Colon Targeted Drug Delivery System
Anatomy of colon

- Ascending Colon
- Caecum
- Appendix
- Ileo-caecal Valve
- Transverse Colon
- Descending Colon
- Sigmoid
- Anus
- Rectum
Application

In local colonic pathologies

Systemic delivery of protein and peptide

Potential site for the treatment of diseases like asthma, arthritis & angina

For the drugs that are absorbed through colon such as steroids

For the treatment of disorders like IBS, colitis, crohn’s disease where it is necessary to attain high concentration of drugs in colon
Limitation and Challenges

- Dissolution in luminal fluid.
- Stability of drugs.
- Binding of drugs to dietary residues, intestinal secretions, mucus or fecal matter.
- Metabolic degradation by colonic microflora.
- Wide range of pH values
Lower surface area and relative “tightness” of the tight junctions in the colon restrict drug transport.

Longer residence time

Requires protection against variety of the gastric enzymes.

Cytochrome P450 3A class of drug metabolizing enzymes have lower activity in colon
### Introduction to colonic drug delivery system

<table>
<thead>
<tr>
<th>Target sites</th>
<th>Disease conditions</th>
<th>Drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical/local action</td>
<td>Inflammatory bowel disease, Irritable bowel syndrome &amp; Crohn’s disease</td>
<td>Hydrocortisone, Budenoside, Prednisolone, Sulphasalazine, Olsalazine, Infliximab, Mesalazine, Balsalazide, 6-Mercaptopurine, Azathioprine, Cyclosporine, etc</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>Metronidazole, Ornidazole, Tinidazole, Mebandazole, etc</td>
<td></td>
</tr>
<tr>
<td>Chronic pancreatitis, Pacreatectomy and Cystic fibrosis</td>
<td>Digestive enzyme supplements</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5-Fluoro uracil</td>
<td></td>
</tr>
<tr>
<td>Systemic action</td>
<td>To prevent gastric irritation</td>
<td>NSAIDS</td>
</tr>
<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td></td>
<td>To prevent first pass</td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>metabolism of orally ingested drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral delivery of peptides</td>
<td>Insulin</td>
</tr>
</tbody>
</table>
Factor affecting Colonic drug Delivery
## A. Gastric emptying

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted state</td>
<td>10 min. to 2 hrs</td>
</tr>
<tr>
<td>Fed state</td>
<td>Higher than 2 hrs</td>
</tr>
<tr>
<td>Small intestinal transit</td>
<td>3-4 hours</td>
</tr>
<tr>
<td>Colonic transit</td>
<td>20-35 hours</td>
</tr>
</tbody>
</table>
DISEASE | EFFECT ON COLONIC ABSORPTION OF DRUGS
---|---
IBD (Crohn’s disease & Ulcerative colitis) | Malabsorption lipophilic drugs. Mucosa & submucosa gets thick & so reduces surface area, reduces diffusion
Diarrhoea | Retention time reduces. Reduces drug absorption & release from dosage form
<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Reduction in bowel movement &amp; decreases the availability of drug at absorption site</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Diarrhoea affects the performance of formulations</td>
</tr>
</tbody>
</table>
c. Gastric and intestinal pH

<table>
<thead>
<tr>
<th>Location</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1.5 – 2</td>
</tr>
<tr>
<td>‣ Fasted state</td>
<td>2 - 6</td>
</tr>
<tr>
<td>‣ Fed state</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>6.6 – 7.5</td>
</tr>
<tr>
<td>‣ Ascending colon</td>
<td>6.4</td>
</tr>
<tr>
<td>‣ Transverse colon</td>
<td>6.6</td>
</tr>
<tr>
<td>‣ Descending colon</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Pharmaceutical approaches for CDDS
Approaches

1. Prodrug
2. Osmotically controlled drug delivery
3. Redox-sensitive polymers
4. pH dependent system
5. Time dependent system
6. Microflora activated system
7. Pressure controlled system
8. Bioadhesive systems
9. Micro particulate system
1. Prodrug approach

A. PRODRUG APPROACH (Drug is conjugated with carrier)

<table>
<thead>
<tr>
<th>I. Azo conjugate</th>
<th>Drug is conjugated with an azo bond.</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. Sulphasalazine for 5-ASA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Glycoside conjugate</th>
<th>Drug is conjugated with glycoside</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. Dexamithasone</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Glucuronide conjugate</th>
<th>Drug is conjugated with Glucuronide</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>IV. Cyclodextrin conjugate (βCD)</th>
<th>Drug is conjugated with cyclodextrin</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>V. Dextran conjugate</th>
<th>Drug is conjugated with dextran</th>
</tr>
</thead>
<tbody>
<tr>
<td>eg. Naproxen-dextran conjugation</td>
<td></td>
</tr>
<tr>
<td>VI. Polymeric conjugate</td>
<td>Drug is conjugated with polymer</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>VII. Amino acid conjugate eg. Proteins.</td>
<td>Drug is conjugated with aminoacid</td>
</tr>
</tbody>
</table>
1) Azo bond conjugate:-

Azoreductase enzyme produced in colon by colonic bacteria which degrades azo bond.

This principle is utilized in preparation of prodrug derivative of active drug for targeting in colon.
Sulphasalazine (SASP) is prodrug of 5-ASA. It is conjugated with sulphapyridine through azo bond.

Sulphasalazine was introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease.
<table>
<thead>
<tr>
<th>Carrier moiety conjugated with 5-amino salicylic acid</th>
<th>Prodrug of 5-amino salicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-aminohippurate (4-amino benzoyl glycine)</td>
<td>ipsalazine,</td>
</tr>
<tr>
<td>p- 4-amino benzoyl-β-alanine</td>
<td>balsalazine</td>
</tr>
<tr>
<td>p-aminobenzoate</td>
<td>HB-313</td>
</tr>
<tr>
<td>nonabsorbable sulphanilamide ethylene polymer</td>
<td>poly-ASA</td>
</tr>
<tr>
<td>a dimer representing two molecules of 5-ASA that are linked via an azo bond</td>
<td>olsalazine (OSZ)</td>
</tr>
</tbody>
</table>
2) Glycoside conjugation:
- Certain drugs can be conjugated to different sugar moieties to form glycosides

- Glycosides are bulky and hydrophilic

- They do not penetrate the biological membranes upon ingestion

- They are poorly absorbed from the small intestine

- When it reaches the colon, it will be cleaved by colonic bacterial glycosidase
Dexamethasone-21-βD-glucoside
(Arrow shows site of action of glycosidase)
3) **Glucuronide conjugations:**

- Same as that of glycoside conjugation.
- Here, glucuronide moiety is joined

- Example: Dexamethasone is tried for conjugation and the results were evaluated in ulcerative colitis induced in the rates.

![Dexamethasone- β-D-glucuronide](image)
4) Cyclodextrin conjugate:

- Cyclodextrin metabolizing enzymes produced by colonic bacteria degrades Cyclodextrin particularly β-CD. This principle can be used for preparation of prodrug with CD.

- The β-CD is practically resistant to gastric acid and salivary and pancreatic amylases. But they are complete degraded by the colonic microflora.

5) Dextran conjugate:

NASIDS were directly coupled to dextran by using carboxylic groups of drugs
6) Amino acid conjugation:

In the amino acid, acid group
- increase hydrophilicity and chain length of carrier amino acid,
- decrease the permeability of amino acids and proteins.

So the amino acid conjugate showed more enzymatic specificity for hydrolysis by colonic enzyme.

Glycine and glutamic acid conjugates of salicylic acid.
2) Osmotic controlled drug delivery

OROS-CT (Alza corporation)

- Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolve.

- Because of its enteric coating, each push-pull unit is prevented from absorbing water in the acidic environment.

- As the unit enter the small intestine, the coating dissolve in this higher pH (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 layer forces drug gel out of the orifice.
Orifice

Semipermeable membrane

Osmotic drug compartment

Osmotic push compartment

Enteric impermeable membrane
3) Redox-sensitive polymers

Novel polymers that are hydrolysed nonenzymatically by enzymatically generated FLAVIN

For azo bond cleavage, mainly 2 approaches
1. Intracellular enzymatic compartment,
2. Extracellular reduction by flavin.

Under anaerobic conditions, bacterial azo reduction by enzymatically generated reduced flavins requires the presence of NADPH as its electron source.

As NADPH oxidized, the electron mediator (reduced flavins) acts as an electron shuttle from the NADPH dependent flavoprotein to the azo compound.
NADPH (OXIDIZED) \rightarrow FLAVIN (REDUCED)

FLAVOPROTEIN \rightarrow ACT AS ELECTRONE SHUTTLE \rightarrow AZO COMPOUND

e- \rightarrow HYDROZO INTERMEDIATE
4. pH dependent approach

- Co-polymers of methacrylic acid and methyl methacrylate are widely used.

Eudragit L: pH 6
Eudragit S: pH 7

- Premature drug release observed.
- To overcome this problem Eudragit FS has been developed.

Eudragit FS: pH 7-7.5: Slow dissolution rate
<table>
<thead>
<tr>
<th>POLYMER</th>
<th>THRESHOLD PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit L 100</td>
<td>6.0</td>
</tr>
<tr>
<td>Eudragit S 100</td>
<td>7.0</td>
</tr>
<tr>
<td>Eudragit® L-30D</td>
<td>5.6</td>
</tr>
<tr>
<td>Eudragit® FS 30D</td>
<td>6.8</td>
</tr>
<tr>
<td>Eudragit® L 100-55</td>
<td>5.5</td>
</tr>
<tr>
<td>Poly vinyl acetate phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate</td>
<td>4.5-4.8</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate 50</td>
<td>5.2</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate 55</td>
<td>5.4</td>
</tr>
<tr>
<td>Cellulose acetate trimellate</td>
<td>4.8</td>
</tr>
<tr>
<td>Cellulose acetate phthalate</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Eudracol™

EUDRACOL™ is a colon-targeted, pH-triggered and sustained-release oral drug delivery technology for multi-unit dosage forms, for both local and systemic therapies.
Eudracol™

How Does EUDRACOL™ Work?
EUDRACOL™ is based on a multi-layer coating system providing drug protection in the gastrointestinal tract and controlled drug release in the colon.
Marketed formulations
delivery of olsalazine
delivery of balsalazine
5. Time dependent delivery

- Difficult to predict in advance.

- The strategy is to resist the drug release in acidic & intestinal environment.

- In this approach, specific lag time is previously determined.
Pulsincap

- It consists of enteric coated capsule containing water soluble cap and water insoluble body.
- The body is loaded with Hydrogel plug and drug layer.
- Enteric coat dissolves in small intestine and the water soluble cap also dissolves.
- The Hydrogel plug absorbs water and swell and release drug at a predetermined lag time of 4 hours.
Hydrogel plug ejected with extensive swelling from the bottom & drug release starts in colon. Mean pulse time is 4 hours.

slow swelling of hydrogel leads to a lag time, which is predetermined by length of the hydrogel plug. Swelling is pH independent.
The Time Clock system consists of a solid dosage form coated with *lipidic barriers containing* carnuba wax and bee’s wax along with surfactants, such as polyoxyethylene sorbitan mono oleate.

This *coat erodes or emulsifies* in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion.
### Bacterial based approach

<table>
<thead>
<tr>
<th>Technique employed</th>
<th>Polymer used</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria dependent/Polysaccharide based</td>
<td>Chitosan</td>
<td>Diclofenac Sodium</td>
</tr>
<tr>
<td></td>
<td>Pectin Chondroitin sulphate</td>
<td>Indomethacin</td>
</tr>
<tr>
<td></td>
<td>Guar gum</td>
<td>Indomethacin Doxamithacin</td>
</tr>
<tr>
<td></td>
<td>Amylose Alginate</td>
<td>5 - ASA 5 - ASA</td>
</tr>
<tr>
<td>Microbial flora</td>
<td>Enzymes produced</td>
<td>Chiefly applied for:</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Majority of them</td>
<td>Azoreductase</td>
<td>Release of 5-ASA from variety of prodrugs</td>
</tr>
<tr>
<td>Lactobacilli</td>
<td>Glycosidase, Glucuronidase</td>
<td>Glycosides &amp; glucuronides</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>Glycosidase, Glucuronidase</td>
<td>Glycosides &amp; glucuronides</td>
</tr>
</tbody>
</table>
7. Pressure-controlled drug-delivery systems

- Muscular contraction of the gut wall generate pressure
- Colon has higher luminal pressure
- System can be developed which withstand the pressure in intestine and ruptures in response to raised pressure in colon.

- **Ethyl cellulose capsules** have been used for this purpose.
8. Bioadhesive systems:-

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

- Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time.

- This longer residence time of drug would have high local concentration or improved absorption.

- Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated for colon.
9. Multiparticulate system

Pellets
Granular matrix
Beads
Microspheres
Nano particles
Multiple unit colon specific tablet

**Figure 1. Structure of multiple-unit colon-specific tablet developed.**
Microbially controlled system

- Microsphere containing different natural polysaccharide
  - Chitosan
  - Guar gum
  - Pectin
  - Dextran
  - Chondroitin sulphate
Evaluation

1. In vitro dissolution study
2. In vitro enzymatic degradation test
3. Relative colonic tissue exposure
4. Relative systemic exposure to drugs
5. $\gamma$-Scintigraphy
6. Magnetic moment imaging study
7. Drug delivery index
8. High frequency capsule
• Invitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine

• Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time)

• Drug release study in phosphate buffer for 3 hours (mean small intestine transit time PH 6.8)
Method 1

- Drug release in buffer medium containing enzymes (e.g. pectinase, dextranase) or cecal contents of rat or guinea pig or rabbit

Method 2

- Suitable medium containing colonic bacteria (Streptococcus faecium or B. ovatus)
BioDis-III (Apparatus III)

- Ideal for the dissolution profiling of extended release dosage forms.

- It is designed to meet or exceed current USP specification.

- It used a reciprocating motion to dip the inner tube into media.

- At the designated time, the entire row of inner tubes raises and moves to the next row of media.
Bio-Dis III

• Capable of running unattended upto 6 days and can store upto 25 programs.

• 7 sample tubes which automatically traverse upto 6 rows of corresponding outer tubes filled with different media.

• With accessories, the appropriate media volume can vary from 100, 300 ml (USP) or 1000 ml.
BioDis III
References

1) http://www.pharmainfo.net/pppc05/colon-specific-drug-delivery-recent-techniques

2) http://jpronline.info/article/view/1943/1132


4) http://www.ualberta.ca/~csps/JPPS6(1)/S.Chourasia/colon.htm
5) http://www.aapspharmscitech.org