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A Review On Colon Targeted Drug Delivery System

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Abstract: During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhoea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon.

Index Terms - targeted drug delivery**,** ulcerative colitis, crohn's disease, and absorption of poorly absorbable drugs.

I. INTRODUCTION

During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhoea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon[1].

1.1 Advantages[1]

1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.
2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs.

1.2 Limitations[1]

1. Multiple manufacturing steps.
2. Incomplete release of drug.
3. Lowering of bioavailability due to binding of drugs to intestinal contents

Factors affecting colon targeted drug delivery[1]

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors

a. Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.

b. pH of colon

The pH of GIT varies between different individuals. The food intake, diseased state, etc. influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

c. Colonic microflora and enzymes

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this microflora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

2. Pharmaceutical factors

a. Drug candidates:

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

b. Drug carriers:

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. the various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule, etc.

DRUGS SUITABLE FOR CDDS[2]

Based on literature review, the following different categories of drugs are suitable for colon drug delivery.

- Drugs used to treat irritable bowel disease (IBD) require local delivery at drug to colon e.g. sulfasalazine, olsalazine, mesalazine, steroids like fludrocortisone, budesonide, prednisolone and dexamethasone.
- Drugs to treat colonic cancer require local delivery e.g. 5-fluorouracil, doxorubicin, and methotrexate.
- Protein and peptide drugs - eliminating drug degradation e.g. growth hormones, calcitonin, insulin, interleukin, interferon and erythropoietin.
- To treat infectious diseases (amoebiasis & helminthiasis) - requires site specific delivery e.g. metronidazole, mebendazole and albendazole.
- To treat rheumatoid arthritis (NSAIDS), nocturnal asthma, angina require delay in absorption due to circadian rhythms
- Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport e.g. glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol, and oxyprenolol.

NEED OF COLON TARGETED DRUG DELIVERY[3]

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Criteria for selection of drug for colonic drug delivery[4]

- **Drug candidate**

  Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used in treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery.

- **Drug carrier**

  The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems.

Polymers for Colon Targeted Drug Delivery[5-8]

The colon is an ideal site for both systemic and local delivery of drugs. Treatment of large intestine disorders such as Crohn's disease, irritable bowel syndrome, ulcerative colitis and colon cancer, where a high concentration of active drug is required, can be improved by colon-targeted drug delivery system. Colon is used for systemic absorption of proteins and peptides also because proteolytic activity of colon mucosa is much less than that observed in small intestine. Drug targeting to specific sites of action offers several advantages over non targeted drugs such as prevention of side effects and reduction of doses.

The colon as a site of drug delivery offers various therapeutic advantages because of its near neutral pH and longer transit time. To reach the colon and release the drug, a dosage form must be formulated taking into account various obstacles introduced by the gastrointestinal tract. Successful delivery of a drug to the colon requires protection of the drug from degradation or release in the stomach and then controlled release of drug in colon. The desired properties of colon targeted drug delivery systems can be achieved by using some polymers either alone or in a combination because it is now recognized that polymers can potentially influence the rate of release and absorption of drugs and play an important role in formulating colon targeted drug delivery systems. Hence an attempt to review different polymers used in colon targeted drug delivery system has been made here.

Biodegradable Polymers

Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs. Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic in acidic pH. Various bacteria present in the colon secretes many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. β-D-galactosidase, amylase, pectinase, β-Dglucosidase, dextranase, α-D-xylosidase. These polymers are inexpensive and are available in a variety of structures. Linear polysaccharides remains intact in stomach and small

intestine but the bacteria of human colon degrades them and thus make them potentially useful in colon targeted drug delivery systems.

Guar gum:

Guar gum is derived from the seeds of the *cyomopsis tetragonolobus* (Fam. Leguminosae). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches (fig. 1). Guar gum is used in colon targeted drug delivery systems due to its drug release retarding property and susceptibility to microbial degradation in large intestine.

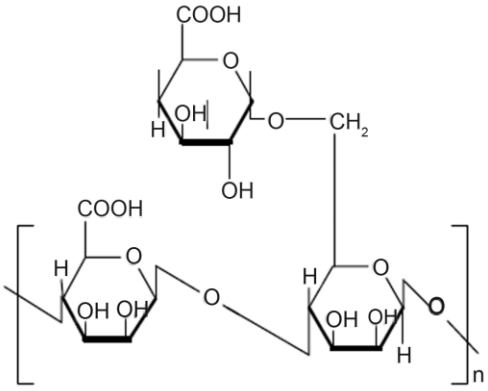

Fig. 1: Structure of Guar Gum

Pectin:

Pectin is a linear, heterogeneous polysaccharide which is mainly composed of galacturonic acid andits methyl ester. These are predominantly linearpolymers of mainly (1→4) linked D-galacturonic acid residue interrupted by 1,2-linked L-rhamnose residue with a few hundred to about one thousand building blocks per molecule (fig. 2). It is one of the major sources of dietary fiber and is extracted from fruit and vegetable cell walls. A novel colon targeted tablet formulation using pectin as a carrier and diltiazem hydrochloride and indomethacin as model drugs has been developed. *In vitro* study showed that prepared dosage forms have limited drug release in stomach and small intestine and released maximum amount of drug in the colon. The study revealed that pectin can be used effectively for colon targeting of both water soluble and insoluble drugs. Calcium/zinc pectinate is a less water soluble pectin salt used in fabrication of colonic delivery system

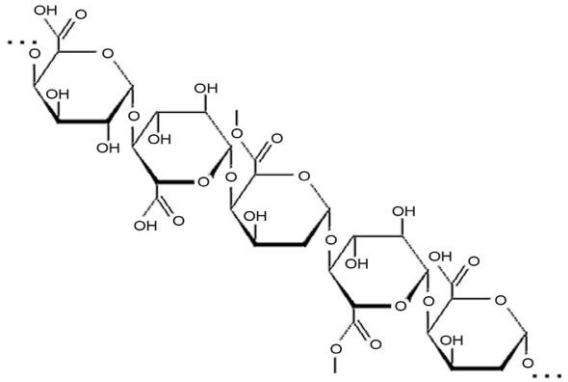

Fig. 2: Structure of Pectin

Spray drying method has been employed to prepare pectin microspheres for oral colon delivery of indomethacin. The prepared microspheres were crosslinked with calcium chloride. The release of Indomethacin from the cross linked pectin microspheres, was more suppressed than its release from non-cross linked microspheres. Drug release from pectin microspheres was increased by the addition of pectinase. Release of indomethacin from pectin microsphere was less in acidic pH while it was stimulated at neutral pH (pH 7.4). The results of the study clearly demonstrated that pectin microspheres prepared by spray drying and crosslinking methods are potential carriers for colon specific drug delivery. Pectin is a poor film former and therefore it is often used in combination with other polymers like hydroxypropylmethylcellulose, chitosan, ethylcellulose. Suresh Kumar *et al.* prepared pectin-hydroxypropyl methylcellulose coated pellets for the colonic delivery of curcumin and reported that pectin-HPMC coated pellets offer a greater degree of protection from premature drug release in the upper GI tract. A mixed film of pectin:ethylcellulose for colon targeted drug

delivery of sennosides and triphala was prepared using non aqueous solvent like acetone and isopropyl alcohol. The results of the study indicated that under simulated colonic conditions, drug release was more pronounced from coated formulations containing higher proportion of pectin. Wei *et al.* performed *in vivo* and *in vitro* study of pectin/ethylcellulose film-coated pellets of 5-fluorouracil for colonic targeting. The pellet cores were coated to different film thicknesses with three different pectin:ethylcellulose formulations. The 1:2 ratio pectin:ethylcellulose-coated pellets with 30% total weight gain (TWG-30%) produced more satisfactory drug-release profiles in simulated gastric, intestinal and colonic fluids. Most of the coated pellets were eliminated from the stomach in 2 h, moved into the small intestine after 2-4 h, and reached the large intestine after 4 h. The TWG-30% formulation showed delayed Tmax, decreased Cmax and prolonged mean residence time compared with uncoated pellets.

Chondroitin Sulfate:

Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate by *Bacteroides* species in the large intestine mainly by *B. thetaiotaomicron* and *B. ovatus*. Chondroitin sulfate consist of β-1,3-Dglucuronic acid linked to N-acetyl-D-galactosamide (fig. 3). Natural chondroitin sulfate is cross linked and readily water soluble but it may not be able to sustain the release of most drugs from the matrix. Chondroitin sulfate is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteroids thetaiotaoimicron and B. ovatus. Chondroitin sulfate* is highly water soluble and this property act as a barrier in the formulation of the colon targeted drug delivery. Rubinstein et al. cross linked chondroitin sulfate with 1,12-diaminododecane. The cross linked chondroitin sulfate was used as a carrier for indomethacin specifically for the large bowel. Cross linking took place between the carboxyl group in chondroitin and the amino group in diaminododecane and formed a dimer of chondroitin sulfate. The degree of cross linking was determined by measuring the amount of methylene blue which was adsorbed as a result of cation exchange. The cross linked polymer was mixed with indomethacin and compressed into tablets. An enhanced release was observed on incubation with rat cecal contents.

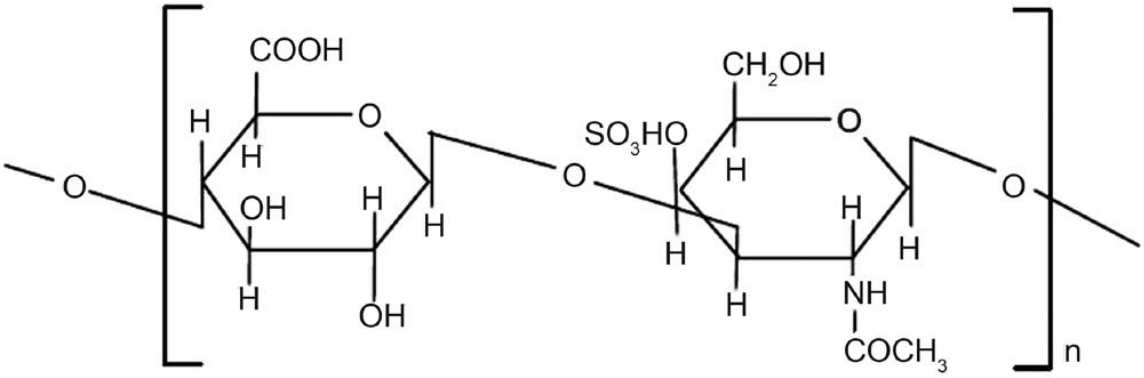

Fig. 3: Structure of chondroitin sulfate

Dextran:

Dextran is a polysaccharide consisting of α-1,6 D-glucose and side chain of α-1,3 D-glucose units (fig. 4). These highly water soluble polymers are available commercially as different molecular weights with a relatively narrow molecular weight distribution. Dextran contains a large number of hydroxyl groups, which can be easily conjugated to drugs and proteins. Dextran gets degraded by the microbial enzyme dextranases, which is found in the colon. Pharmacodynamically, conjugation with dextran has resulted in prolongation of the effect, alteration of toxicity profile, and a reduction in the immunogenicity of drug. Dextran was oxidized using sodium periodate and coupled the aldehyde product with the α-amino group of 5-amino salicylic acid (5-ASA). It was reported that less oxidized dextran yields the minimum 5-amino salicylic acid conjugation, which were susceptible to dextranase hydrolysis while highly oxidized dextran yields the maximum 5-ASA conjugation, which were resistant to dextranase hydrolysis. Therefore, it was concluded that dextran can potentially be used to treat bowel inflammatory diseases. The prepared dextran hydrogels were characterized by equilibrium degree of swelling and mechanical strength. Degradation study of the hydrogels was done *in vitro* using dextranase, *in vivo* in rats and in a human fermentation model. The study indicated that the equilibrium degree of swelling, mechanical strength and degradability of the hydrogels can be controlled by changing the chemical composition. Dextran hydrogels degraded *in vivo* in the cecum of rats but not in the stomach suggesting that dextran hydrogels can be used as drug carriers for colonspecific drug delivery.

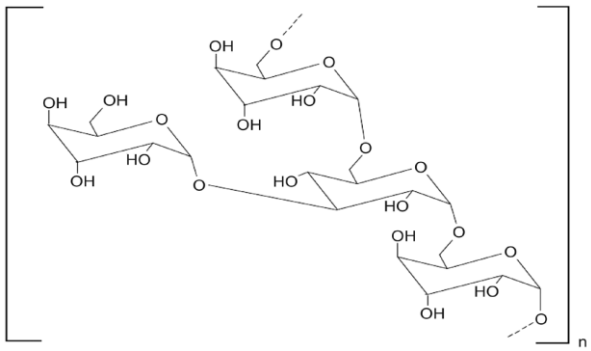

Fig. 4: Structure of dextran

Chitosan:

Chitosan is functional linear polymer obtained from the alkaline deacetylation of chitin. Chitosan is consisting of the repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are linked by (1-4) β-bonds (fig. 5). Chitosan is a nontoxic, biodegradable, biocompatible and bioactive polymer. Chitosan is used as excipient and drug carrier in drug delivery systems. Chitosan is used for the colon targeted drug delivery because it has a tendency to dissolve in acidic pH of stomach but get swollen in the intestinal pH. Lorenzo-Lamosa *et al.* designed a system consist of chitosan microcores entrapped within acrylic microspheres for the colonic delivery of sodium diclofenac. The drug was efficiently entrapped within chitosan microcores using spray-drying and then microencapsulated into Eudragit. The release rate was adjustable by changing the chitosan molecular weight or the type of chitosan salt. Furthermore, by coating the chitosan microcores with Eudragit, perfect pH-dependent release profiles were attained. A combined mechanism of release is proposed, which considers the dissolution of Eudragit coating, the swelling of chitosan microcores and the dissolution of sodium diclofenac and its further diffusion through the chitosan gel cores. This work presented new approaches for the modification of chitosan as well as a new system with a great potential for colonic drug delivery. Chitosan capsules were used for colonic delivery of an antiulcerative colitis drug. 5-Aminosalicylic acid (5-ASA) was used as model drug. A marked increase in the release of drug from chitosan capsule was observed in the presence of the rat cecal content. From the results of this study it was concluded that chitosan capsules could be an effective carrier for the colon targeted delivery of antiinflammatory drugs. Chitosan film was prepared and cross linked with citrate. Under acidic conditions, the drug was released quickly but in neutral condition, the release of drug was low. To control the release of the drug, chitosan/citrate film was again coated with alginate. The study revealed that chitosan along with citrate can be used for drug targeting to specific site. Hydrogel beads of chitosan were formed with tripolyphosphate and protein release was investigated *in vitro* under different conditions. It was observed that under colonic environment, protein release was high due to the degradation of the beads. A chitosan dispersed system was newly developed for colon-specific drug delivery which was composed of drug reservoir and the outer drug release-regulating layer dispersing chitosan powder in hydrophobic polymer. It was observed that the thickness of the outer layer controls the drug release rate. Since the dispersed chitosan dissolves easily under acidic conditions, an additional outer enteric coating was also provided to prevent the release of drug from chitosan dispersed system in the stomach. Different salts of chitosan were prepared by dissolving chitosan in various acidic solutions and then spray drying these solutions. From the results of the study it was concluded that drug release was reduced in acidic and alkaline pH when drug was mixed with chitosan salts.

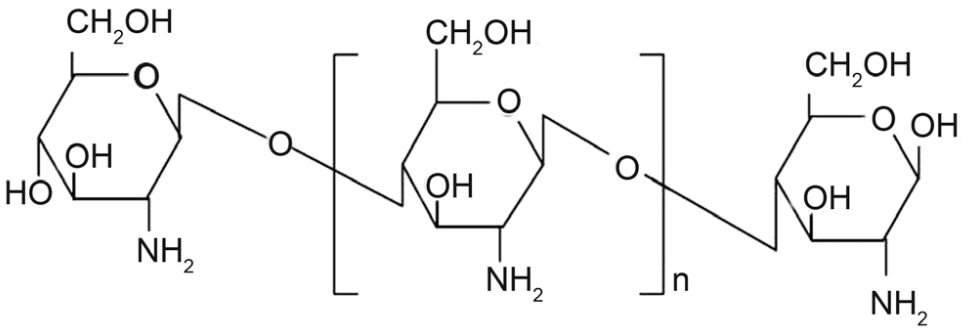

Fig. 5: Structure of chitosan

Cyclodextrin:

Cyclodextrin is a cyclic oligosaccharide consisting of six to eight glucopyranose units joined by α-(1→4) glucosidic linkage (fig. 6). These are potential high performance carrier molecules that have the ability to alter physical, chemical and biological properties of the drug molecule through the formation of inclusion complexes. Cyclodextrins consist of six, seven or eight glucose monomers arranged in a ring shape and these are denoted as α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, respectively.

Cyclodextrins consist an internal lipophilic cavity, which can make complex with hydrocarbon materials. Cyclodextrins are slowly hydrolysable in upper gastrointestinal tract while it gets fermented to small saccharides by colonic microflora and get absorbed in large intestine. Cyclodextrins are used to improve the drug properties such as solubility, stability, bioavailability. Antiinflammatory drug was conjugated with primary hydroxyl groups of alpha, beta, and gamma cyclodextrins through an ester or amide linkage. The *in vivo* drug release behavior of these drugcyclodextrin conjugates was investigated in rat. The results reveal that these conjugates were stable in stomach and in small intestine. The study suggested that cyclodextrins can be used for colon specific delivery of drug.

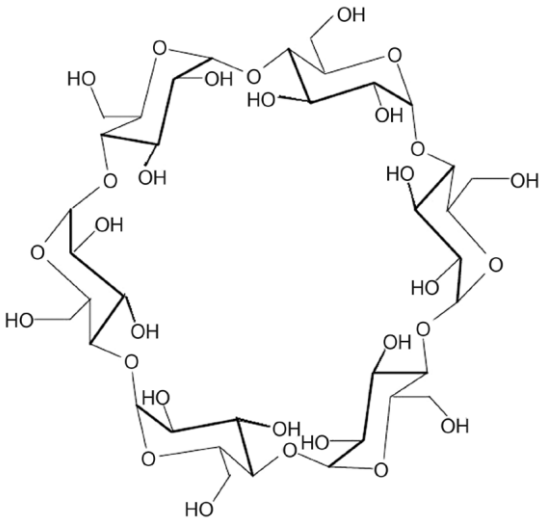

Fig. 6: Structure of α-cyclodextrin

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