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# Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue

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**Abstract**

Colon targeted drug delivery is an active area of research for local diseases affecting the colon, as it improves the efficacy of therapeutics and enables localized treatment, which reduces systemic toxicity. Targeted delivery of therapeutics to the colon is particularly advantageous for the treatment of inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease. Advances in oral drug delivery design have significantly improved the bioavailability of drugs to the colon; however in order for a drug to have therapeutic efficacy during disease, considerations must be made for the altered physiology of the gastrointestinal (GI) tract that is associated with GI inflammation. Nanotechnology has been used in oral dosage formulation design as strategies to further enhance uptake into diseased tissue within the colon. This review will describe some of the physiological challenges faced by orally administered delivery systems in IBD, the important developments in orally administered nano-delivery systems for colon targeting, and the future advances of this research.

***From the Clinical Editor:*** Inflammatory Bowel Disease (IBD) poses a significant problem for a large number of patients worldwide. Current medical therapy mostly aims at suppressing the active inflammatory episodes. In this review article, the authors described and discussed the various approaches current nano-delivery systems can offer in overcoming the limitations of conventional drug formulations.



*Key words:* Colon targeted drug delivery; Nano-delivery systems; Oral administration; Inflammatory bowel disease; Colitis

Inflammatory bowel disease (IBD) is the umbrella term for a group of chronic relapsing gastrointestinal (GI) diseases which include ulcerative colitis (UC) and Crohn's disease (CD).[1] While UC and CD are considered distinct conditions, they can share many clinical features and are both characterized by cycles of relapsing and remitting mucosal inflammation. For UC, this inflammation is confined to the colon, extends proximally from the rectum and is continuous, in some cases involving the entire colon (pancolitis). Crohn's inflammation can affect any region of the GI tract, with the terminal ileum and the colon commonly affected. The inflammation is generally discontinuous in manner.[1] Although the exact cause of disease is undefined, certain factors have been suggested to play a role, such as genetics, microbiome, environmental stress and immune dysfunction.[2]

There is currently no cure for IBD, with therapeutic strategies aimed toward attaining and maintaining remission from inflammatory episodes. Steroids are commonly prescribed for acute exacerbations of both UC and CD, but prolonged use can lead to undesirable systemic side-effects.[3,4] Other therapies for IBD include aminosalicylates, antibiotics, and immuno-suppressive agents. While these medications can temporarily induce and maintain remission, 70% of IBD patients will require at least one surgical intervention in their lifetime.[5,6] A systematic review by Talley et al[5] highlighted the variable performance of current IBD therapies across IBD phenotype, location, stage and severity of disease.

Conventional oral formulations are limited for use in IBD as they are generally designed to achieve systemic delivery of therapeutics, which results in adverse effects and toxicity following distribution of drug around the body. Oral formulations achieving a localized effect are preferred in rational drug

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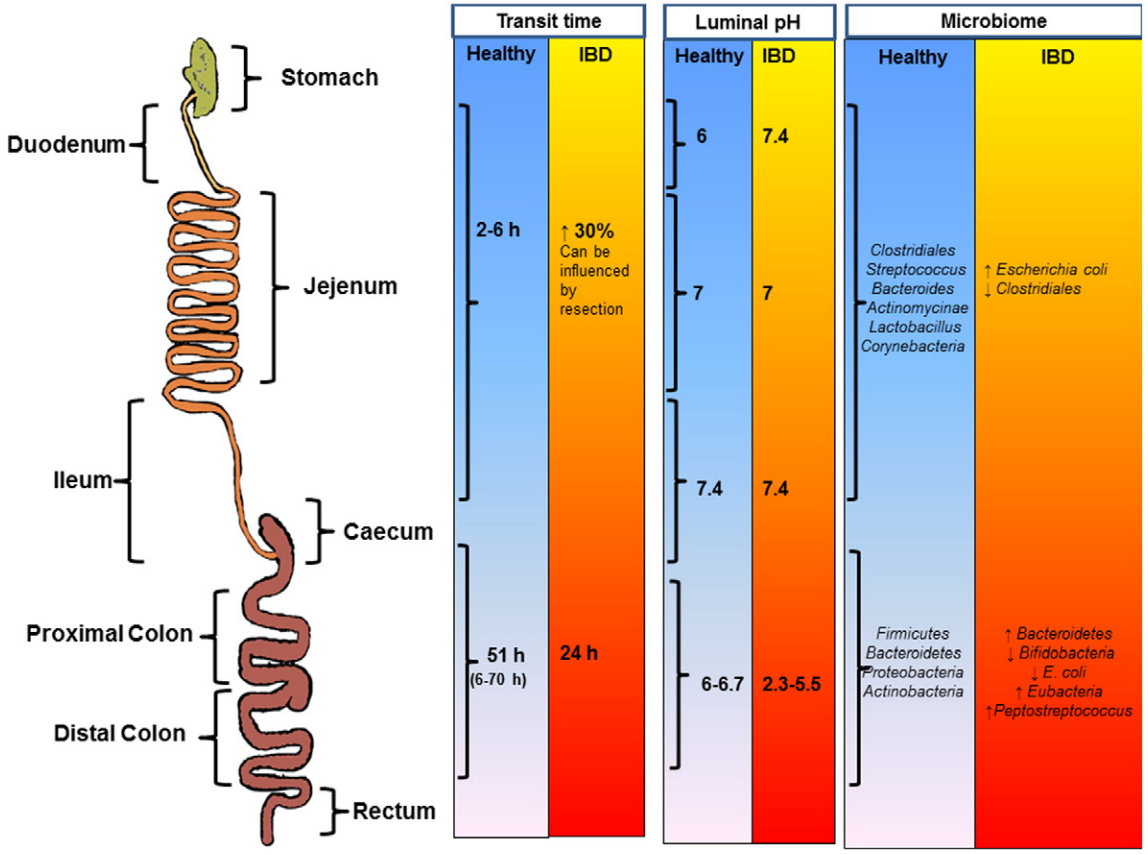


Figure 1. Physiological and microbial changes to the GI tract in inflammatory bowel disease. IBD patients have increased orocecal transit times in the absence of small intestinal bacterial overgrowth (SIBO).[39] Tissue resection[59] or SIBO[39] can significantly reduce transit time. IBD patients exhibit minor elevation in small intestinal pH,[45,46] however there are significant decreases seen in the colonic pH of both CD and UC patients.[21,47] These changes in pH and motility may facilitate the widespread changes in commensal populations in the GI tract, affecting the small intestine and the colon.[29,42]

delivery design for IBD. This ensures that drug will be delivered to the site of action within the GI tract, but will not be absorbed or will be poorly absorbed. Current therapeutic approaches specifically indicated for IBD rely on conventional dosage forms such as delayed or controlled release mechanisms. Their design is based on exploiting physiological conditions in the GI tract, in particular the colon.[7] For example, prodrugs of 5-aminosalicylic acid (5-ASA), such as sulfasalazine or olsalazine, rely on the enzymatic activity of colonic bacteria to cleave the prodrug into active moieties.[8] Similarly non-starch polysaccharide coatings, such as the COLAL-PRED® (prednisolone sodium metasulfobenzoate) system, and matrix formulations rely on enzymatic degradation that is specific to colonic bacteria.[9] Another approach involves the use of pH-specific soluble coatings and matrices, which rely on the pH gradient of the GI tract to activate release,[7] while time-dependent release systems use GI transit times as a guide to activate release of the drug.[10]

These approaches are associated with inconsistent efficacy and inter-patient variability.[5] One reason for varied efficacy of these conventional colon targeted delivery approaches may lie in the diverse physiological changes and variability in the GI tract that present with chronic and active inflammation in IBD patients—including pH, GI transit time and the colonic microbiome.[5,11] Attempts to overcome these issues have focused on improved understanding of the physiology of the GI tract during active IBD and following GI tract resection, as well as rational design of oral formulations. These considerations not only improve biodistribution of therapeutics to the colon, but also confer specific accumulation and cellular uptake within diseased tissue.[12,13] Recent pharmaceutical advances have applied nanotechnology to oral dosage form design in an effort to overcome the limitations of conventional formulations.[14] This review will describe some of the physiological challenges faced by orally administered delivery systems in IBD, the important developments in orally administered nano-delivery systems for colon targeting, and the future direction of this research.

## General physiological considerations for colonic drug delivery

Drug delivery to the colon relies on a number of physiological factors to ensure optimal efficacy following oral administration (Figure 1). Considerations should be made during formulation design to the residence time of the formulation in the GI tract, how the GI environment affects the delivery of the formulation and dissolution of the drug at the site of action, the intestinal fluid volume, and the propensity of the formulation or drug to be metabolised in the GI tract through enzymatic or microbial