International Journal of Enhanced Research in Science, Technology & Engineering
ISSN: 2319-7463, Vol. 11 Issue 12, December-2022, Impact Factor: 7.957

Keratin Based Drug Delivery System-A Boon Approach in Treatment and Management of Inflammatory Bowel Disease (IBD)

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ABSTRACT

IBD, leading to great advances in the treatment as well as diagnosis of IBD. In this review, we have systemically reviewed the pathogenesis of IBD and highlighted recent advances in host genetic factors, gut microbiota, and environmental factors and especially, in abnormal innate and adaptive immune responses and their interactions, which may hold the keys to identify novel predictive or prognostic biomarkers and develop new therapies. Protein-based biomaterials have been used in many biotechnology and biomedicine applications. This article briefly introduces the use of keratin in Ulcerative Colitis, and then focuses on the recent researches on the application of keratin in drug delivery systems. Keratins are associated with pathogenesis of various colorectal diseases including IBD & Cancer. In the intestinal epithelium principally expressed keratins are keratin 8, 18 & 19. Keratins are a type of intermediate filament proteins which is a part of cellular cytoskeleton have important regulatory functions on the colonic mucosa. Keratin also functions in cell-death signalling pathways in particular apoptosis mediated by FaS & Tumour Necrosis Factor (TNF-α). TNF-α, functionally triggers a series of molecular signals for biological functions such as inflammation and cell-death. Keratin is shown to modulate tumour necrosis factor's action. If keratin undergoes post translational modifications specifically-Phosphorylation then it has the ability to modulate TNF - α. This process (PTM - Phosphorylation) has potential to alter the stability, sub-cellular location & enzymatic activity of proteins (Keratin) with diverse roles in cell.

Keywords: **Keratin, Mucoadhesive, Biomarker, Concomitant.**

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are classified as chronic inflammatory bowel diseases (IBD) which have similar symptoms and lead to digestive disorders and inflammation in the digestive system. Given the fact that the prevalence of this disease is higher at younger ages and that it disrupts half the life of the patient, it will, most likely, become a major health problem in the near future, even in developing countries. A number of factors can be attributed to the prevalence of CD and UC, some of which include geographical location, inappropriate diet, genetics, and inappropriate immune response [1]. The inflammation of the intestinal mucosa in IBD is characterized by episodes of abdominal pain, diarrhoea, bloody stools, weight loss, and the influx of neutrophils and macrophages that produce cytokines, proteolytic enzymes, and free radicals that result in inflammation and ulceration [2]. The hallmark of active inflammatory bowel disease is a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B cells and T cells). Increased numbers and activation of these cells in the intestinal mucosa elevate local levels of tumour necrosis factor α (TNF-α), interleukin-1β, interferon-γ, and cytokines of the interleukin-23–Th17 pathway [3]. Keratins are highly dynamic and are subject to post-translational modifications including phosphorylation, acetylation and glycosylation. These affect the filament dynamics and hence solubility of keratins and may contribute to protection against degradation [4]. The principally expressed keratins (K) of the intestinal epithelium are K8, K18 and K19. In the colon, keratins have been shown to regulate electrolyte transport, likely by targeting ion transporters to their correct location in the colonocytes [5]. TNF-α is a pro-inflammatory cytokine, the levels of which are increased in blood, colonic tissue and stools of patients with Ulcerative colitis K8 and K18 have been noted to co-localize with cytoplasmic domain of TNF receptor 2 (TNFR2) and moderate TNF-induced, Jun NH2-terminal kinase intracellular signalling and NFκB activation [6,7].Phosphorylation of K8 on Ser

and Thr residues typically promotes disassembly of filaments into ULF and increases filament protein solubility and triggers reorganisation of the keratin filament K8, K18, K19 [9,10]. The mucosal keratins are the intermediate filament proteins that are preferentially expressed in epithelial cells that line the inner and outer surfaces of animal tissues. These mucosal keratins consist of a large family (K1-K20) of cytoplasmic proteins. Of this keratin phosphorylation has been extensively studied in K8/K18/K19 partly because of their higher relative solubility. Stimulation of cells, in case of cell stress or apoptosis keratin filament reorganization with increased keratin solubility [11]. Reduced K8 phosphorylation in inflamed mucosa compared to proximal uninflamed colon is shown in IBD patients, along with reduced K8, K18, K19 compared to controls [12,13]. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption [27]

MATERIAL AND METHODS

A. Serotonergic receptor modulators: Tegaserod, an aminoguanidine indole derivative of serotonin, is a selective partial agonist of pre-synaptic 5HT4 receptors on submucosal IPANs It augments 5HT1 receptor mediated release of Ach and CGRP from submucosal IPANs, thereby potentiating the peristaltic reflex [19]
B. Neurokinin receptor modulators: Aprepitant, a highly selective antagonist of the G-protein coupled neurokinin-1 receptor. By acting as a competitive antagonist, aprepitant is thought to attenuate the likelihood of the complex vomiting reflex initiation significantly. [15]
C. CRF_1 receptor antagonists: Antalarmin, a novel CRH receptor type 1 antagonist, decreases the activity of the HPA axis and LC–NE system, suppresses neurogenic inflammation, and blocks CRH-induced skin mast cell degranulation, in addition to blocking the development and expression of conditioned fear and stress-induced colonic hyperfunction.[17]
D. Alpha adrenergic agonists: Clonidine, an imidazole derivate that acts as an agonist of alpha-2 adrenoceptors. It stimulates alpha 2-adrenergic receptors in the brain stem resulting in decreased sympathetic outflow from the CNS and decreased peripheral resistance, renal vascular resistance, HR and BP [18]
E. Chloride channel activators: Lubiprostone, acts by specifically activating ClC-2 chloride channels. Activation of ClC-2 chloride channels causes an efflux of chloride ions into the lumen, which in turn leads to an efflux of sodium ions through a paracellular pathway to maintain isoelectric neutrality. As a result, water follows sodium into the lumen in order to maintain isotonic equilibrium, thereby increasing intestinal fluid secretion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation.[19]
F. Linaclotide, a first-in-class, 14-amino acid peptide of the guanylin peptide family and acts as a selective agonist at the guanylate cyclase–C (GC–C) receptor on the luminal surface of intestinal enterocytes. The endogenous ligands of GC–C (guanylin peptide hormones guanylin and uroguanylin bind to the receptor to promote intestinal secretions in response to a meal. Activation of GC–C by guanylin peptides, including linaclotide, results in increased levels of cyclic guanosine monophosphate (cGMP), a second messenger that plays a critical role in the regulation and secretion of intestinal fluid.[20]
G. TRPV1 antagonists: TRPV1 and TRPA1 are polymodal nociceptors playing an important role in thermo-mechanical- and chemo-sensation, and play a complex role in hyperalgesia and neurogenic inflammation. Their endogenous activators are often produced during inflammation, e.g., lipoxygenase products, the acidified pH of the inflamed tissue, and the gastrointestinal mucosa is frequently exposed to their exogenous agonists, such as capsaicin, allyl isothiocyanate, allicin etc [21]
H. Bile acid binders: Some evidence suggests that certain genetic variants may influence response to the bile sequestrant colesevelam, a medication that may be preferable to cholestyramine.[22]
I. Mast cell stabilizers and 5-aminosalicylic acid (5-ASA) [23,30]
J. Spherical carbon adsorbent: AST-120 is a preparation consisting of spherical carbon particles that adsorb bacterial toxins, inflammatory mediators and bile acid products and prevent them from entering systemic circulation. In a phase II randomized, controlled eight-week trial of AST-120 in 115 patients, improvements in pain and bloating were short-lived [24]
K. Linaclotide was shown to be well tolerated and efficacious for the treatment of patients with IBS-C in 2 randomized, double-blind, placebo-controlled studies, as well as additional post-hoc analysis [25,29]
L. Targeting opioid receptors: Expression of the κ-opioid receptor is increased during inflammation and chronic visceral hypersensitivity. The mixed μ-opioid receptor agonist and δ-opioid receptor antagonist eluxadoline was approved in May 2015 for the treatment of IBS-D. Patients with IBS-D receiving eluxadoline in a phase II dose-ranging study had greater efficacy compared with patients receiving placebo after 12 weeks. Asimadoline is a κ-opioid receptor agonist currently in development for the management of patients with IBS-D with moderate-to-severe pain [26,28]

Future Advances: **Keratin based Mucoadhesive system**

A. Material and Methods Hydroxypropyl methylcellulose, Keratin, Carbopol-934P Eudragit RL-100

B. *Characterization of dosage form:*

Film weight and thickness: For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance (Fisher Brand PS-200). The average weights were calculated. Similarly, three films of each formulation were taken and the film thickness was measured using micrometre screw gauge (Mitutoyo MMO-25DS) at three different places and the mean value was calculated.

Surface pH of films:

For determination of surface pH three films of each formulation were allowed to swell for 2 h on the surface of an agar plate. The surface pH was measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings was recorded[20].

Percent swelling:

After determination of the original film weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37±0.2°. Increase in the weight of the films (n = 3) was determined at preset time intervals (1-5 h). The percent swelling, %S, was calculated using the following equation: Percent Swelling (%S) = $(X_t - X_o/X_o) \times 100$, where X_t is the weight of the swollen film after time t, X_o is the initial film weight at zero time[23]

Folding endurance:

Three films of each formulation of size (2 × 2 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance.

***In vitro* residence time:**

The *in vitro* residence time was determined using IP disintegration apparatus. The disintegration medium was 800 ml of pH 6.6 phosphate buffer (PB) maintained at 37±2°. The segments of rat intestinal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface using pH 6.6 PB and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point.

Drug polymer interaction (FTIR) study:

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2 mg of Silymarin alone, mixture of drug and polymer, drug loaded microspheres were weighed and mixed properly with potassium bromide uniformly. A small quantity of the powder was compressed into a thin semi-transparent pellet by applying pressure. The IR-spectrum of the pellet from 500–4000 cm

CONCLUSION

*T*he pathophysiology of IBD is unclear, but is thought to include genetic, immunologic, microbial, physiologic stress response, and psychosocial components. Management of patients with IBS includes lifestyle changes, dietary modification, use of psychotropic medications, psychological therapies, and over-the-counter agents targeting GI motility. Concomitant Keratinized based drug delivery system with TNF can prove to be a boon for relief in IBD. Mucoadhesive dosage forms might be a useful tool for the efficient design of novel mucoadhesive drug delivery systems for Management of IBD with aid of concomitant use of Keratin.

1. Ethics statement animal experimentation: Not performed
2. Funding: No funding required
3. No conflict of Interests

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