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COLON TARGETED DRUG DELIVERY SYSTEM: A REVIEW ON TREATMENT OF ULCERATIVE COLITIS

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ABSTRACT
Colon specific drug delivery has gained increased importance not just for delivery of the drugs within the treatment associated with the colon, but also as a possible site for the systemic delivery of therapeutic peptides and proteins. To realize successful colon targeted drug delivery, a drug need to be shielded from degradation, release and absorption within the upper portion of the alimentary tract then to be ensured abrupt or controlled release within the proximal colon effects. The review, mainly compares with the first approach for ulcerative colitis such as CDDS namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of producing process. May be a chronic mucosal inflammatory condition which will affect any parts of the colon, and is characterised by periods of remission and active disease related to symptoms of abdominal pain, diarrhea, rectal bleeding and fecal urgency.

KEYWORDS: To realize successful colon targeted drug delivery, a drug need to be shielded from degradation, release and absorption within the upper portion of the alimentary tract then to be ensured abrupt or controlled release within the proximal colon effects.

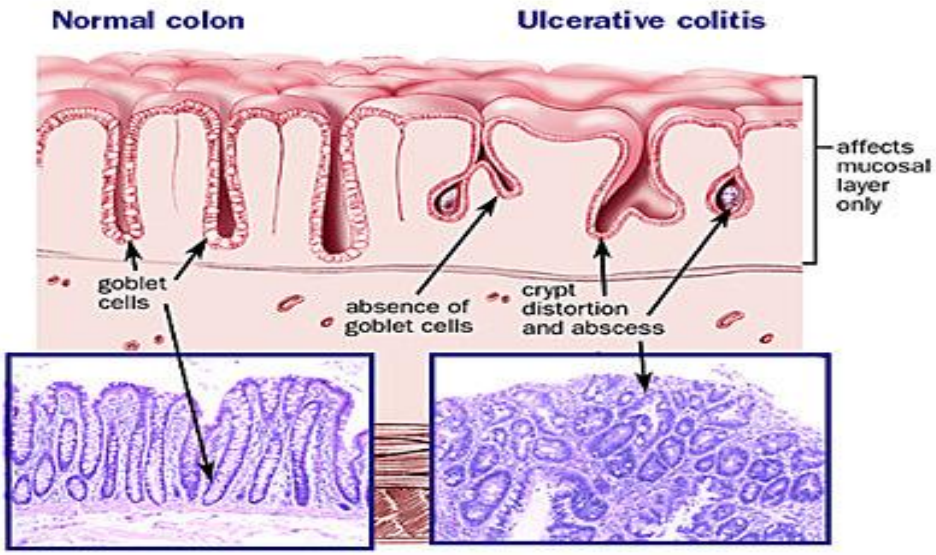
INTRODUCTION
Ulcerative colitis (UC colonic mucosa, is reconded first-line treatment for patients with mild-to- moderate colitis . it's available in both the oral and topical formulations, 5-ASA is usually well tolerated and has proven to be effective in symptom improvement also as within the induction and maintenance of colitis remission.

For 5-ASA to be effective in mild-to-moderate colitis drug must be ready to directly targeted the mucosa of the terminal ileum and colon, where it negatively regulates cyclooxygenase and lipoxygenase pathway to stop formation of prostaglandin and leukotriene, increases the expression of peroxisome proliferator-activated receptors. the discharge of oral mesalamine formulations end in the fast absorption of 5ASA within the upper (GI) tract, with systemically absorbed drug having little clinical effects.

The main goal of the varied formulations currently available on the market is to optimised dug delivery to the affected colon and minimised systemic absorption. This promotes maximal therapeutics efficacy at rock bottom possible dose, which is turn reduces side effects.

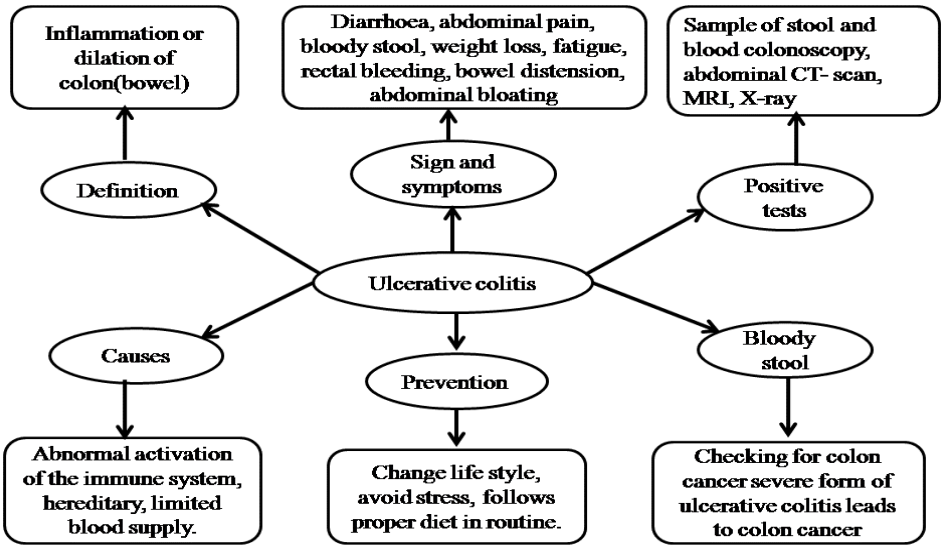
Besides non-pharmacologic therapy which incorporates nutrional supports and surgical intervension, Pharmacologic therapy is an integral a part of the general treatment of colitis. All the drugs are aimed to regulate the disease allowing the patient to perform normal daily activities. the most pharmacologic groups of medicine used for colitis treatment includes aminosalicylate, corticosteroids, immunosuppressive agents, antimicrobial and inhibitor of TNF-Alfa.

In addition, for maintaining remission in various GI diseases, including colitis, live bacterial cell biotherapeutics i.e. Probiotics, alone or combined with prebiotics as synbiotics, also are administered. For prevention and maintaining of remission in colitis various probiotics were clinically examined during the last decade, among which non-pathogenic E-coli, lactobacilli, streptococcusthermophilus, enterococci, coliforms, Bactroids etc.



Signs and symptoms of Ulcerative colitis

1) The cases of ulcerative colitis includes various symptoms such that weight reduction, tachycardia, fever, anaemia and bowl distension.
2) It is generally related with full remission of symptoms in the interim.
3) Both male and female sexes are equally affected.
4) In ulcerative colitis site of inflammation broaden to the more proximal areas of the colon over time.



Comparative Risk factors are influencing in Ulcerative Colitis and Crohn's disease

Hormonal Influences

A consistant effects was not seen for the development of UC. In distinction to this, the meta-analysis by Cornish and colleagues identified an elevated risk for both CD and UC with OC use. Corrao and colleagues postulated that up to 7% of UC and 11% of CD cases could be attributable to OC use. In constract to the OC data postmenopausal hormones use was associated with an elevated risk of UC but not CD. These divergent results could potentially br due to the different intrinsic hormones that exists in premenopausal OC users compared with users of hormonal theropy who are mostly postmenopausal.

In a study of 65 women with IBD, kane, and colleagues found no difference in disease course by menopausal status. However, women who used hormone therapy had a significantly reduced likelihood of disease flare.

Diet

Diet exerts a strong influence on the composition of the intestinal microbiome. Consequently, pre-illness diet could be a significant risk factor for the pathogenesis of IBD. Rising rate of UC and CD particularly in area of asia with westernization of diet, characterized by a reduction in fiber consumption and increase in processed foods and food with high fat content-provide preliminary evidence that temporal changes in dietary habits may account for some of the regional variation in disease

distribution and rising incidence rates of IBD. A larger prospective adult study similarly demonstrated a strong inverse association between intake of dietary fiber and the risk of CD with weaker effects on UC.

Fiber intake from fruits and vegetables (soluble fibre) was protectind against CD, whereas insoluble fibre intake from cereals, whole grains, or bran did reduce the risk of CD or UC. The data on dietary fat intake are less consistent. Many studies have failed to identified an association between overall fat intake and the risk of CD and UC. Dietary intake of carbohydrates are not been associated with CD and UC risk. If increases protein intake of animal may be associated with increased of risk of CD.

There have been few studies examining the association between micronutrients intake and the risk of CD and UC. There are also limited data on wheather diet predisposes patients to disease flare.

Depression, Stress, Sleep factors

Depression and anxiety are common in pateints with IBD. However, evidence suggest that pre-illness stress, depression, or anxiety may influence the risk of IBD development. Depression and stress also can mediate their effect through the autonomic nervous system, particularly activation of the sympathetic nervous system. Furthermoer, release of neuropeptides can influence immune cell activation, and stress can increase intestinal permeability. Less consistent epidemiologic data exist in humans. In a multi-institutional cohort, the presence of depression or anxiety was associated with an increased risk of CD-related surgery. There are less data on whether education on stress management and coping or treatment of depression is associated with an improvement in disease course. Psychologic counselling was similarly associated with an improvement in health-related quality of life as well as well as reduction in symptomatic relapses and outpatient office visits.

- **Classic risk factors**

Cigarette smoking and appendectomy

The described environmental factor that is consistently associated with CD is cigarette smoking. Current smokers have a 2-fold increased risk of CD compared with person who have never used tobacco products. Former smokers experience an increased in CD risk of magnitude in between that of never and current smokers. The risk of CD in former smokers last several years after smoking cessation. In constrast, current smokers appears to be protected against the development of UC. However smoking cessation significantly increases the risk of development of UC. The effect of cigarette smoking may be mediated through alteration of the composition of the intestinal microbiome, influencing the reactivity of intestinal immune cells and the generation of free radical-mediated oxidative stress. Similar to observations regarding smoking and IBD incidence, also has divergent effects on CD and UC. Conversely rate of smoking is lower than average in those countries with a high incidence of IBD, such as Sweden and Canada.

- **Current Oral 5-ASA Formulations.**

Drug Names	Proprietary Name	Formulations	Site of release
Salfasalazine	Azulfidine salazopyrin	5-ASA and Sulfapyridine linked by azo-bond.Tablet	colon
Salfasalazine	Azulfidine EN-tabs Salazopyrin EN-tab	As above, but tablets coated with cellulose acetate phthalate	colon
Olsalazine	Dipentum	5-ASA dimer linked by azo-bond.Gelatin, Capsule	colon
Olsalazine	Dipentum	5-ASA dimer linked by azo-bond.Tablet	colon
Balsalazide	Colazide	5-ASA and 4-aminobenzoyl B-alanine (4ABA) linked by azo-bond, Capsule	colon
Mesalazine	N American Asacol	Eudragit s-Coated tablets (release at pH>7)	Terminal ileum, colon
Mesalazine	United kingdom, Italy, Netherland Asacol	Eudragit s-Coated tablets (release at pH>7)	Terminal ileum, colon
Mesalazine	Ipocol Mesren	Eudragit S-Coated tablets (release at pH> 7)	Terminal ileum, colon
Mesalazine	Salafolk Mesasal Claversal	Eudragit-L coated tablets (release at pH> 6) Tablets, Granules	Distal ileum, colon
Mesalazine	Pentasa	Ethylcellulose coated microgranules (time independent release) available as tablet, capsule and sachet.	Duodenum, jejunum, ileum, colon
Mesalazine	Mezavant	Eudragit-S coated tablet containing inner core of multi-matrix system	Terminal ileum, Colon

Novel colon targeted delivery system (CODESTM)
CODESTM may be a unique CDDS technology that was designed to avoid the inherent problems related to pH or time dependent systems. CODESTM may be a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a singular mechanism involving lactulose, which acts as a trigger for site specific drug release within the colon.

The premise of the technology is that the enteric coating protects the tablet while it's located within the stomach then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation because it passes through the alkaline pH of the tiny intestine. Once the tablet arrives within the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding by the system sufficient to affected in dissolution of the acid soluble coating and subsequent drug release.

Osmotic controlled drug delivery (OROS-CT)
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 are often one osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a troublesome gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a membrane An orifice is drilled through the membrane next to the drug layer.

Immediate after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolved. The drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water within the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the tiny intestine, the coating dissolves during this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel within the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the speed of water transport through the semipermeable membrane.

Oral Controlled Release Drug Delivery System
Oral drug administration is the most suitable and beneficial approaches as the oral route contributes greater active surface area as compare to all drug delivery system for delivery of various drugs. The drug release pattern of the oral controlled release drug delivery system controls the level of plasma concentration within the therapeutic level, through a defines rate and time, resulting in constant therapeutic activity. Research on OCRDDS with either furture advancement in the delivery pattern or innovation in formulation of drugs is ongoing work for several formulation scientists. The most important specifications for the novelty of a drug delivery system are, first is controlled release drug delivery, and is passage of the active entity to the specific site for the activity.

The controlled release oral drug delivery system is the most commonly used approach for controlling the release of drugs, which are given orally. Several complementary terms such as prolonged release, sustain release, extended release, modify release are used to evaluate controlled release drug delivery system that are designed to sustain the rate of release of drugs over an elongated period of time. Innovation in the drug dosage form is essential for attaining a useful controlled oral release drug delivery system.

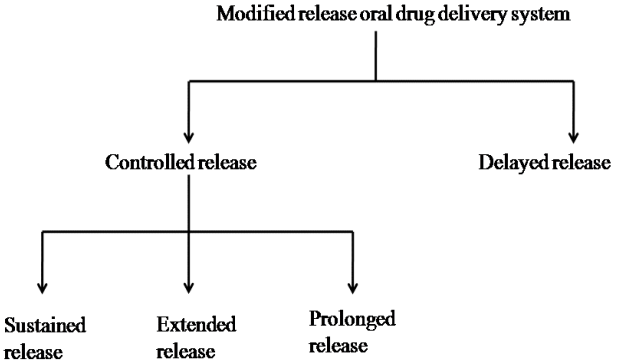


Fig: Modified release oral drug delivery system.

Advantages of Oral Controlled Release Drug Delivery System

1. Approximately constant drug level at the specific site of action
2. Protection of peak-trough fluctuation
3. Reduction in dose of drug
4. Decreased dosage frequency
5. Reduced side effects
6. Improved patients compliances
7. Taste making
8. Enteric prevention
9. Colon targeting
10. Sustained pH–independent release pattern
11. Pulsatile release pattern
12. Enhancement in bioavailability of some drugs due to spatial control

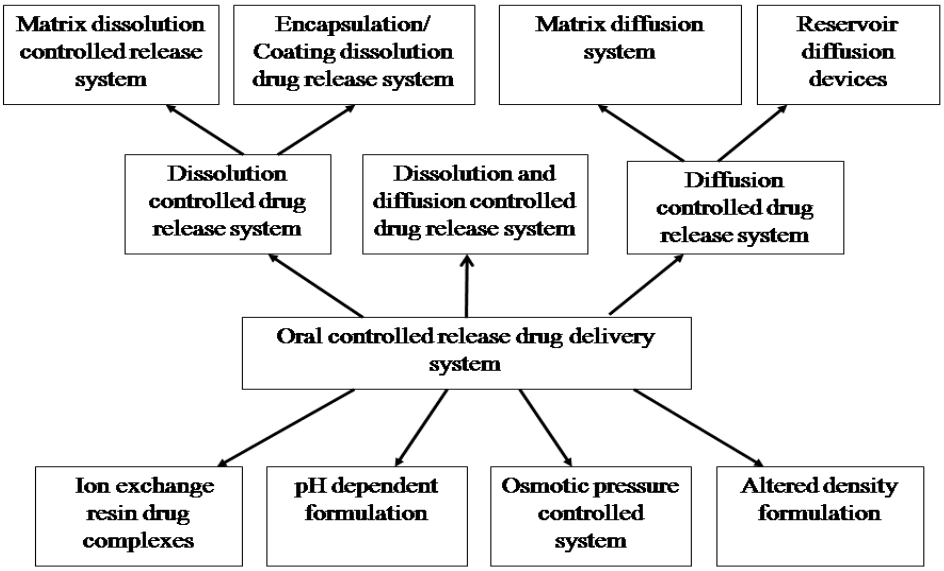


Fig: Approaches of oral controlled release drug delivery system.

- **Criteria for selection of drugs for CDDS.**

Criteria	Pharmacological Class	Non-peptide drugs	Peptide drugs
Drugs poorly absorbed from upper GIT.	Antihypertensive and antianginal drugs	Isosorbides, Theophyllin, ibuprofen	Cyclosporine, Desmopressin
Drug For the colon cancer	Antineoplastic drugs	pseudoephedrine	Epoetine, Glucagon
Drugs that degrade in stomach and small intestine.	Peptides and proteins	Bromophenaramine 5-Flourouracil, Doxorubicin	Gonadoreline, Insulin, interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerine and corticosteriods	Bleomycin, Nicotine	Protirelin, semorelin, Saloatonin
Drugs for targeting	Antiarthritis and antiasthamatic drugs	Prednisolone, Hydrocortisone	Somatropine, Urotoilitin

- **Polysaccharides investigated for colon-specific drug delivery.**

Drug moiety used	Polysaccharide investigated	Dosage form prepared
Diclofenac Sodium	Chitosan	Enteric coated chitosan microspheres
Insulin	Chitosan	Enteric coated chitosan capsules
Indomethacin	Pectin (Used as Calcium Salt)	Matrices
Ropivacaine	Amidated pectin	Matrix tablet
Dexamethasone	Guar gum	Matrix tablet
Bovine serum albumin – BSA	pH- sensitive dextran	As hydrogel
Indomethacin	Chondroitin sulphate	Matrix tablet
Radioactive tracer	Starch	Enteric coated capsules
5 – ASA	Alginate as calcium salt	Double coated swellable beads
Theophylline	Locust bean gum	Film
Paracetamol	Amidated pectin	Matrix tablet
Theophylline	Dextran fatty acid esters	As film

CONCLUSION

The various approaches are being researched in attempts to understand and achieve the desired goal of targeting the delivery to a specific organ, the colon. The colon specificity is more likely to be achieved with system that utilized natural materials that are degraded by colonic bacterial enzymes. However commercial product for oral administration based on the mentioned CDDSs for all the drugs needed for the treatment of colitis. CDDSs are considered therapeutics benefits to the patients in terms of both local and systemic treatment.

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