td>
<td>Drug release was only 2.5-4 % in simulated upper GI fluids. When the dissolution study was continued in simulated colonic fluid containing 4 % w/v rat caecal content, tablets compression coated with 60, 70 and 80 % of guar gum release another 70, 55 and 41 % of drug, respectively.</td>
<td>Krishnaiah et al., 2002</td>
</tr>
<tr>
<td>Sennoside</td>
<td>Matrix tablets</td>
<td>Matrix tablets released 4-18% drug in the upper GIT. The tablets with 50% guar gum released 43% and 96% of drug with and without rat caecal fluids, respectively.</td>
<td>Munira &amp; Pundarikakshud, 2004</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Matrix tablet</td>
<td>In vivo study revealed that the matrix tablets reached the colon; not being subjected to disintegration in the upper region of the GI system in all the subjects.</td>
<td>Fatmanur et al., 2004</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>Matrix tablet</td>
<td>Matrix tablets released only 5-12% of drug in the upper GIT. In simulated colonic fluids, the matrix tablets were acted upon by colonic bacterial enzymes releasing the entire quantity of drug.</td>
<td>Al-Saidan et al., 2005</td>
</tr>
<tr>
<td>diethylcarbamazine citrate (DEC)</td>
<td>Matrix tablets</td>
<td>The colon targeted matrix tablet containing 45% of guar gum was most likely to provide targeting of DEC for local action in the colon. The colon targeted matrix tablet of DEC showed no change either in physical appearance, drug content or in dissolution pattern after storage at 300± 20C / 65 ± 5% RH for 2 month. FT-IR spectrum showed no interaction between DEC and guar gum.</td>
<td>Upendra et al., 2010</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>Matrix tablets</td>
<td>The release profile of Naproxen Sodium from the matrix tablets is dependent upon the gelling property of Guar gum and degradation of Guar gum by colonic bacteria. In Stomach, the release rate was much slower; however, the drug was released quickly in the lower part of GIT after 4 hours. Results clearly indicate that there is an increase in the release of the drug to 98.930±0.38% due presence of ceecal content.</td>
<td>Rajyalakshmi et al., 2012</td>
</tr>
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### 1.7.2 Drugs

Theophylline

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<tr>
<td>Matrix tablets</td>
<td>The matrix tablets were prepared by wet granulation method by employing varying concentrations of guar gum and cellulose acetate phthalate. All the formulations were evaluated for weight variation, friability and assay and in-vitro drug release studies.</td>
<td>Our study explains that guar gum matrix tablets which are coated with CAP (formulation F4) were found to be suitable for chronotherapeutic delivery of Theophylline to treat the symptoms of nocturnal asthma. The drug release kinetics for F4 formulation follows zero order kinetics with peppa’s drug release mechanism.</td>
<td>Venugopalaiah et al., 2011</td>
</tr>
<tr>
<td>Core coat tablet</td>
<td>The formulation consisted of a core tablet containing HPMC used for achieving controlled release of drug, and a Eudragit S100:ethyl cellulose (EC) coating capable of delaying the drug release. The system was optimized using a $3^2$ full factorial design and were evaluated for lag time, $t_{50}$ and $t_{80}$. The optimum formulation consisted of Eudragit S100:EC in a 60:40 ratio and a coating level of 7.5% (w/w).</td>
<td>Results showed that the tablets prepared according to the optimized values released no drug in the upper part of gastrointestinal tract; drug release was initiated at pH 6.4 (colon) after a lag time of 5 h. In vivo evaluation (pharmacokinetic studies and roentgenography) in rabbits revealed that the tablet remained intact until it reaches the colon and the drug release was initiated after a lag time of 5 h.</td>
<td>Patel &amp; Amin 2011</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Guar gum microspheres were prepared by emulsification technique. Coating of microspheres was performed using solvent evaporation method with pH sensitive Eudragit polymers. The particle size and surface morphology, entrapment efficiency and degree of swelling of microspheres</td>
<td>Theophylline was efficiently microencapsulated in guar gum microspheres at different polymer concentrations (1-4%). Coating of guar gum microspheres by Eudragit led to decelerate the in vitro drug release of drug. Moreover in vitro drug release studies also performed with 2% rat caecal content</td>
<td>Soni et al., 2011</td>
</tr>
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were examined. The in vitro drug release studies were performed in pH progression medium and also in the presence of 2% rat caecal content. showed marked increment in drug release. The controlled release of drug after a lag time was achieved with developed formulation for chronotherapeutic delivery.

| Insoluble hard gelatin capsule body, filled with eudragit microcapsules | Microcapsules were prepared in four batches, with Eudragit L-100 and S-100 (1:2) by varying drug to polymer ratio and evaluated for the particle size, drug content and in vitro release profile and from the obtained results; one better formulation was selected for further fabrication of pulsatile capsule. Different hydrogel polymers were used as plugs, to maintain a suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. | In vitro release studies of pulsatile device revealed that, increasing the hydrophilic polymer content resulted in delayed release of theophylline from microcapsules. The gamma scintigraphic study pointed out the capability of the system to release drug in lower parts of GIT after a programmed lag time for nocturnal asthma. Programmable pulsatile, colon-specific release has been achieved from a capsule device over a 2–24 h period, consistent with the demands of chronotherapeutic drug delivery. | Mastiholimath et al., 2007 |

| Beads | Alginate and chitosan beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S100. All formulations were evaluated for particle size, encapsulation efficiency, swellability and in vitro drug release. | The studies showed that formulated alginate and chitosan beads can be used effectively for the delivery of drug to colon and a coat weight of 20% weight gain was sufficient to impart an excellent gastro resistant property to the beads for effective release of drug at higher pH values. | Khan et al., 2010 |

| Matrix tablet | Matrix-tablets were prepared by direct compression of mixtures of HEC, a hydrophilic swellable polymer, with the inert insoluble ethylcellulose (EC) or a micro-crystalline cellulose (MCC) polymer, in which drug was dispersed. Eudragit S100 | The results of release studies, indicated that the Eudragit S100 enteric-coated matrix tablets were successful in achieving gastric resistance and timed-release of the drug, assuring an adequate lag time for the intended colonic targeting, followed by a controlled-release | Alvarez-Fuentes et al., 2004 |
was used as pH-sensitive coating polymer. The influence of varying the cellulose-derivative combinations and their relative ratios as well as the level of the coating polymer was investigated.

The best results were given by the 27% coated 1:0.3:0.7 (w/w) drug/MCC/HEC tablets, which, after a 260 min lag time, regularly released the drug, achieving about 90% of release after 10 h.

Matrix tablet

The effects of varying the type of pectin (low and high methoxylated, or amidated), the pectin:Emdex ratio and the level of the pH-dependent polymeric coating on drug release behavior were investigated. Release tests were performed using sequential liquids simulating the physiological variation of pH and the effect of the presence or not of pectinolytic enzymes into the simulated colonic medium was evaluated.

Twenty seven % (w/w) was the minimum coating amount for obtaining an adequate lag time before the onset of drug release. Comparison of the results obtained in the presence or not of pectinolitic enzymes allowed selection of the high methoxylated pectin as the most interesting candidate for specific colonic delivery since it was the least water-soluble and the most susceptible to enzymatic degradation, thus assuring a greater site-specificity of drug release.

Tablet in capsule system

The system comprising of Eudragit S-100 coated minitablets was designed for chronotherapeutic delivery of theophylline in view to specifically target the nocturnal peak symptoms of asthma. The drug-loaded core minitablets were produced by wet granulation procedure using alcoholic solution of PVP K 30 as a binder. Different coat weights of Eudragit S-100 were applied to the drug loaded core minitablets in a conventional coating pan to produce the pH sensitive minitablets.

SEM revealed a distinct continuous acrylic coat free from cracks or pores. In vitro dissolution studies performed following pH progression method demonstrated that the drug release from the coated minitablets depended on the coat weights applied and pH of the dissolution media. The studies showed that a coat weight of 10% weight gain was sufficient to impart an excellent gastro resistant property to the tablets for effective release of the drug at higher pH values.

Mura et al., 2003

Shivakumar et al., 2007

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Diclofenac sodium

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<td>Pellets in a capsule</td>
<td>The pellets (DS 100mg) were filled into the treated capsule shells, plugged with HPMC, HPC and sodium alginate at different concentrations and completely enteric coated with 5% CAP. Formulation was assessed by in vitro drug release studies in simulated gastric fluid for 2h, simulated intestinal fluid for 3h &amp; simulated colonic fluid for 7h.</td>
<td>The formulation was found to be intact for 2 hours in simulated gastric fluid. The enteric coating and cap of the capsule dissolved in simulated intestinal fluid, exposing the hydrogel plug and facilitated slow and controlled release of the drug from the pellets in the colonic medium.</td>
<td>Sindhu et al., 2007</td>
</tr>
<tr>
<td>Matrix tablet</td>
<td>Different batches of matrix tablet of Diclofenac sodium- guar gum were prepared using wet granulation method and evaluated by different in vitro tests and release profiles. Three polymeric binders were used in different proportion to produce nine different batches.</td>
<td>Hpmc and PVPK30 based tablet formulations showed high release-retarding efficiency and release higher amount of drug in lower part of GIT. Guar gum based matrix tablets are good candidates for preparing modified release Diclofenac tablet formulations for lower GI tract specific drug delivery.</td>
<td>Pratik shah and Pragna shelat, 2010</td>
</tr>
<tr>
<td>Compression coated tablet</td>
<td>A rapidly disintegrating Diclofenac sodium core tablets were compressed-coated with a mixture of time dependent hydrophilic swellable polymer (HPMC) and pH responsive soluble polymer eudragit S 100 (ED) in different ratios.</td>
<td>The core tablets compression-coated with HPMC and ED mixture in the ratio 6:4 was found to be suitable for targeting Diclofenac sodium to the colon owing to its minimal drug release in physiological environment of stomach and small intestine and releases 92% of drug in the target area.</td>
<td>Chickpetty et al., 2010</td>
</tr>
<tr>
<td>Matrix tablet</td>
<td>Six matrix tablets formulations (F1-F6) of Diclofenac sodium containing varying proportions of guar gum, 10-60% of tablet weight were prepared by wet granulation method and evaluated in vitro for their release profile. Four matrix tablets formulations (F7-F10) of Diclofenac with guar gum (40%) were</td>
<td>The tablets having same concentration of guar gum without probiotics (F4) showed a 54.47% cumulative release of Diclofenac after 24 hr while that in presence of probiotics (F9) was 73.01%. These drug release studies were conducted without rat caecal content. In another set of experiments, the drug release studies were</td>
<td>Prashant et al., 2010</td>
</tr>
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prepared incorporating varying concentration of commercial spores of *lactobacillus* and *bifidobacterium* species that are commonly found in colon microflora. carried out in presence of rat caecal content. In such experiments, more than 95% drug was released from f4 and f9 formulations after 24 hr.

| Compression coated tablet | The present research work is aimed to develop colon targeted compression-coated delivery systems for Diclofenac sodium by using different proportion of GG and LBG mixture in the ratio 1:1 in combination with HPMC as a coating materials. Effect of proportion of GG-LBG mixture: HPMC ratio on percent of drug release in upper part of gastrointestinal tract and in the colon was studied on developed formulations. | Compression-coated formulation released 0 to 6.70 % of Diclofenac sodium in the upper GIT. The compression-coated formulation containing GG-LBG mixture: HPMC in the ratios 9:1, 8:2, 7:3, 6:4 and 5:5 released 35.84%, 47.62%, 78.61%, 94.82% and 98.03% of Diclofenac sodium respectively in Simulated colonic fluid indicating the susceptibility of gum mixture to the rat caecal contents. | Chickpetty and Baswaraj, 2010 |

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### 1.7.3 Excipients

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<tr>
<td>Indomethacin</td>
<td>Matrix tablets</td>
<td>Matrix tablets were prepared by wet granulation method. Guar gum as a carrier, 10% starch paste, HPMC, citric acid and the mixture of talc and magnesium stearate at 2:1 ratio were used. Coating was carried out by using 10% Eudragit L 100. Prepared formulations were evaluated for hardness, drug content uniformity and in vitro drug release studies in rat caecal contents. The highest in vitro dissolution profile at the end of 24 h was shown by IF6 followed by IF7, IF8. The other formulation IF4, IF3, IF2 and IF1 were failed to target in colon and these formulation releases the majority of drug within 10 h of study. It may be due to the less proportion of guar gum to retard the drug release.</td>
<td>Mahesh et al., 2011</td>
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<td>5-FU</td>
<td>Matrix tablets</td>
<td>A $3^2$ full factorial design was used for the formulations of matrix tablets using amount of pectin and amount of starch paste, each at three levels. The evaluated responses were hardness, percent cumulative drug release (% CDR) at 5th h and t90%. The optimized formulation consisting of pectin (66.67%, w/w) and starch paste (15%, w/w) released negligible amount of drug at pH 1.2 and pH 7.4 whereas significant (p &lt; 0.05) drug release was observed at pH 6.5 in presence of 4% (w/v) rat caecal contents.</td>
<td>Rakesh et al., 2011</td>
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<tr>
<td>Paracetamol</td>
<td>Matrix tablets</td>
<td>Matrix tablets polysaccharides were prepared by wet granulation technique starch paste. The matrix tablets were evaluated by different IPQC tests, content uniformity, matrix index and in vitro drug release study. Drug release profile in simulated gastric, intestinal fluid from the dissolution studies was taken for selecting the best formulation. The matrix tablet containing dextrin as a carrier and ethyl cellulose as a binder released lower amounts (8-11%) of drug in simulated gastric fluid. Matrix tablets containing dextrin released 95-98% of paracetamol in simulated colonic fluid with 4% human faecal matter solution.</td>
<td>Priyanka et al., 2012</td>
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<td>Diclofenac sodium (DS)</td>
<td>Triple-layer matrix tablets</td>
<td>Matrix tablet granules containing centre layer of matrix granules containing DS which was covered on either side by guar gum granule layers containing 70/80/87% of guar gum as release retardant layers. The tablets were evaluated for hardness, thickness, drug content and drug release studies. Tablets containing</td>
<td>Chavda et al., 2012</td>
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87% of guar gum in guar gum layers and 50% of guar gum in DS matrix granule layer were found to have prolonged drug release. The results clearly indicate that guar gum could be a potential hydrophilic carrier in the development of oral controlled drug delivery systems.

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<tr>
<th>Material</th>
<th>Coating Method</th>
<th>Description</th>
<th>Reference</th>
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<tr>
<td>Tinidazole</td>
<td>Core coated tablets</td>
<td>The main aim of the present work is to design and evaluate timed release oral colon targeted drug delivery system for tinidazole which would release negligible amount of drug in the first 6 hours lag period when the drug is in the upper GIT followed by complete release of the drug in the colon, in a controlled manner in the next 18hours. The tinidazole core tablets are prepared by wet granulation using MCC as diluents and then coated with Eudragit® NE 30D to achieve time dependent release profile for colon targeting. The prepared tablets were evaluated for various tabletting parameters and based on the pharmacopeial tests conducted and the study of release kinetics of the prepared tablets, FE4 having the Eudragit® NE30D polymer coat load of 25%w/w was selected as the optimized formula as it showed timed release profile for achieving colon targeting of tinidazole.</td>
<td>Sravya et al., 2012</td>
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<tr>
<td>Metronidazole</td>
<td>Compression coated tablets</td>
<td>Matrix, enteric coated and compression coated tablets of metronidazole containing various proportions of sesbania gum were prepared using PVPK30 as binder. Matrix tablets and enteric coated tablets of metronidazole released 41–71% and 25–28% of the metronidazole, respectively, in the physiological environment of stomach and small intestine depending on the proportion of sesbania gum used in the formulation. The compression coated formulations (CS2) released less than 5% of metronidazole in the physiological environment of stomach and small intestine. When the dissolution study was continued in simulated colonic fluids, the compression coated tablet with 150 mg of sesbania gum coat released another 76% of metronidazole after degradation by colonic bacteria at the end of 12 hr.</td>
<td>Biresh Sarkar and Vikram Sharma; 2012</td>
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1.8 RESEARCH BACKGROUND

Many approaches have been attempted for the development of colon-specific delivery systems that rely on gastro-intestinal pH, transit times, enterobacteria and luminal pressure for site-specific delivery (Sinha and Kumria, 2001). Each of these technologies represent a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up manufacturing. Recent research into the utilization of the metabolic activity and the colonic microenvironment in the lower gastrointestinal tract has attained great value in the design of novel colon-targeted delivery systems based on natural biodegradable polysaccharides. It appears that microbially-controlled systems based on natural polysaccharides have the greatest potential for colonic delivery, particularly in terms of site-specificity and safety because of the presence of the biodegradable enzymes only in the colon (Ofoefule et al., 2001).

In recognition of this, it was thought to design microbially triggered matrices of an inexpensive and abundantly available okra gum (OG), obtained from the pods of Albemoschus esculentus, could be exploited as novel carrier for colon specific drug delivery. Okra, also known as GUMBO, GOMBO and OCRA belong to the family Malvaceae, is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid (Agarwal et al., 2001). OG has been investigated as binding agent in tablet dosage forms and has been shown to produce tablets with good hardness and desired controlled drug release profile (Tavakoli et al., 2004). It has been used as a stabilizer, thickener, swelling agent and binder in the food and pharmaceutical industries.

Advantageously colonic drug delivery system would be valuable when a delay in absorption is therapeutically desirable in treatment of chronic medical conditions like nocturnal asthma and rheumatoid arthritis had apparent circadian rhythm and peak symptoms in the early morning (Gothoskar et al., 2004). Asthma is a chronic inflammatory disease of the airways, characterized
by hyper responsiveness to a variety of stimuli. The factors associated with nocturnal worsening of asthma may include airway cooling, allergen exposure, gastroesophageal reflux (GERD), increased cholinergic tone, hormonal change and so on. The mechanisms are not entirely understood. Both healthy individuals and subjects with nocturnal asthma have circadian variation in lung function, which is best around 4pm and worst around 4am. However, the variation of airway caliber size in subjects with nocturnal asthma is more pronounced and usually exceeds 20%.

The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours (Skloot G, 2002). The worsening of asthma at night commonly referred to as nocturnal asthma (Figure 1.6). Circadian variation in pulmonary function, as well as the effect of therapeutic interventions, can be readily demonstrated by having patients record peak expiratory flow rate values at different times of the day and night, using a peak flow meter. Nocturnal worsening of asthma has become a recognized and important problem that must be considered in the management of this disorder. It is quite common, as a survey of almost 8000 patients with varying degrees of asthma found that approximately 75 percent of asthmatics awaken at least once a week with symptoms, 64 percent three times per week, and 39 percent every night (Turner-Warwick M, 1988). The treatment of nocturnal asthma requires a chronopharmacologic approach, in which more intense therapy is targeted to coincide with the time that the disease is the worst (Figure 1.7).
Figure 1.6 Potential mechanisms that contribute to the worsening of asthma at night. Epi = epinephrine; Temp = temperature.

Figure 1.7 Epidemiology of nocturnal asthma

Theophylline is a bronchodilator used in the symptomatic treatment of mild bronchial asthma and reversible bronchospasm acts by inhibiting cyclic nucleotide phosphodiesterase (BP, 2007) and hence it is selected as a drug candidate for the treatment of nocturnal asthma considering its short half life (7-9h), good oral bioavailability (Sweetman SC, 2002) (96%) and good colonic absorption (Quadros et al., 1995). It is required to develop such formulation containing Theophylline, when administered in the evening should release the drug after 4-5h to achieve an elevated Theophylline level overnight when the risk of asthma is found to be maximum.
Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown etiology and a major cause of disability. It is characterized by joint synovial inflammation and progressive cartilage and bone destruction resulting in gradual immobility (Harris ED, 1990). The closest similarity with the daily pattern of RA symptoms, such as morning stiffness, joint pain and functional disability, seems to exist for interleukin (IL)-6. Pro-inflammatory hormones start to rise before the onset of RA symptoms and before endogenous cortisol in these patients is activated to counteract the inflammatory cascade of disease symptoms. It should be also noted that rhythmic fluctuations of the nocturnal secretion and the peripheral metabolism of endogenous cortisol, as well as changes in the activation of biologically inactive to active cortisone in the synovial cells, may play a role in the pathophysiology of RA (Figure 1.8). In patients with RA, inflammation induced changes in synovial fluid composition, oedema of the synovium and periarticular structures, as well as redistribution of interstitial fluid while sleeping, contribute to clinical stiffness of the joints that is most pronounced in the morning. The aim of rheumatoid arthritis treatment is to reduce inflammation in the joints, relieve pain, prevent or slow joint damage, reduce disability and provide support to help you live as active a life as possible. (Cutolo et al., 2003; Schmidt et al., 2005; Cutolo et al., 2007; Kurana and Berney, 2005; Choy et al., 2001)

![Figure 1.8 Epidemiology of rheumatoid arthritis](image)
Diclofenac sodium belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs) is considered to be first line agent which generally used for the treatment of RA. The primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX) and it appears to inhibit DNA synthesis (Botti and Youan, 2004). Since the therapy involves frequent administration of drug, chances of patient noncompliance increase drastically. Additionally, patients suffering from rheumatoid arthritis feel more pain in the morning hours. In this case taking medication at night is an obvious solution and hence drug need to be administered 4 to 6 hours before achieving their maximum benefits, as a result peak will occur at patients waking and the effect will be decline as patient start to wake up. With orally administering conventional Diclofenac sodium formulation, it is difficult to achieve the desired clinical effect, because it elicits patients’ noncompliance of administration in the early morning to coordinate the rhythm of these diseases, due to rapid absorption of the conventional formulation.

It is imperative to design a drug delivery system that administered at bedtime but releasing drug during morning hours would be ideal in this case. However, in comparison to the conventional formulation, colon specific drug delivery is very effective and more convenient for administration. Thus in present investigation orally-administered tablets of natural polysaccharide okra gum were prepared that would ensures chronotherapeutic delivery of drugs in colon for the treatment of diseases like asthma and rheumatoid arthritis.
1.9 REFERENCES


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