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Budesonide Nanoparticles For Ulcerative Colitis And Crohn's Disease: Recent Advances In Colon-Specific Drug Delivery

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Abstract: Inflammatory bowel disease (IBD), which primarily includes ulcerative colitis and Crohn's disease, remains a major therapeutic challenge due to its chronic relapsing nature and localized inflammation within the colon. Conventional oral therapies with corticosteroids such as budesonide are limited by extensive hepatic first-pass metabolism, low systemic bioavailability, and undesirable side effects. To overcome these challenges, colon-targeted nanoparticle-based delivery systems have emerged as a promising approach to improve drug localization, reduce systemic exposure, and enhance therapeutic efficacy. Budesonide-loaded nanoparticles, particularly those formulated using natural polymers such as chitosan, alginate, and other biodegradable carriers, have demonstrated significant potential in modulating drug release and improving mucoadhesion in the colonic environment. Various formulation strategies, including nanoprecipitation, ionic gelation, and emulsification techniques, have been explored to achieve optimal particle size, high encapsulation efficiency, and controlled release profiles. Preclinical studies highlight that nanoparticle systems not only protect the drug in the upper gastrointestinal tract but also enable targeted release in the colon, where local conditions favor solubility and absorption. Furthermore, nanoparticles enhance drug residence time at the site of inflammation, thereby minimizing dosing frequency and reducing systemic corticosteroid-associated toxicity. This review consolidates recent advances in budesonide-loaded nanoparticle formulations for ulcerative colitis and Crohn's disease, focusing on formulation techniques, physicochemical characterization, in vitro and in vivo performance, and therapeutic outcomes. The evidence strongly supports nanoparticle-based colon-specific delivery of budesonide as a superior alternative to conventional dosage forms, offering a promising platform for future clinical translation in IBD management.

Index Terms - IBD, ulcerative colitis, Crohn's disease, IBD management, Nanoparticles, Nanoparticles loaded Capsule.

I. INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing, and immune-mediated condition of the gastrointestinal tract that primarily includes ulcerative colitis (UC) and Crohn's disease (CD). Both disorders significantly impair quality of life, with symptoms such as abdominal pain, diarrhea, rectal bleeding, and weight loss, and they frequently require lifelong management (Torres et al., 2017). The global incidence of IBD has increased markedly in the past two decades, with high prevalence in Western countries and a rising trend in Asia, indicating that both genetic predisposition and environmental factors play critical roles in disease development (Ng et al., 2018). Despite numerous therapeutic advances, IBD continues to present challenges due to its heterogeneous pathology, fluctuating disease course, and the limitations associated with current therapies (Edsbäcker, S., & Andersson, T. et al., 2004). UC is characterized by continuous mucosal inflammation restricted to the colon, starting from the rectum and extending proximally to varying extents. In contrast, CD can affect any part of the gastrointestinal tract from mouth to anus, often with discontinuous "skip lesions," transmural inflammation, and complications such as fistulae and strictures (Neurath, 2019). Both conditions involve complex interactions between genetic susceptibility, epithelial barrier dysfunction, dysregulated immune responses, and altered gut microbiota. While current therapies aim to control inflammation and induce remission, relapse is common, and many patients eventually require surgical intervention (Koziolek, M et al., 2016). Corticosteroids remain a cornerstone for inducing remission in moderate to severe IBD. Budesonide, a synthetic glucocorticoid with high topical anti-inflammatory activity and relatively low systemic bioavailability, is widely prescribed for the treatment of UC and CD (Ali, H, et al., 2014). Compared with conventional steroids such as prednisone, budesonide undergoes extensive first-pass hepatic metabolism, resulting in fewer systemic side effects (Edsbäcker & Andersson, 2004). Commercial formulations such as controlled-release capsules (Entocort®) are designed to target drug release to the ileum and ascending colon. However, these formulations are not fully effective in achieving site-specific delivery across the entire colon. A significant portion of the drug is absorbed in the upper gastrointestinal tract before reaching the inflamed colonic tissue, leading to suboptimal efficacy, variable bioavailability, and dose-related side effects (Koziolek et al., 2016). Consequently, there is a strong demand for advanced drug delivery systems that can transport budesonide directly to the colon and sustain its release at the site of inflammation (Beloqui, A. et al., 2014). The colon presents unique challenges for oral drug delivery. Compared to the stomach and small intestine, colonic fluid is limited in volume, less viscous, and contains a dense microbial population (Hua et al., 2015). Drugs intended for colonic targeting must survive the acidic gastric environment, avoid premature absorption in the small intestine, and be released in a controlled manner within the colon. Nanoparticle-based systems have emerged as promising carriers to overcome these challenges. Nanoparticles offer advantages such as protection of the encapsulated drug from premature degradation, enhanced mucoadhesion, controlled release profiles, and the possibility of functionalization with targeting ligands (Lamprecht et al., 2001). By tailoring surface chemistry and polymer composition, nanoparticles can respond to colonic stimuli such as pH, redox potential, or bacterial enzymes, enabling site-specific drug release (Gao, J, et al., 2024).

Recent advances in budesonide-loaded nanoparticles have demonstrated improved therapeutic efficacy in preclinical models of IBD. These formulations not only prolong drug residence time in the colon but also enhance local bioavailability, reduce systemic exposure, and minimize steroid-associated adverse effects. Natural polymers such as chitosan, alginate, and pectin, as well as synthetic polymers like poly(lactic-co-glycolic acid) (PLGA), have been extensively investigated for encapsulating budesonide due to their biocompatibility and ability to provide controlled release (Beloqui et al., 2016). In animal models of colitis, budesonide nanoparticles significantly reduced inflammation, improved histological outcomes, and lowered pro-inflammatory cytokine levels compared to conventional formulations (Viscido, A., et al., 2014). Despite these advances, translation to clinical practice remains limited. Key challenges include scaling up nanoparticle production, ensuring stability during storage, maintaining reproducibility across batches, and meeting stringent regulatory requirements for nanomedicines. Furthermore, long-term safety and tolerability of chronic nanoparticle administration require thorough evaluation in clinical trials. Nevertheless, the potential of budesonide nanoparticles for colon-targeted therapy is substantial, as they combine the efficacy of corticosteroids with reduced systemic toxicity and enhanced local action (Yang, M., et al., 2020). This review aims to provide a comprehensive overview of recent developments in colon-specific delivery of budesonide using nanoparticle-based approaches. It will discuss the pathophysiology of IBD, limitations of conventional budesonide formulations, various nanoparticle design strategies, and preclinical and clinical findings. Additionally, future perspectives and challenges in translating these systems to clinical use will be highlighted. By integrating current evidence, this review underscores the potential of nanoparticle-mediated delivery of budesonide as a promising therapeutic strategy for patients with UC and CD (Alshammari, N.D., et al., 2024)

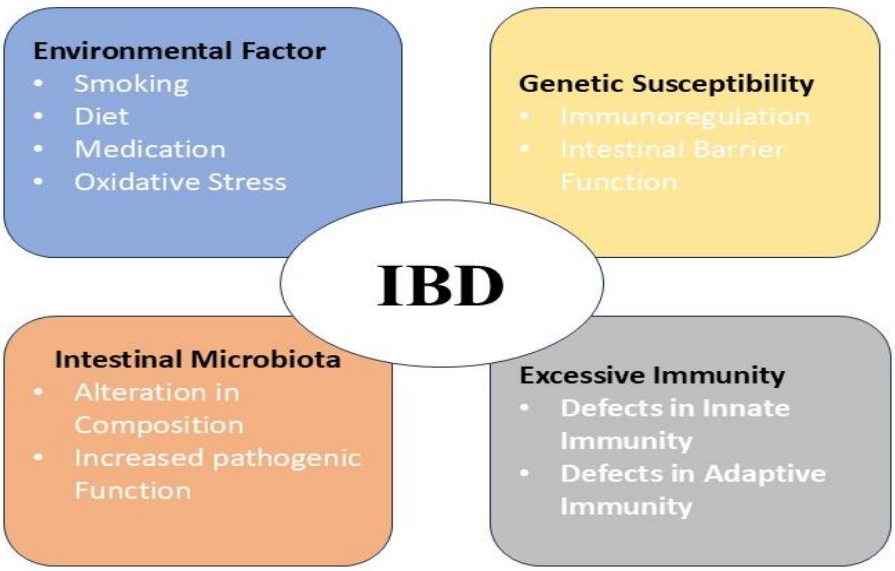

Fig. No. 1: *Various Factors of IBD*

II. Pathophysiology of Ulcerative Colitis and Crohn's Disease

Inflammatory bowel disease (IBD) encompasses two major clinical entities—ulcerative colitis (UC) and Crohn's disease (CD)—both characterized by chronic, relapsing inflammation of the gastrointestinal (GI) tract. While they share overlapping features, their pathophysiological mechanisms and patterns of involvement differ considerably.

Ulcerative Colitis

UC is restricted to the colon and rectum, with inflammation typically beginning in the rectum and extending proximally in a continuous manner. Unlike CD, which is transmural, UC inflammation is confined to the mucosal and submucosal layers. The hallmark pathological features include continuous mucosal ulceration, crypt abscesses, goblet cell depletion, and distorted mucosal architecture (Ordás et al., 2012). The pathogenesis involves an inappropriate immune response to intestinal microbiota in genetically predisposed individuals. Dysregulation of innate immunity, epithelial barrier dysfunction, and exaggerated adaptive immune responses—particularly Th2-type cytokines such as interleukin (IL)-5 and IL-13—play central roles. Increased infiltration of neutrophils, along with elevated levels of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), perpetuate mucosal injury and impair epithelial healing (Ungaro et al., 2017). Clinically, UC presents with bloody diarrhea, abdominal pain, urgency, and tenesmus. The chronic inflammatory state also increases the long-term risk of colorectal carcinoma.

Crohn's Disease

Crohn's disease can affect any part of the GI tract from the mouth to the anus, but most commonly involves the terminal ileum and colon. Unlike UC, inflammation in CD is discontinuous ("skip lesions") and transmural, leading to complications such as strictures, fistulas, and abscesses (Torres et al., 2017). Histological features include granuloma formation, transmural lymphoid aggregates, and architectural distortion of the intestinal wall. The immunopathogenesis of CD is linked to an exaggerated Th1 and Th17 response, with increased secretion of interferon-gamma (IFN-γ), IL-17, and IL-23, leading to persistent activation of macrophages and dendritic cells. This drives the release of pro-inflammatory cytokines such as TNF-α and interleukin-6, sustaining chronic tissue injury (Neurath, 2019). Genetic susceptibility also plays a major role, with polymorphisms in *NOD2*, *ATG16L1*, and *IL23R* genes strongly associated with CD development. Clinically, CD manifests with abdominal pain, chronic diarrhea, weight loss, and malnutrition. Transmural inflammation predisposes to complications, including fibrotic strictures and penetrating disease.

Shared Mechanisms

Despite differences, UC and CD share common features:

1. **Epithelial barrier dysfunction**, leading to increased intestinal permeability.
2. **Aberrant immune responses** to commensal gut microbiota.
3. **Cytokine-driven inflammation**, with TNF-α acting as a pivotal mediator in both diseases.
4. **Microbiota dysbiosis**, with reduced diversity and altered composition favoring pro-inflammatory bacterial species.

III. Limitations of Current Budesonide Therapy

Budesonide, a second-generation corticosteroid, is widely used in the management of inflammatory bowel disease (IBD), particularly mild-to-moderate ulcerative colitis and Crohn's disease. Its therapeutic appeal lies in its high topical anti-inflammatory activity and low systemic bioavailability due to extensive first-pass metabolism in the liver. Despite these advantages, conventional budesonide therapy faces several limitations that reduce its long-term effectiveness in IBD treatment.

1. Extensive First-Pass Metabolism

Although budesonide undergoes rapid absorption in the upper gastrointestinal tract, it is subject to extensive hepatic first-pass metabolism, resulting in only 10–15% oral bioavailability (Edsbäcker & Andersson, 2004). This necessitates higher or repeated dosing, which may increase the risk of systemic corticosteroid-related side effects over prolonged use.

2. Non-Specific Gastrointestinal Absorption

Commercial budesonide formulations such as *Entocort EC*® and *Budenofalk*® rely on pH-dependent coatings designed for ileocolonic release. However, variations in gastrointestinal pH and motility among patients can lead to premature drug release or incomplete delivery to the inflamed colonic tissue (Koziolek et al., 2016). This reduces site-specific therapeutic concentrations and compromises efficacy.

3. Limited Retention at the Site of Inflammation

Even when budesonide is successfully released in the colon, rapid mucosal absorption and clearance from the site of inflammation restrict its local residence time. This results in suboptimal drug exposure in inflamed tissues, limiting mucosal healing (Beloqui et al., 2016).

4. Systemic Side Effects

Although budesonide is associated with fewer systemic effects compared to conventional corticosteroids such as prednisolone, chronic use still carries risks of adrenal suppression, osteoporosis, hypertension, and glucose intolerance (Stallmach et al., 2011). These adverse events highlight the need for targeted formulations that minimize systemic drug exposure.

5. Variable Clinical Response

Clinical trials have shown that while budesonide is effective in inducing remission in Crohn's disease and ulcerative colitis, relapse rates remain high after discontinuation of therapy (Lichtenstein et al., 2009). Inter-individual variability in drug metabolism and differences in colonic disease distribution contribute to inconsistent therapeutic outcomes.

6. Lack of Controlled Release in Severe Disease

In severe colonic inflammation, accelerated transit time and altered luminal conditions may cause premature drug release and reduced mucosal absorption (Hua et al., 2015). Conventional dosage forms fail to adapt to such pathological changes, further compromising efficacy in advanced disease states.

IV. Need for Colon-Specific Nanoparticle Delivery of Budesonide

The limitations of conventional budesonide therapy highlight the urgent need for innovative drug delivery strategies that can enhance therapeutic efficacy while minimizing systemic side effects. Colon-specific

delivery systems, particularly nanoparticle-based formulations, have emerged as a promising solution to overcome the inherent challenges associated with oral corticosteroid administration.

Firstly, the non-specific absorption of budesonide in the stomach and small intestine reduces its availability at the site of inflammation in the colon. Nanoparticles can protect the drug from premature release and degradation in the upper gastrointestinal tract, ensuring that a higher fraction reaches the colon intact. By controlling particle size, surface charge, and polymer composition, nanoparticles can be engineered to remain stable in gastric and intestinal fluids and release the drug in response to colonic-specific triggers such as pH, enzymatic activity, or reactive oxygen species (Hua et al., 2015).

Secondly, the rapid clearance of conventional budesonide from inflamed mucosa limits local drug retention and efficacy. Nanoparticles, particularly those prepared with mucoadhesive polymers like chitosan, can adhere to the colonic mucosa, prolonging residence time and sustaining drug release. This localized action enhances anti-inflammatory effects at the target site while reducing systemic exposure, thereby lowering the risk of adrenal suppression, osteoporosis, and other corticosteroid-related side effects (Beloqui et al., 2016).

Furthermore, poorly soluble drugs like budesonide face dissolution challenges in the colon due to limited luminal fluid volume. Nanoparticle formulations improve solubility and dispersibility through increased surface area and encapsulation in hydrophilic matrices, facilitating more efficient drug absorption and bioavailability (Lamprecht et al., 2001). Stimuli-responsive nanoparticles can further optimize delivery by releasing the drug in response to specific pathological cues within the inflamed colon, ensuring maximum therapeutic effect where it is needed most.

Lastly, patient variability in gastrointestinal pH, motility, and disease severity often leads to inconsistent outcomes with conventional dosage forms. Nanoparticle-based systems provide the flexibility to fine-tune release profiles, enhancing reproducibility and consistency of drug exposure across different patients. This approach aligns with the principles of precision medicine, offering tailored treatment that addresses the heterogeneous nature of IBD (Hua et al., 2015).

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