CHAPTER 1

INTRODUCTION
# Table of contents

<table>
<thead>
<tr>
<th>Section No.</th>
<th>Description</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Introduction to colon targeted drug delivery systems (CTDDS)</td>
<td>4</td>
</tr>
<tr>
<td>1.1.1</td>
<td>Factors to be considered in designing CTDDS</td>
<td>5</td>
</tr>
<tr>
<td>1.1.2</td>
<td>Classification of CTDDS</td>
<td>10</td>
</tr>
<tr>
<td>1.1.3</td>
<td><em>In-vitro</em> evaluation /Dosage form evaluation</td>
<td>15</td>
</tr>
<tr>
<td>1.1.4</td>
<td><em>In-vivo</em> methods for evaluation of dosage form</td>
<td>15</td>
</tr>
<tr>
<td>1.1.5</td>
<td>Drug candidates suitable for colonic delivery</td>
<td>17</td>
</tr>
<tr>
<td>1.1.6</td>
<td>Introduction to Crohn’s disease</td>
<td>18</td>
</tr>
<tr>
<td>1.1.7</td>
<td>Types of formulation for colon targeted drug delivery systems</td>
<td>19</td>
</tr>
<tr>
<td>1.2</td>
<td><strong>Introduction to drug</strong></td>
<td>20</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Introduction to Metronidazole</td>
<td>20</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Introduction to Satranidazole</td>
<td>24</td>
</tr>
<tr>
<td>1.3</td>
<td><strong>Introduction to polymers</strong></td>
<td>26</td>
</tr>
<tr>
<td>1.3.1</td>
<td>Eudragit® S100</td>
<td>26</td>
</tr>
<tr>
<td>1.3.2</td>
<td>Hydroxypropylmethylcellulose</td>
<td>27</td>
</tr>
<tr>
<td>1.3.3</td>
<td>Polyethylene oxide</td>
<td>28</td>
</tr>
<tr>
<td>1.3.4</td>
<td>Ethyl cellulose</td>
<td>29</td>
</tr>
<tr>
<td>1.3.5</td>
<td>Pectin</td>
<td>30</td>
</tr>
<tr>
<td>1.4</td>
<td><strong>Aim of present investigation</strong></td>
<td>31</td>
</tr>
<tr>
<td>1.5</td>
<td><strong>References</strong></td>
<td>33</td>
</tr>
</tbody>
</table>
List of Tables

<table>
<thead>
<tr>
<th>Table No.</th>
<th>Description</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Summary of anatomical and physiological features of small intestine and colon</td>
<td>7</td>
</tr>
<tr>
<td>1.2</td>
<td>Drug metabolizing enzymes in the colon that catalyze reactions</td>
<td>9</td>
</tr>
<tr>
<td>1.3</td>
<td>Various biodegradable polysaccharides</td>
<td>12</td>
</tr>
<tr>
<td>1.4</td>
<td>Drug candidates for CTDDS</td>
<td>17</td>
</tr>
<tr>
<td>1.5</td>
<td>List of marketed products of metronidazole</td>
<td>23</td>
</tr>
<tr>
<td>1.6</td>
<td>List of marketed combination products of metronidazole</td>
<td>23</td>
</tr>
<tr>
<td>1.7</td>
<td>List of marketed products of satranidazole</td>
<td>26</td>
</tr>
</tbody>
</table>

List of Figures

<table>
<thead>
<tr>
<th>Figure No.</th>
<th>Description</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Anatomy of Gastrointestinal tract</td>
<td>6</td>
</tr>
<tr>
<td>1.2</td>
<td>Colon targeting by prodrug approach</td>
<td>13</td>
</tr>
<tr>
<td>1.3</td>
<td>Osmotically controlled CTDDS</td>
<td>14</td>
</tr>
</tbody>
</table>
1.1) INTRODUCTION TO COLON TARGETED DRUG DELIVERY SYSTEMS (CTDDS)

Ongoing research in the area of oral delivery of drugs, a discipline which has basked in the spotlight of pharmaceutical sciences for the past 70 years, has led to improved and profound insights into the physiology, biology and physical chemistry (pharmacokinetics, partitioning phenomenon) of organs, compartments, cells, membranes, cellular organelles and functional proteins (e.g. transporters) associated with absorption processes of drugs in the gastrointestinal tract (GIT). Majority of the research has focused on delivery of drug to the small intestine. The large intestine, however, because of its remoteness and relatively different physiology acquired the status of an outcast. From last two decades, interest in area development of oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders.1

Colonic delivery offers several potential therapeutic advantages as a site for drug delivery, (a) The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. (b) The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. (c) The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. (d) Reduced proteolytic activity in the colon may be helpful in achieving reasonable absorption of certain drugs that are enzymatically labile in small intestine. (b) Reduced fluid motility and motility in the colon when compared with small intestine is advantageous formulation consists of multiple components such as permeation enhancers that must reach epithelial layer to achieve close spatial proximity with each other. (e) The colonic region has somewhat less hostile environment with less diversity and less intensity of activity as compared to stomach and small intestine.2-4

Targeting of drugs to the colon is of increasing importance for local treatment of inflammatory bowel diseases (IBD) of the colon such as ulcerative colitis and crohn’s disease (CD).5,6 The prevalence of ulcerative colitis and CD ranges from 10 to 70 per 100,000 people, but recent studies in Manitoba, Canada, and Rochester, MN, have shown prevalence as high as 200 per 100,000 people.7,8 Such inflammatory conditions are usually treated with conventional oral dosage forms.9,10 Treatment might be more
effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted on the colon. Site-specific means of drug delivery could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of the gastrointestinal tract.\textsuperscript{11,12} CTDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis.\textsuperscript{13,14} Colonic drug delivery can be achieved by oral or rectal administration. With regard to rectal route, the drugs do not always reach the specific sites of the colonic disease and the sites of colonic absorption. To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage form must be formulated taking into account the obstacles of gastrointestinal tract.\textsuperscript{15,16}

1.1.1) Factors to be considered in designing CTDDS

Formulations for colonic delivery are, in general, delayed-released dosage forms which may be designed either to provide a ‘burst release’ or a sustained / prolonged / targeted. Factors to be considered for designing CTDDS are explained below:

\textbf{(A) Anatomy and physiology of colon}\textsuperscript{17-21}

Most digestion and absorption occurs in the small intestine. The small intestine has 3 parts: the duodenum, the jejunum, and the ileum. Enzymes and other substances made by intestinal cells, the pancreas, and the liver are secreted into the small intestine and breakdown starches, sugars, fats, and proteins. Absorption of nutrients occurs through the millions of tiny fingerlike projections called villi and the even tinier projections on the villi called microvilli. Any undigested material moves to the large intestine. The large intestine has 3 parts: the cecum, the colon, and the rectum. The main function of the large intestine is to remove water and salts (electrolytes) from the undigested material and to form solid waste (feces) that can be excreted. The remaining contents of the large intestine move to the rectum, where feces are stored until they leave the body through the anus as a bowel movement.
In mammals colon is further subdivided into the ascending colon, transverse colon, the descending colon and the sigmoid colon. The colon from cecum to the mid transverse colon is also known as the right colon. The remainder is known as the left colon. The location of the parts of the colon are either in the abdominal cavity or behind it in the retroperitoneum.

**Ascending colon:** The ascending colon is on the right side of the abdomen. It is the part of the colon from the cecum to the hepatic flexure (the turn of the colon by the liver). It is retroperitoneal in most humans. In grazing animals the cecum empties into the spiral colon.

![Anatomy of Gastrointestinal tract](image)

**Figure 1.1: Anatomy of Gastrointestinal tract**

**Transverse colon:**
The transverse colon is the part of the colon from the hepatic flexure (the turn of the colon by the liver) to the splenic flexure (the turn of the colon by the spleen). The transverse colon hangs off the stomach, attached to it by a wide band of tissue called the greater omentum. On the posterior side, the transverse colon is connected to the posterior abdominal wall by a mesentery known as the transverse mesocolon. The transverse colon is encased in peritoneum, and is therefore mobile (unlike the parts of the colon immediately before and after it). As the path progresses from intestine the the solid content increases as water gets absorbed.
Descending colon:
The descending colon is the part of the colon from the splenic flexure to the beginning of the sigmoid colon. It is retroperitoneal in two-thirds of humans. In the other third, it has a (usually short) mesentery.

**Table 1.1: Summary of anatomical and physiological features of small intestine and colon**

<table>
<thead>
<tr>
<th>Region of Gastrointestinal Tract Characteristics</th>
<th>Characteristics</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>150-250</td>
</tr>
<tr>
<td>Ileum</td>
<td>200-350</td>
</tr>
<tr>
<td>Large Intestine</td>
<td></td>
</tr>
<tr>
<td>Cecum</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>
<tr>
<td>Internal diameter (cm)</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>3-4</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>6</td>
</tr>
<tr>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
</tr>
<tr>
<td>Fasted</td>
<td>1.5-3</td>
</tr>
<tr>
<td>Fed</td>
<td>2-5</td>
</tr>
<tr>
<td>Small intestine</td>
<td></td>
</tr>
<tr>
<td>Duodenum (fasted)</td>
<td>~ 6.1</td>
</tr>
<tr>
<td>Duodenum (fed)</td>
<td>~ 5.4</td>
</tr>
<tr>
<td>Ileum</td>
<td>~ 7-8</td>
</tr>
<tr>
<td>Large intsetine</td>
<td></td>
</tr>
<tr>
<td>Cecum and colon</td>
<td>~ 5.5-7</td>
</tr>
<tr>
<td>Rectum</td>
<td>7</td>
</tr>
</tbody>
</table>

Sigmoid colon:
The sigmoid colon is the part of the large intestine after the descending colon and before the rectum. The name *sigmoid* means S-shaped. The walls of the sigmoid colon
are muscular, and contract to increase the pressure inside the colon, causing the stool to move into the rectum.

(B) pH of the colon\textsuperscript{17,22}

High pH gradient exists between the different parts of GIT. pH gradient between saliva and gastric juice and between gastric juice and intestinal juice is considerably high but that between different parts of intestine is low. The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state, and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeting drug to the colon. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. The pH difference between the stomach and the small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in the pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by colonic bacteria to produce large amounts of lactic acid resulting in drop in the pH to about 5.0

(C) Colonic microflora\textsuperscript{17,23}

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut Microflora residing in high number in the colon. Colon consists of a more than 500 different types of enzyme liberating symbiotic anaerobes. These enzymes derived from microbes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent i.e. release drug from the polymeric prodrugs. There is a vast difference in the microflora count of intestine and cecum. This is due to the retardation of movement of the contents within the gastro intestinal tract due to widening of the intestinal lumen as it moves from the ileum to the cecum and to the ascending colon. These facts and the bag shaped nature of the cecum make this site the favourite region for microbial settlement.

Intestinal microflora count: $10^3$ CFU/ml

Colonic microflora count: $10^{12}$ CFU/ml
During illness and antibiotic therapy there is reversible destruction of microbes. The most important anaerobic bacteria are bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium and Clostridium.

Table 1.2: Drug metabolizing enzymes in the colon that catalyze reactions

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Microorganism</th>
<th>Metabolic reaction catalyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Oxide reductase,</td>
<td>E. coli</td>
<td>Reduce N-Oxides and sulfoxides</td>
</tr>
<tr>
<td>Sulfoxide reductase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucosidase</td>
<td>Clostridia, Eubacteria</td>
<td>Cleavage of β-glycosidases of Alcohols and phenols</td>
</tr>
<tr>
<td>Hydrogenase</td>
<td>Clostridia, Lactobacilli</td>
<td>Reduce carbonyl groups and aliphatic double bonds</td>
</tr>
<tr>
<td>Sulfatase</td>
<td>Clostridia, Eubacteria, Streptococci</td>
<td>Cleavage of O-sulfates and sulfamates</td>
</tr>
<tr>
<td>Esterases and amidases</td>
<td>E. coli, P. vulgaris, B. subtilis, B. mycoides</td>
<td>Cleavage of esters or amidases of carboxylic acids</td>
</tr>
<tr>
<td>Glucuronidase</td>
<td>E. coli, A. aerogenes</td>
<td>Cleavage of β-glucuronidases of Alcohols and phenols</td>
</tr>
<tr>
<td>Nitroreductase</td>
<td>E. coli, Bacteroids</td>
<td>Reduce aromatic acid and heterocyclic nitro compound</td>
</tr>
<tr>
<td>Azoreductase</td>
<td>Clostridia, Lactobacilli, E. coli</td>
<td>Reductive cleavage of azo compounds</td>
</tr>
</tbody>
</table>

(D) Transit time to colon

Gastric emptying of dosage form 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. Arrival time of a drug or dosage form in the colon is subject to the vagaries of the gastric emptying and intestinal transit time. Under normal conditions transit time to colon is between 5 to 7 h.

Approximate transit time of different organs.

- Stomach - 2 h
- Upper small intestine - 1 h
- Lower small intestine - 2 h

So, overall transit time is approximately 5 h.
But this transit time varies with fed and fasted state of GIT. Under fasted state transit time is between 3 to 5 h and in fed state it is between 6 to 10 h.

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

1.1.2) Classification of CTDDS

CTDDS can be classified as follows:

1) pH dependent systems.
2) Time dependent systems.
3) Bacterial enzyme dependent system.
4) Covalent linkage of a drug with a carrier
5) Redox release system.
6) Bioadhesive systems.
7) Coating with microparticles.
8) Osmotic controlled drug delivery.

1) pH dependent systems

pH of human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum.

The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction.

These processes distribute the drug throughout the large intestine and improve the potential of CTDDS.
Disadvantages of pH dependent systems

- Lack of consistency in the dissolution of polymer at the desired site.
- Moreover, many factors such as the presence of short chain fatty acids, residues of bile acids, carbon dioxide or other fermentation products can reduce the colonic pH to approximately 6 which can certainly affect the release of drug in the colon.
- Certain disease state does alter the pH of the colon.

2) Time dependent systems\textsuperscript{17}

Strategy of time released system is to resist the acidic environment of stomach and release the drug after predetermined lag time, after which release of drug take place.

**Factors affecting release from time dependent systems**

Residence time plays a key role here along with it Fed and fasted state of the subject and the interdigestive phase may prolong emptying time of stomach.

Residence time of stomach (approx.) – 2 h

small intestine (approx.) – 2 to 4 h

**Disadvantages of time dependent systems:**

Individual to individual variation arises due to health, pathologic state, concomitant medication which causes Premature / Delayed drug release.

3) Bacterial enzyme dependent system\textsuperscript{17,26,27}

The bioenvironment inside the human GIT is characterized by the presence of complex microflora especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary component or other materials.

Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, have been exploited in designing drugs for colon targeting.
Table 1.3: Various biodegradable polysaccharides

<table>
<thead>
<tr>
<th>Polysaccharide</th>
<th>Bacterial species that degrade polysaccharide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar gum</td>
<td>Bacteroids, Ruminococcus</td>
</tr>
<tr>
<td>Pectin</td>
<td>Bacteroids, Bifidobacterium, Eubacterium</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Dextran</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Xylan</td>
<td>Bacteroids, Bifidobacterium</td>
</tr>
<tr>
<td>Amylose</td>
<td>Bacteroids, Bifidobacterium</td>
</tr>
<tr>
<td>Cyclodextran</td>
<td>Bacteroids</td>
</tr>
<tr>
<td>Arabinogalactan</td>
<td>Bifidobacterium</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Bacteroids</td>
</tr>
</tbody>
</table>

Actually, upon passage of the CTDDS through the GIT, it remains intact in the stomach and small intestine where very little microbially degradable activity is present that is quite insufficient for cleavage of polymer coating.

Release of the drugs from polysaccharide based formulation is supposed to take place after degradation of polysaccharide by the enzymes released from bacterias present in the colonic microflora.

4) Covalent linkage of the drug with a carrier

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine.

This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug.

The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon.

Site specific drug delivery through site specific prodrug activation may be accomplished by the utilization of some specific property at the target site, such as altered pH or high activity of certain enzymes relative to the non-target tissues for the prodrug-drug conversion.
5) Redox sensitive polymers

Novel polymers that hydrolyzed nonenzymatically by enzymatically generated flavins are being developed for colon targeting.

Under anaerobic conditions, bacterial azo reduction by enzymatically generated reduced flavins where the initial substrate thought to be involved in cellular electron transport requires the presence of NADPH as its electron source.

As NADPH is oxidized, the electron mediator (reduced flavins) acts as an electron shuttle from the NADPH dependent flavoprotein to the azo compound.

Reduction of the azo bond to the hydroazo intermediate requires a low electron density within the azo region, and thus substitution of electron-withdrawing groups will favor this reaction.

Redox potential is an expression of the total metabolic and bacterial activity in the colon and it is believed to be insensitive to dietary changes.

The mean redox potential in proximal small bowl is -67 ± 90 mv, in the distal small bowl is -196 ± 97 mv and in the colon is -145 ± 72 mv.

Microflora-induced changes in the redox potential can also be used as a highly selective mechanism for targeting to the colon.

6) Bioadhesive systems

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects.

Dissolution of dosage form and simultaneous absorption from upper GIT lead to low intracolonic drug concentration as well as absorption of drugs result in the generation of side effects.
Bioadhesion is a process whereby drug remains in contact with a particular organ for a longer period of time.

It may be used for improved absorption of poorly absorbable drugs.

Polymers: polycarbophils, polyurethanes and poloxamers.\textsuperscript{28,29}

7) Coating with microparticles\textsuperscript{30}

It consists of small silica particles (5-10 µm in diameter) covalently linked to a drug.

8) Osmotic controlled drug delivery\textsuperscript{31,32}

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 with in a hard gelatin capsule.

Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable 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.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{osmotic_push_pull_unit.png}
\caption{Osmotically controlled CTDDS\textsuperscript{27}}
\end{figure}

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 semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine.

1.1.3) *In-vitro evaluation / Dosage form evaluation*²²

Basically three methods exist depending on the type of the preparation i.e. whether it is pH dependent system or system degraded by bacterial microflora.

1) **Testing in different buffer solution for pH sensitive polymer**

Coats / Carrier should remain intact for 2 h in 0.1 N HCl (pH 1.2) and Sorensen’s or Phosphate buffer (pH 7.4). It should start releasing the contents at colonic pH of 6.8.

2) **Addition of colonic bacterial strains in buffer solution**

The most widely used microbial strains used to test colon targeting and enzymatic biodegradation of the carrier are microorganisms with azoreductases and glycosidases.

3) **Addition of colonic bacterial strains in fermenter**

Fermenter with commonly found human colonic bacteria like Streptococcus faecium or Bacteriode ovatus under anaerobic conditions can also be used.

4) **Addition of rat fecal mass in buffer solution**

In invivo conditions one can use colonic microflora obtained from feces. Rat fecal mass obtained after enzyme induction for 7 days gives sufficient enzymatic activity.

1.1.4) *In-vivo methods for evaluation of dosage form*²²

1) **String technique:** In these a tablet was attached to a piece of string and the subject swallowed the tablet, leaving the free end of the string hanging from his mouth. At various time points, the tablet was withdrawn from the mouth by pulling out the string and physically examining the tablet for the signs of disintegration. In some studies the tablets were recovered by inducing a vomiting reflex.

2) **Endoscope technique:** It is an optical technique in which a fibre scope (gastrocope) is used directly monitor the behaviour of the dosage form after ingestion.
This method requires administration of a mild sedative to facilitate the swallowing of the endoscopic tube.

3) Radiotelemetry: A capsule consisting of pH probe attached to radio transmitter is inserted inside the body.

The changes in the pH is captured by the pH probe and is transmitted by the radio transmitter to the recorder.

4) Roentgenography: The inclusion of the radio-opaque material into a solid dosage form enables it to be viewed by X-ray.

By incorporating barium sulphate into a pharmaceutical dosage form, it is possible to follow the movement, location and the integrity of the dosage form after oral administration by placing the subject under fluoroscope and taking a series of X-ray at various time points.

5) Gamma scintigraphy: Gamma emitting radioactive isotope can be detected by gamma camera

**Advantage:** It gives qualitative estimation of dosage form quantitative drug release from it.

**Disadvantage:** Requires qualified personnel

- It is not possible to label all the compounds
- Gamma scintigraphy assembly is expensive

**Selection of radioisotopes:**

**Neutron activating isotopes**

- Direct compression tablets, capsules: Indium-111 (In-111) and Technetium-99m (Tc-99m)

**Positron emitting isotopes: emit photons**


**Uses:**

- Determination of GI transit times
- Invivo disintegration and site specificity
- Invivo performance of sustained action dosage form
- Correlation of Pharmacokinetic parameters: Pharmacoscintigraphy
1.1.5) Drug candidates suitable for colonic delivery

Drug delivery selectively to the colon through oral route is becoming increasingly popular for the treatment of large intestinal diseases and for systemic absorption of peptides and protein drugs. The best Candidates for CTDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. Drug Carrier is another factor which influences CTDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example; aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems. Drug candidates for CTDDS are also selected on the basis of disease condition and site of action required (refer table 1.4).

Table 1.4: Drug candidates for CTDDS

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Disease condition</th>
<th>Drugs and active agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic action</td>
<td>Oral delivery of peptides</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Oral delivery of vaccines</td>
<td>Typhoid</td>
</tr>
<tr>
<td></td>
<td>To prevent gastric irritation</td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>To prevent first pass metabolism of orally</td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>ingested drugs</td>
<td></td>
</tr>
<tr>
<td>Local/Topical action</td>
<td>Inflammatory Bowel Diseases, Irritable bowel</td>
<td>Hydrocortisone, Budenoside, Prednisolone, Sulfasalazine, Olsalazine, Mesalazine, Balsalazide and Antibiotics</td>
</tr>
<tr>
<td></td>
<td>disease and CD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td>5-Flourouracil.</td>
</tr>
</tbody>
</table>

It is well recognized that peptides and proteins are well absorbed intact from the gastrointestinal tract, but the bioavailability is invariably extremely low, with exceptions, such as di and tripeptide analogues and cyclosporine. A variety of protein and peptide drugs like calcitonin, interferon, interleukins, erythropoietin, growth hormones and even insulin are being investigated for their systemic absorption using colon-specific delivery. Inflammatory bowel diseases (IBD) such as ulcerative colitis and CD require selective local delivery of the drug to the colon. Sulfasalazine
is the most commonly prescribed medication for such diseases.\textsuperscript{37} The other drugs used in IBD are steroids such as dexamethasone, prednisolone and hydrocortisone. In colonic cancer, anticancer drugs like 5-fluorouracil, doxorubicin and nimustine are to be delivered specifically to the colon. The site-specific delivery of drugs like, metronidazole (MTZ), satranidazole (STZ) mebendazole, tinidazole, ornidazole and albendazole are used in the treatment of infectious diseases such as amoebiasis and helmenthiasis. Because of small extent of paracellular transport, the colon is a more selective site for drug absorption than the small intestine. Drug shown to be well absorbed include glibenclamide, diclofenac, theophylline, ibuprofen, metoprolol and oxprenolol.\textsuperscript{22} CTDDS for theophylline could prove beneficial for asthmatic patients since asthma shows a diurnal rhythm. The incidence of asthmatic attacks is, for example, greatest during the early hours of the morning. Because dosage forms remain longer in the large intestine than in the small intestine, CTDDS could be used to prolong drug release.\textsuperscript{38}

1.1.6) Introduction to Crohn’s disease\textsuperscript{39,40}

Current research work is focused on developing CTTDS for CD. CD is a chronic inflammatory disease of the intestines. It primarily causes ulcerations (breaks in the lining) of the small and large intestines, but can affect the digestive system anywhere from the mouth to the anus. It is named after the physician who described the disease in 1932. It also is called granulomatous enteritis or colitis, regional enteritis, ileitis, or terminal ileitis.

CD is related closely to another chronic inflammatory condition that involves only the colon called ulcerative colitis. Together, CD and ulcerative colitis are frequently referred to as inflammatory bowel disease (IBD). Once the diseases begin, they tend to fluctuate between periods of inactivity (remission) and activity (relapse). IBD most commonly begins during adolescence and early adulthood (usually between the ages of 15 and 35). CD tends to be more common in relatives of patients with CD.

In the early stages, CD causes small, scattered, shallow, crater-like ulcerations (erosions) on the inner surface of the bowel. With time, the erosions become deeper and larger, ultimately becoming true ulcers (which are deeper than erosions), and causing scarring and stiffness of the bowel. As the disease progresses, the bowel becomes increasingly narrowed, and ultimately can become obstructed. Deep ulcers
can puncture holes in the wall of the bowel, and bacteria from within the bowel can spread to infect adjacent organs and the surrounding abdominal cavity.

When CD narrows the small intestine to the point of obstruction, the flow of the contents through the intestine ceases. The symptoms of small intestinal obstruction then appear, including severe abdominal cramps, nausea, vomiting, and abdominal distention. Deep ulcers can puncture holes in the walls of the small intestine and the colon, and create a tunnel between the intestine and adjacent organs. If the ulcer tunnel reaches an adjacent empty space inside the abdominal cavity, a collection of infected pus (an abdominal abscess) is formed. Individuals with abdominal abscesses can develop tender abdominal masses, high fevers, and abdominal pain.

1.1.7) Types of formulation for colon targeted drug delivery systems

Colon targeted drug delivery system have been classified into two types:

a) **Single unit CTDDS**: It may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon.

b) **Multiparticulate CTDDS**: In comparison to single unit systems, these systems offer potential benefits, like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. Multiparticulate formulations enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time, as compared to single unit systems. Because of their smaller particle size as compared to single unit dosage forms these systems tend to be more uniformly dispersed in the GIT and also ensure more uniform drug absorption.
1.2) INTRODUCTION TO DRUG

1.2.1) Introduction to Metronidazole

Introduction

Chemical name: 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole or 2-methyl-5-nitroimidazole-1-ethanol

Derivatives: Hydrochloride, Benzoate and Mesylate

Empirical formula: \( \text{C}_6\text{H}_9\text{N}_3\text{O}_3 \)

Molecular weight: 171.16

Structural formula:

![Structural formula of Metronidazole](image)

Appearance: White to offwhite, crystalline odourless powder

Melting point: Crystals- 158 to 160 °C

Solubility: Slightly soluble in water and ethanol, very slightly soluble in ether.

Mechanism of action

MTZ is a prodrug; it requires reductive activation of the nitro group by susceptible organisms. MTZ, taken up by diffusion, is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it is non-enzymatically reduced by reacting with reduced ferredoxin, which is generated by pyruvate oxido-reductase. This reduction causes the production of toxic products to anaerobic cells, and allows for selective accumulation in anaerobes.

MTZ metabolites are taken up into bacterial DNA, and form unstable molecules. This function only occurs when MTZ is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria.

Pharmacokinetics

Preparations of MTZ are available for oral, intravenous, intravaginal, and topical administration.

Absorption: The drug usually is absorbed completely and promptly after oral intake, reaching concentrations in plasma of 8 to 13 mg/ml within 0.25 to 4 h after a single
500-mg dose. (Mean effective concentrations of the compound are 8 mg/ml or less for most susceptible protozoa and bacteria.) A linear relationship between dose and plasma concentration pertains for doses of 200 to 2000 mg. If given with food, absorption is enhanced in dogs, but delayed in humans. Peak levels occur about one hour after dosing. With the exception of the placenta, MTZ penetrates well into body tissues and fluids, including vaginal secretions, seminal fluid, saliva, and breast milk. Therapeutic concentrations also are achieved in CSF.

**Distribution:** MTZ is rather lipophilic and is rapidly and widely distributed after absorption. It is distributed to most body tissues and fluids, including to bone, abscesses, the CNS, and seminal fluid. It is less than 20% bound to plasma proteins in humans. Volume of distribution is approximately that of total-body water. Less than 20% of the drug is bound to plasma proteins.

**Metabolism and Excretion:** After an oral dose, over 75% of labeled MTZ is eliminated in the urine largely as metabolites; only about 10% is recovered as unchanged drug. The liver is the main site of metabolism, and this accounts for over 50% of the systemic clearance of MTZ. The two principal metabolites result from oxidation of side chains, a hydroxy derivative and an acid. The hydroxy metabolite has a longer half-life (about 12 h) and contains nearly 50% of the antitrichomonal activity of MTZ. Formation of glucuronides also is observed. Small quantities of reduced metabolites, including ring-cleavage products, are formed by the gut flora. The urine of some patients may be reddish brown owing to the presence of unidentified pigments derived from the drug. Oxidative metabolism of MTZ is induced by *phenobarbital*, *prednisone*, *rifampin*, and possibly *ethanol*. *Cimetidine* appears to inhibit hepatic metabolism of the drug.

**Half-Life**\(^{36}\): The half-life of MTZ after single, intravenous infusion has been reported as 7.3 ± 1.0 h. Elimination half-lives of MTZ in dogs is 4-5 h and in horses is 2.9-4.3 h.

**Dosage and Administration**\(^ {37}\)
A maximum of 4 g should not be exceeded in a 24-h period. For prophylactic use, the appropriate dose should be infused shortly before surgery and repeated every eight h for the next 24 h. In the elderly patients and in hepatic disease, the pharmacokinetics of MTZ may be altered: therefore monitoring of serum levels may be necessary to adjust MTZ dosage accordingly.
**Therapeutic Uses**

The uses of MTZ for antiprotozoal therapy have been reviewed extensively. MTZ cures genital infections with *T. vaginalis* in both females and males. It is an effective amebicide and is the agent of choice for the treatment of all symptomatic forms of amebiasis, including amebic colitis and amebic liver abscess. It is also used for the therapy of giardiasis and trichomoniasis. It is used for the treatment of serious infections owing to susceptible anaerobic bacteria, including *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptococcus*, *Peptostreptococcus*, *Eubacterium*, and *Helicobacter*. The drug is also given in combination with other antimicrobial agents to treat polymicrobial infections with aerobic and anaerobic bacteria. MTZ is being used increasingly as primary therapy for *Clostridium difficile* infection, the major cause of pseudomembranous colitis. Finally, MTZ is used in the treatment of patients with CD who have perianal fistulas, and it can help control CD.

**Contraindications**

- Patients with evidence of a history of blood dysterias should not receive MTZ since occasionally leucopenia has been observed during its administration.
- Active organic disease of the central nervous system.
- Pregnancy (first trimester)

**Adverse effects**

Rash, pruritis, urticaria, nausea, anorexia, furry tongue, dry mouth, abdominal discomfort, glossitis, stomatitis (which may be associated with *Candida* overgrowth), Metallic or unpleasant taste in the mouth, headaches and dizziness, Joint pains, Nasal congestion, lack of co-ordination, ataxia, convulsive seizures, confusion, irritability, depression, weakness, insomnia, disorientation and peripheral neuropathy.

**Interactions**

**Alcohol:** MTZ taken in combination with alcohol may produce abdominal cramps, nausea, vomiting, headache and flushing.

**Disulfiram:** In a clinical trial of combined therapy with disulfiram and MTZ in the treatment of chronic alcoholics, severe acute psychotic reactions occurred in 6 out of 29 patients.

**Warfarin:** MTZ inhibits the breakdown of the more potent S-isomer of warfarin. This is the pharmacologically active metabolite of the racemic parent molecule. Therefore, the activity of warfarin is enhanced by MTZ.
**Phenobarbitone:** Decreases the effect of MTZ probably due to increased metabolism.

**Cyclophosphamide and Carmustine:** MTZ should be used with caution in patients who are receiving cyclophosphamide or carmustine as a drug interaction shown in mice, leads to increased toxicity.

**Marketed Products**

**Table 1.5: List of marketed products of metronidazole**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dosage Form</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldezole®</td>
<td>200 mg, 400 mg tablets, 200 mg suspension and 500 mg injection</td>
<td>Albert David</td>
</tr>
<tr>
<td>Antamebin®</td>
<td>200 mg tablets and 200 mg suspension</td>
<td>Raptakos</td>
</tr>
<tr>
<td>Aristogyl®</td>
<td>200 mg, 400 mg tablets and 100 mg suspension</td>
<td>Aristo</td>
</tr>
<tr>
<td>Balgy®</td>
<td>1% gel</td>
<td>Bal Pharma</td>
</tr>
<tr>
<td>Compeba®</td>
<td>200 mg tablets</td>
<td>IDPL</td>
</tr>
<tr>
<td>Flagyl®</td>
<td>200 mg, 400 mg tablets and 200 mg suspension</td>
<td>NPIL</td>
</tr>
<tr>
<td>Metrogyl®</td>
<td>200 mg, 400 mg tablets, 200 mg suspension and 500 mg injection, 1% dental and vaginal gel</td>
<td>J B Chemicals</td>
</tr>
<tr>
<td>Metron®</td>
<td>200 mg, 400 mg tablets and 200 mg suspension</td>
<td>Alkem</td>
</tr>
<tr>
<td>Metgyl®</td>
<td>200 mg and 400 mg tablets</td>
<td>Jagsonpal</td>
</tr>
<tr>
<td>Unimezol®</td>
<td>200 mg, 400 mg tablets and 200 mg suspension</td>
<td>Unichem</td>
</tr>
<tr>
<td>Met®</td>
<td>400 mg tablets</td>
<td>Ind-Swift</td>
</tr>
</tbody>
</table>

**Table 1.6: List of combination products of metronidazole**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Combination and Dosage Form</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdogyl-N®</td>
<td>200 mg metronidazole + 300 mg nalidixic acid tablets and suspension</td>
<td>Glaxo Smithkline Beechem</td>
</tr>
<tr>
<td>Amibex®</td>
<td>300 mg metronidazole + 100 mg furazolidine tablets</td>
<td>Ind-Swift</td>
</tr>
<tr>
<td>Aristogyl-F®</td>
<td>400 mg metronidazole + 100 mg Furazolidine + 50 mg Simethicone tablets</td>
<td>Aristo</td>
</tr>
</tbody>
</table>
Table 1.6: List of combination products of metronidazole (continued)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Combination and Dosage Form</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metrohex®</td>
<td>1% metronidazole + 0.25% chlorhexidine gel</td>
<td>Dr. Reddy’s Laboratory</td>
</tr>
<tr>
<td>Metrokind-P®</td>
<td>1% metronidazole + 5% povidone iodine gel</td>
<td>Mankind</td>
</tr>
<tr>
<td>Diof®</td>
<td>600 mg metronidazole + 200 mg ofloxacin tablets</td>
<td>Zuventus</td>
</tr>
<tr>
<td>Stedmox-M®</td>
<td>200 mg metronidazole + 250 mg amoxicillin capsules</td>
<td>Stedman</td>
</tr>
<tr>
<td>Dyrade-M®</td>
<td>200 mg metronidazole + 250 mg diloxanide tablets and suspension</td>
<td>Cipla</td>
</tr>
<tr>
<td>Gramogyl®</td>
<td>100 mg metronidazole + 100 mg norfloxacin suspension</td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>Fenigyl®</td>
<td>200 mg metronidazole + 200 mg norfloxacin tablets and suspension</td>
<td>Finecure</td>
</tr>
</tbody>
</table>

1.2.2) Introduction to Satranidazole

Introduction

Chemical name: 1-methylsulfonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone.

Empirical formula: C₁₈H₁₁N₅O₅S

Molecular weight: 289.27 g/mol

Structural formula:

![Structural formula of Satranidazole]

Appearance: White to offwhite, crystalline odourless powder

Melting point: 184–189°C

Solubility: Sparingly soluble in water and ethanol.
Mechanism of action

It is similar in action to that of MTZ. Satranidazole has been shown to damage DNA as a consequence of reduction of the nitro group. The features of the damage viz. helix destabilization, strand breakage and the release of thymine derivatives are typical of 5-nitroimidazole drugs. However, satranidazole shows some properties which differ from other 5-nitroimidazoles. For example, its reduction potential of -230 mV is higher than those of other 5-nitroimidazoles and is more typical of 2-nitroimidazole drugs. Further, its electron stoichiometry for reduction being 4 is again more typical of 2-nitroimidazoles than the non-integral values of 5-nitroimidazoles as is the pattern of nitrite release and this may be a consequence of the unusual C-N bonding at C2 of the imidazole ring not seen in other drugs of this type. The lowered electron values for reduction in the presence of DNA are also characteristic of nitroimidazoles and indicate that an electron affinic reduced intermediate is capable of abstracting electrons from DNA, thereby oxidizing it, causing strand breaks presumably in the region of thymidine residues.

Pharmacokinetics

Satranidazole is not official in any pharmacopoeia and is not marketed in US and Europe. Pharmacokinetics of STZ is not extensively studied. The only pharmacokinetic study carried out was in the golden hamster (Mesocricetus auratus) at a dose of 80 mg/kg po which was compared with MTZ at same dose. Blood and liver samples were collected at frequent time intervals and assayed for MTZ and satranidazole by HPLC. Satranidazole exhibited significantly higher plasma concentrations than MTZ at 1 and 2 h post-dose, but the comparative $C_{\text{max}}$ values were not significantly different. The satranidazole plasma elimination half-life of 1.01 h was significantly shorter than the corresponding MTZ half-life of 3.62 h. The comparative liver pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$ and $T_{1/2}$, did not differ significantly. Satranidazole however exhibited significantly higher liver concentrations at 1 h post-dose and $C_{\text{max}}$ values were approximately 35% higher.

Excretion: Half-life: 14 h in human
Dosage and Therapeutic uses\textsuperscript{67}

It possesses potent antiprotozoal activity against Entamoeba histolytica, Treponema vaginalis, and Giardia

Amoebic liver abscess: 300 mg bid for 10 days (Adult dose).

Giardiasis: 600 mg as a single dose (Adult dose).

Trichomoniasis: 600 mg as a single dose (Adult dose).

Contraindications\textsuperscript{67}

Pregnancy and lactation.

Adverse effects\textsuperscript{67}

Headache, dry mouth, weakness and dizziness.

Interactions\textsuperscript{67}

STZ taken in combination with alcohol may produce abdominal cramps, nausea, vomiting, headache and flushing. May result in disulfiram-like reaction when used with alcohol.

Marketed Products

Table 1.7: List of marketed products of satranidazole

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Dosage Form</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satrogyl\textsuperscript{97}</td>
<td>300 mg satranidazole tablets</td>
<td>Alkem</td>
</tr>
<tr>
<td>Satromax\textsuperscript{96}</td>
<td>300 mg satranidazole tablets</td>
<td>Indchem</td>
</tr>
<tr>
<td>Satrogyl O\textsuperscript{95}</td>
<td>300 mg satranidazole and 200 mg ofloxacin tablets</td>
<td>Alkem</td>
</tr>
<tr>
<td>Satromax O\textsuperscript{96}</td>
<td>300 mg satranidazole and 200 mg ofloxacin tablets</td>
<td>Indchem</td>
</tr>
</tbody>
</table>

1.3) INTRODUCTION TO POLYMERS

1.3.1) Eudragit\textsuperscript{®} S100\textsuperscript{68,69}

The aim of the present investigation was to design and develop CTDDS. Eudargit S100 dissolves above pH 7.0 and thus helps protect the system against harsh acidic condition of stomach and thus it may act as one of the guiding tool to target drug to colon.

Nonproprietary names

- Ph Eur: Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)
- USP/NF: Methacrylic Acid Copolymer, Type B
- JPE: Methacrylic Acid Copolymer S
- Ph. Mex.: Polimetacrilatos Tipo B
Description
White powder with a faint characteristic odour.

Chemical name
Poly (methacrylic acid, methyl methacrylate) 1:2

Chemical structure

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_2 \quad \text{CH}_2 \\
\text{C} \quad \text{C} \\
\text{C} = \text{O} \\
\text{OH} \\
\text{CH}_3 \\
\end{array}
\]

The ratio of the free carboxyl groups to the ester groups is approximately 1:2 in Eudragit S 100.

Solubility
1 g Eudragit S 100 dissolves in 7 g methanol, ethanol, in aqueous isopropyl alcohol and acetone (containing approx. 3 % water), as well as in 1 N sodium hydroxide to give clear to slightly cloudy solutions.

Eudragit S 100 is practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.

Safety
A daily intake of 2mg/kg body weight of Eudragit (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

Regulatory Status
Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK. Included in Canadian list of Applicable Non-medicinal Ingredients.

1.3.2) Hydroxypropylmethylcellulose

Nonproprietary names
- BP: Hypromellose
- USP: Hypromellose
- PhEur: Hypromellose
JP: Hydroxypropylmethylcellulose

**Description**

Hypromellose is an odorless and tasteless, white or creamy fibrous or granular powder

**Chemical name**

Cellulose hydroxypropyl methyl ether

**Chemical structure**

![Chemical structure of Hypromellose](image)

**Solubility**

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

**Safety**

WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.

**Regulatory Status**

GRAS listed. Accepted for use as food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, syrups, suspensions and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in Canadian list of Applicable Non-medicinal Ingredients.

1.3.3) Polyethylene oxide[^68]

**Nonproprietary names**

USPNF: Polyethylene oxide

**Description**

White to off-white, free flowing powder. Slight ammonical odor.
Chemical name
Polyethylene oxide

Chemical structure

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
n
\end{array}
\]

Solubility
Polyethylene oxide is soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.

Safety
Animal studies suggest that polyethylene oxide has a low level of toxicity regardless of route of administration.

Regulatory Status
Included in the FDA Inactive Ingredients Guide (sustained release tablets). Included in Canadian list of Applicable Non-medicinal Ingredients.

1.3.4) Ethyl cellulose

Nonproprietary names
- BP: Ethylcellulose
- USPNF: Ethylcellulose
- PhEur: Ethylcellulosum

Description
Ethylcellulose is tasteless, free flowing, white to light tan-colored powder.

Chemical name
Cellulose ethyl ether

Chemical structure
Solubility
Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethyl acetate, ethanol (95%), methanol, and toluene.

Safety
As ethyl cellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake.

Regulatory Status
GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions and tablets; topical emulsions and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in Canadian list of Applicable Non-medicinal Ingredients.

1.3.5) Pectin

Nonproprietary names
USPNF: Pectin

Description
Pectin occurs as a coarse or fine, yellowish-white, odorless powder that has a mucilaginous taste.

Chemical name
Pectin

Chemical structure
Solubility
Soluble in water, insoluble in ethanol (95%) and other organic solvents.

Safety
Pectin is generally regarded as an essentially nontoxic and nonirritant material.

Regulatory Status
GRAS listed. Accepted for use as food additive in Europe. Included in the FDA Inactive Ingredients Guide (dental paste; oral powders; topical pastes). Included in nonparenteral medicines licensed in the UK. Included in Canadian list of Applicable Non-medicinal Ingredients.

1.4) AIM OF THE PRESENT WORK
Medical rational for the development of oral CTDDS include: (a) the opportunity to reduce adverse effects in the treatment of colon inflammation and colon motility disorders by topical delivery of drugs at the mucosal level; (b) the elucidation of the mode of action of some nonsteroidal anti-inflammatory drugs (NSAID), that were found to interfere with the proliferation of colon polyps (first stage in colon carcinoma), possibly in a local manner; (c) the recognition, that certain classes of drugs are well absorbed from colon (d) the anticipation that protein drugs can be absorbed better from the large bowel owing to hypothetic reduced proteolytic activity in this organ and (e) the unique metabolic activity of the colon, which makes it an attractive organ for drug delivery system designers.

The present investigation focuses on targeting of drugs to the colon for local treatment of IBD, specifically CD. CD is a chronic inflammatory disease of the intestines in which the wall of the small or large intestine becomes sore, inflamed, and swollen requiring acute as well as chronic therapy. The area most frequently affected by CD is the end of the small intestine and beginning of the large intestine. Metronidazole and satranidazole are useful in mild to moderate conditions of CD by acting against anaerobic bacteria thus, providing localized effect against colonic anaerobic bacteria. Current marketed preparations of metronidazole and satranidazole are conventional immediate release tablets (Refer Table 1.5, 1.6 and 1.7), and thus do not provide localized effect in colon. Thus, there is a need to develop colon specific drug delivery systems for these drugs.
Colon targeting systems are commonly designed using the approaches like: pH-dependent release, time-dependent release, or bacterial degradation in the distal ileum/colon. Colonic delivery systems based solely on time or pH dependency of release have not been reliable because of the inherent variability of pH and transit times through the upper GIT. Polysaccharide which specifically degrade by colonic bacterial enzymes, suffer from the same constraint as pH-dependent carriers do; a premature release of their drug load to a certain extent in the upper segments of the GIT. This early discharge is inherent and associated with the swelling of the carrier, a crucial process, which allows cleavage by colonic enzymes. For that reason, most enzymatically controlled colonic drug carriers cannot function optimally without the aid of a protective coat (primary carrier), whether pH-dependent or depending on the erosion of a physical barrier.

Improvement of the colonic drug carriers could be accomplished by integrating different approaches (at least two) into a single platform. It is postulated that only binary platforms might be able to realistically target diseased areas or cells in the epithelium of the large bowel following oral ingestion. Binary platforms assessed in the current study are, (a) combination of time & pH dependent colonic drug delivery systems, and (b) polysaccharide and pH dependent colonic drug delivery systems, for acute and chronic treatment of CD. The present study had the following well defined objectives:

1. To develop time & pH dependent immediate release CTDDS of MTZ, and evaluate for their physico-chemical and release characteristics.
2. To develop polysaccharide & pH dependent immediate release CTDDS of STZ, and evaluate for their physico-chemical and release characteristics.
3. To assess whether the time & pH dependent immediate release CTDDS developed for MTZ, works for STZ and vice-versa (Flip-flop study).
4. To develop polysaccharide & pH dependent sustained release CTDDS of MTZ, and evaluate for their physico-chemical and release characteristics.
5. To develop pulsatile release multi-particulate CTDDS of MTZ using mixed single coating system of pH dependent and pH independent polymers.
6. To optimize the mixed coat combination of pH dependent and pH independent polymers using factorial design, and evaluate the statistically optimized formulation for in-vivo performance by single dose pharmacokinetic study.
7. To assess stability of all the developed formulations at accelerated stability conditions.

1.5) REFERENCES


