Report on pharmaceutical approaches to colon targeted drug delivery systems
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ABSTRACT
Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. The various strategies for targeting orally administered drugs to the colon include covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bioadhesive systems and osmotic controlled drug delivery systems. The approach that is based on the formation of prodrug involves covalent linkage between drug and carrier. The presence of azo reductase enzymes play pivotal role in the release of drug from azo bond prodrugs while glycosidase activity of the colonic microflora is responsible for liberation of drugs from glycosidic prodrugs. Natural polysaccharides have been used as tools to deliver the drugs specifically to the colon. Formulation coated with enteric polymers releases drug when pH move towards alkaline range while as the multicoated formulation passes the stomach, the drug is released after a lag time of 3-5 h that is equivalent to small intestinal transit time. Drug coated with a bioadhesive polymer that selectively provides adhesion to the colonic mucosa may release drug in the colon. The review is aimed at understanding pharmaceutical approaches to colon targeted drug delivery systems for better therapeutic action without compromising on drug degradation or its low bioavailability.

Keywords: pH-sensitive polymers, Timed released systems, Bioadhesive systems, Osmotic controlled drug delivery systems.

INTRODUCTION
The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the gastrointestinal tract (GIT) depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT offers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron’s disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of perorally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after peroral application. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices.

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.

Azo bond conjugates
Sulphasalazine is introduced for the treatment of rheuma-
Amino acid conjugates

The drug is conjugated with tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylates. Various prodrugs have been prepared by the conjugation of drug acids), they reduce the membrane permeability of amino acids and pro-
clearance of a variety of drugs. Bacteria of the lower GIT, however, secrete glucuronidase and can deglucuronidate a variety of drugs in the intestine. Since the deglucuronidation process results in the release of active drug and en-
ableness its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.3

Cyclodextrin conjugates

In an oral drug delivery system, the hydrophilic and ionizable Cyclodextrins (CyDs) can serve as potent drug carriers in the immediate release and delayed release formulations, while hydrophobic CyDs can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conju-
gates of a drug with CyDs can be a versatile means of constructing a new class of colon targeting prodrugs-soluble drugs.4,5

Dextran conjugates

Dextran ester prodrugs of metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone were synthesized and proved the efficacy of the prodrugs for delivering drugs to the colon. In this study, methyl prednisolone and dexamethasone were covalently attached to the dextran by the use of a succinate linker. In addition dexamethasone was attached by glutaric acid to investigate the effect of linker molecule on hydrolysis kinetics.6,7

Table 1: Approach and Basic features of covalent linkage of a drug with a carrier

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Approach Covalent linkage of a drug with a carrier</th>
<th>Basic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Azo conjugates</td>
<td>The drug is conjugated via an azo bond.</td>
</tr>
<tr>
<td>1.2</td>
<td>Cyclodextrin conjugates</td>
<td>The drug is conjugated with cyclodextrin.</td>
</tr>
<tr>
<td>1.3</td>
<td>Glucuronide conjugates</td>
<td>The drug is conjugated with glucuronides.</td>
</tr>
<tr>
<td>1.4</td>
<td>Dextran conjugates</td>
<td>The drug is conjugated with dextran.</td>
</tr>
<tr>
<td>1.5</td>
<td>Amino acid conjugates</td>
<td>The drug is conjugated with polar and non-polar amino acids.</td>
</tr>
</tbody>
</table>

Table 2: pH sensitive polymers

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Polymers</th>
<th>Threshold pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eudragit L 100</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>Eudragit S 100</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>Eudragit L 30 D</td>
<td>6.6</td>
</tr>
<tr>
<td>4</td>
<td>Eudragit FS 30 D</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>Eudragit L 100 - 55</td>
<td>5.5</td>
</tr>
<tr>
<td>6</td>
<td>Polyvinyl acetate phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>7</td>
<td>Hydroxypropyl methyl cellulose phthalate</td>
<td>4.5</td>
</tr>
<tr>
<td>8</td>
<td>Hydroxypropyl methyl cellulose phthalate 50</td>
<td>5.2</td>
</tr>
<tr>
<td>9</td>
<td>Hydroxypropyl methyl cellulose phthalate 55</td>
<td>5.4</td>
</tr>
<tr>
<td>10</td>
<td>Cellulose acetate phthalate</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 3: Coated colonic dosage form

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Drug</th>
<th>Coating Polymer</th>
<th>Dissolution pH</th>
<th>Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mesalazine</td>
<td>Eudragit L</td>
<td>6.0</td>
<td>Claversal</td>
<td>GSK</td>
</tr>
<tr>
<td>2</td>
<td>Mesalazine</td>
<td>Eudragit S</td>
<td>7.0</td>
<td>Asacolitin</td>
<td>HBG</td>
</tr>
<tr>
<td>3</td>
<td>Mesalazine</td>
<td>Eudragit L</td>
<td>6.0</td>
<td>Salofalk</td>
<td>Dr. Falk</td>
</tr>
<tr>
<td>4</td>
<td>Mesalazine</td>
<td>Ethylcellulose</td>
<td></td>
<td>Pentasa</td>
<td>FERRING</td>
</tr>
<tr>
<td>5</td>
<td>Sulfasalazine</td>
<td>Cellulose acetate</td>
<td>6.2 - 6.5</td>
<td>Azulfidine</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>6</td>
<td>Sulfasalazine</td>
<td>Eudragit L 100 -55</td>
<td>5.5</td>
<td>Col-Pileon</td>
<td>HBG</td>
</tr>
<tr>
<td>7</td>
<td>Budesonide</td>
<td>Eudragit S</td>
<td>6.0</td>
<td>Budenofalk</td>
<td>Dr. Falk</td>
</tr>
</tbody>
</table>
Embodiments in matrices

The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the colon for liberation of entrapped drug.

Embodiments in biodegradable matrices and hydrogels

Embodiments in biodegradable matrices

The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharidases and results in the degradation of the matrices.

A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans and locust bean gum have been investigated for their use in colon targeted drug delivery systems.

Embodiments in biodegradable hydrogels

Hydrogels are usually formed by the covalent cross linking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble. Heterogenous polymer mixtures may also be used to form hydrogels without the need for covalent cross linking. Various hydrogels based on the azo polymeric networks have been developed for site-specific delivery of drugs to the colon.\(^{14, 15}\)

Embedding in pH-sensitive matrices

Extrusion-spherization and pelletization have been used for the preparation of pH-sensitive matrix pellets for colon targeted drug delivery.\(^{16}\) Nykanen et al.\(^{17}\) used ibuprofen as model drug and Eudragit® S and Aqoat AS-HF as enteric polymers for developing site-specific systems for release of a drug in the lower part of the small intestine or in the colon.

Timed release systems

This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place. The lag time in this case is the time requires to transit from the mouth to colon.\(^{18}\)

Redox-sensitive polymers

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes nonenzymatically by enzymatically generated flavins are being developed for colon targeting.\(^{19, 20}\) A common colonic bacterium, Bacteroides fragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model compound, 4, 4'-dihydroxyazobenzene were studied. It was found that the azo compounds were reduced at different rates and the rate of reduction could be correlated with the redox potential of the azo compounds. 4,4'-Dihydroxyazobenzene (E\(_{1/2}\) -470 mV) was reduced at the fastest rate of 0.75 mol l\(^{-1}\) h\(^{-1}\) amaranth (E\(_{1/2}\) -568 mV) at 0.30 mol l\(^{-1}\) h\(^{-1}\) Orange II (E\(_{1/2}\) -568 mV) at 0.2 mol l\(^{-1}\) h\(^{-1}\) and tartrazine (E\(_{1/2}\) -700 mV) at 0.08 mol l\(^{-1}\) h\(^{-1}\).

Bioadhesive systems

Bioadhesive 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 characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophil, polyurethanes and polyethylene oxide polypropylene oxide copolymers have been investigated as materials for bioadhesive systems.\(^{21}\)

Coating with microparticles

Many of the protozoans especially Entamoeba histolytica remains confined in the large intestine, which necessitates high
intraocolonic drug concentration.\textsuperscript{23}

Prepared and evaluated a formulation that was rather diverted from the mainstream of conventional therapy. It consisted of small silica particles covalently linked to a potent antiamoebic drug, 2-(4-aminophenoxymethyl)-5-nitro-1-methylimidazole. Silica-drug particles were injected into mice, hamsters and guinea pigs. It was found that trophozoites phagocytosed the particles in vivo and in vitro, followed by rapid cell death due to the released drug.

**Osmotic controlled drug delivery**

The OROS-CT (Alza Corporation) 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. As the unit enter the small intestine, the coating dissolve in this higher pH environment (\( \text{pH} > 7 \)), water enters the unit, causing the osmotic push compartment to swell and concomitantly forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane.\textsuperscript{24}

**CONCLUSION**

Improved drug delivery systems are required for drugs currently in use to treat localized diseases of the colon. The advantages of targeting drugs specifically to the diseased colon are reduced incidence of systemic side effects, lower dose of drug, supply of the drug to the biophase only when it is required and maintenance of the drug in its intact form as close as possible to the target site. To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. Several systems are currently being investigated as potential means for targeting of drugs to colon. The various strategies for targeting orally administered drugs to the colon include covalent linkage of a drug with a carrier, coating with \( \text{pH} \)-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bioadhesive systems and osmotic controlled drug delivery systems. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. The colon is rich in harboring excellent microflora, which can be used to target the drug release in the colon. The need is to identify the appropriate approach, which can results in the delivery of drugs in a safe, effective and less expensive manner with minimum fluctuation in terms of release of drugs at target site.

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**REFERENCES**


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