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Novel Approaches of Drug Delivery System for Inflammatory Bowel Disease

Miss [1]Nisha Tukatram Patil ,[2] Dr . Ashish Vilas kulkarni , [3]Pooja Deshmukh ,[4] Suraj Allishe

[1]M pharm , [2] M pharm ,Ph.D, [3] M pharm ,[4] M pharm

Department of Pharmacology, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune.

***Corresponding Author :** Miss Nisha Tukaram Patil

Address: Department of Pharmacology, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India.

Abstract : Ulcerative colitis and Crohn's disease are forms of IBD, which is a long term disease that features repeated inflammation of the colon. However, its precise cause is still unknown; this disease seems to be caused by genetic susceptibility, immune dysfunction, and influences of bacterial organisms. Current treatments aim to control disease progression and alleviate symptoms through corticosteroids immunosuppressants, and 5-aminosalicylates (5-ASAs). However, conventional oral, parenteral, and rectal drug delivery methods often present challenges, such as poor specificity and systemic side effects. To overcome these limitations, innovative drug delivery systems are being explored to enhance targeting of inflamed tissues and reduce systemic exposure. Nanoparticles, which adhere to mucosal layers and penetrate inflamed sites, have emerged as a promising approach. Lipid-based systems like liposomes, prodrugs such as modified 5-ASA derivatives, and hybrid nanoparticles are being investigated for their ability to improve drug distribution and efficacy. Additionally, leukosomes, specialized carrier systems that modulate inflammation, have shown potential in preclinical models. This review provides an overview of these advanced drug delivery strategies, highlighting their potential to optimize IBD treatment .

Key words : colon, Crohn's disease, drug delivery, drug design, drug therapy, gene therapy, inflammatory bowel disease, ulcerative colitis

Introduction : Crohn's disease and ulcerative colitis are the two main forms of IBD – a chronic disorder characterised by periodic bouts of inflammation in the GI tract with no known triggers. It is generally categorized into two primary types: Crohn's disease and ulcerative colitis[1]. IBD is more common in the industrialized western countries of the world. Currently, about 1.4 million persons in America and 2.2 million persons in Europe are living with an IBD [2]. The incidence rates of the disorders are fairly close, standing between 50 and 250 per 100,000 people every year in both zones [3]. The genetic factors people have have been shown to complicate and weaken the structure and functionality of the intestinal wall, which perhaps leads to the disease. Hence, the light microscopy showed evidence of humoral and cell-mediated immunity in IBD development; while the electron microscopy revealed that the pathophysiology mechanisms that control IBD severity or progression of disease [4]. In general, these mechanisms fulfill an immunosurveillance function of the immune system to antigens in the intestine that are released when broken in IBD and their potential to induce inflammation and tissue damage [5]. corticosteroids and 5 ASA are considered suitable for the therapy, such as mesalazine or olsalazine are taken for the weak form of the disease; peripheral blood and for the prevention of relapses and for the management of UC. Hence to moderate and severe IBD, more effective drugs include corticosteroids especially prednisolone.The side effect of coriticosteroids are both acute and chronic, the acute side effects such as hypertension hyperglycemia ,osteoporosis, glaucoma and chronic side effects such depression among others [6]. The immunosuppressive activity is still an issue and remains as challenge for researchers using an agent is definitely associated with increase has high susceptibility to infections as well as maligmoma [7,8] .Therefore, treatment of IBD is reached a therapeutic adequate with high intensity . Efficacy or the risk of side effects of a drug where short- and long term may further exacerbate health related 'quality of life' in the elderly Patients [9].

Inflammatory Bowel Disease pathogenesis:

There is no single mechanism can account for the IBD. Enteric bacteria, which may include normal intestinal flora, cause a dysregulated mucosal immune response that result in chronic mucosal inflammation in genetically susceptible individuals. This dysregulated response is caused by a variety of environmental factors, genetic factors, enteric microflora, and the mucosal immune system [10-12] .IBD have a hereditary component has long been supported by a number of population studies demonstrating a familial vulnerability to both conditions[13-15]. Recently, a direct link between a certain gene and the likelihood of developing Crohn's disease (CD) was found for the first time. The NOD2 gene, which codes for a protein that stimulates NF-κB, a critical transcription factor involved in bacterial identification and the start of the

inflammatory response, is found in the IBD locus. Moreover, endogenous and environmental factors finds crucial role in the development and course of IBD[15-17] .so that patients and their family members have been found with increased intestinal permeability [13]. Experimental colitis models used in animal research also typically reveal this pattern of inflammation[18] .An aberrant or heightened immune response to intestinal pathogens is a hallmark of both kinds of IBD, with the enteric microbiota most likely acting as a trigger. As effector cells, CD4+ T cells are essential for promoting the inflammatory processes that lead to the onset and advancement of IBD [17]. Activated CD4+ cells have been found in the lamina propria of both experimental animals and IBD patients, according to numerous investigations cytokines, mostly generated by lymphocytes, play a major role in the pathogenesis of disease contributing to an imbalanced immune response [18,19].Studies on patients and experimental models of Crohn's disease show that the cytokine balance is upset, favoring a T helper cell type 1 (TH1) response[17.] This change encourages granulomatous inflammation, which is indicated by a rise in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), and interferon-gamma (IFN-γ) [20,21]. A significant decrease in the synthesis of suppressor cytokines, including as TGF-β and IL-10, which are normally released by regulatory T cells (TH3 or Tr1), coincides with the heightened TH1 response in IBD. The TH1 response by itself may not be as important in the development of IBD as this breakdown in oral tolerance [19]. Unlike Crohn's disease (CD), ulcerative colitis (UC) is widely believed to be largely a TH2-mediated immune response. Human studies, however, have produced contradictory results about this issue. [13,18]. The development of antibodies, including perhaps autoantibodies, and the recruitment of acute inflammatory cells are associated with ulcerative colitis (UC). Interleukin-5 (IL-5) has been found to have a major impact on the immune response observed in UC. The specific antigens that trigger this immune response are still unclear [18].

1.1Rectal route of administration:

There are few advantages of rectal administration over parentral or peroral use [22] .The luminal-released drugs reduces the first-pass effect because they do not enter the portal circulation [23]. Enemas ,foams ,suppositories include simple rectal and local therapy to the rectum and large colon [24] .this gives optimum drug release at site of inflammation hence, minimises undesirable pharmacological effects due to low systemic absorption [25]. Patients with mild to moderate disease extent of distal UC should be treated with rectal preparations. Besides, what is more, particularly when there are many sick people, they are also applied in addition to dosing the administered medications. [26]. Products such as enemas and foams with dissolved active components can get to the rectum, sigmoid colon, as well as the descending colon while.[27] Local Scale suppositories can only release medication to the lower rectum [28].

1.2 Micro- and Nanoparticles :

New dimensions of the DDS, improved and newly derived polymers, new drug carriers and advance drug delivery systems have been well explored in experimental colitis model [29]. At the present time, nanoparticles of different size using in drug delivery targeted in research. [30]. Many polymers have been studied and tried for the synthesis of biodegradable particle including polymers like polycaprolactone, polyglycolic acid, polyanhydrides, polyesters, polyphosphazenes and polyphosphoesters [31] .It can be understood that the level of particle adhesion increases and their behaviour with cells and tissues varies based on the size of the particles [32,33] . It is established that, the concentration of particles in the healthy GI tract depends with the size of the particles, in that 500 nm can penetrate the absorbent cells of the intestines known as enterocytes through endocytosis. [34] The sampled regions constituting inflamed tissue are characterized generally by a higher nano- and micro- particles deposition than the healthy colonic mucosa. The particle deposition process was thereby, found to be size dependent albeit 10 µm particles formed Particles of 1000 nm were present in minimal concentrations in Inflammatory regions, The denser regions indicated a higher likelihood of accumulation at 100 nm. [35]. That is why it can be concluded that smaller particles have higher probabilities of penetration through the mucous barrier than larger particles. Microparticles offer very low potentialities of crossing an intact mucous layer because of diffusion and translocation potentialities of drug carriers decline as their size increases.[36] This size-dependent effect likely does not very much, despite the fact that particle diffusion is promoted by changes in mucus composition. To develop pH sensitive particle drug carriers for drug delivery systems, several new approaches for surface modification of the particles have been developed and experimented. In fact, several pharma-made strategies as follows; muco-adhesion [37], bio-adhesion [38], mucopenetration [39] and active absorption through M cells, endothelium targeting has been established to augment the treatment for IBD

1.3 Liposomal drug carriers:

Artificially produced liposome is small membrane enclosed structure with an aqueous core surrounded by one or more phospholipid layer. For that reason, hydrophilic and hydrophobic active substances may be incorporated into one carrier liposomes [40]. Hydrophilic medications are contained by embedding aqueous active chemicals into the liposome core, whereas hydrophobic compounds can dissolve in the lipid membrane.[41] It is often taken to the site of diseased dress by liposomes of drugs enzymes, vaccines, nutrient and many others [42]. The liposomes which are currently being developed with PEG coated surfaces that are designed specifically for the targeting of solid tumors , Galactosylated liposomes therefore used in targeting liver tumors and many others [43].Alterations on the outer shell of liposomes are important in targeted drug delivery system .Slightly positive charged liposomes have been found to have better affinity with healthy mucosa [46]. Although anionic liposomes exhibit good binding characteristics towards the inflamed mucosa there are further advanced liposomal drug delivery system developed for IBD site specifc drug delivery is still unexplored [55.]

1.4 Self Micro-Emulsifying Drug Delivery Systems (SMEDDS):

SMEDDS are novel formulations having exclusively pharmaceutical intention of improving the bio availability of the compounds with poor permeability. They may be mixtures of oil ,surfactants and at least one active matter [44,]. The SMEDDS as a pharmaceutical technology for IBD oral administration bioavailability of drugs is modified by an incresed drug dissolution and absorption due to surfactant-mediated membrane induced permeation changes [45] .The directions for applying SMEDDS for the management of the IBD turns into a problem because of the inflammations-produced disorders and interferences with the bile fluid secretion and movement, water and electrolyte absorption along the intestines. Thus, the potential of SMEDDS for IBD treatment is somewhat limited because it is hard to sustain the production of the drug-loaded micro- and nanoscale droplets [46].

1.5 Colon Targeted Drug Delivery : Tablets and capsules

Despite the rare availability of colon targeted commercial products, strategies for selectively delivering the medication to its colon deployments can be made through the use of film-coated tablets or capsules [47]. Illustration of colonic drug release using a pH sensitive polymer coated system of drug delivery has been provided in figure 1 Using Ion pair technique on coated tablet of Eudragit L 100 polymers for enhancing the delivery of recently synthesized anti-tumour necrosis factor α domain antibody [48] . This tablet was able to show that the drug was released freely when placed in a medium with a pH> 6 although the drug was not expelled from the tablet when left in an acidic environment for 2hrs. The V565 in monkeys was also shown to release in vivo within the intestine sustaining the drug release profile making it suitable for topical IBD treatment .

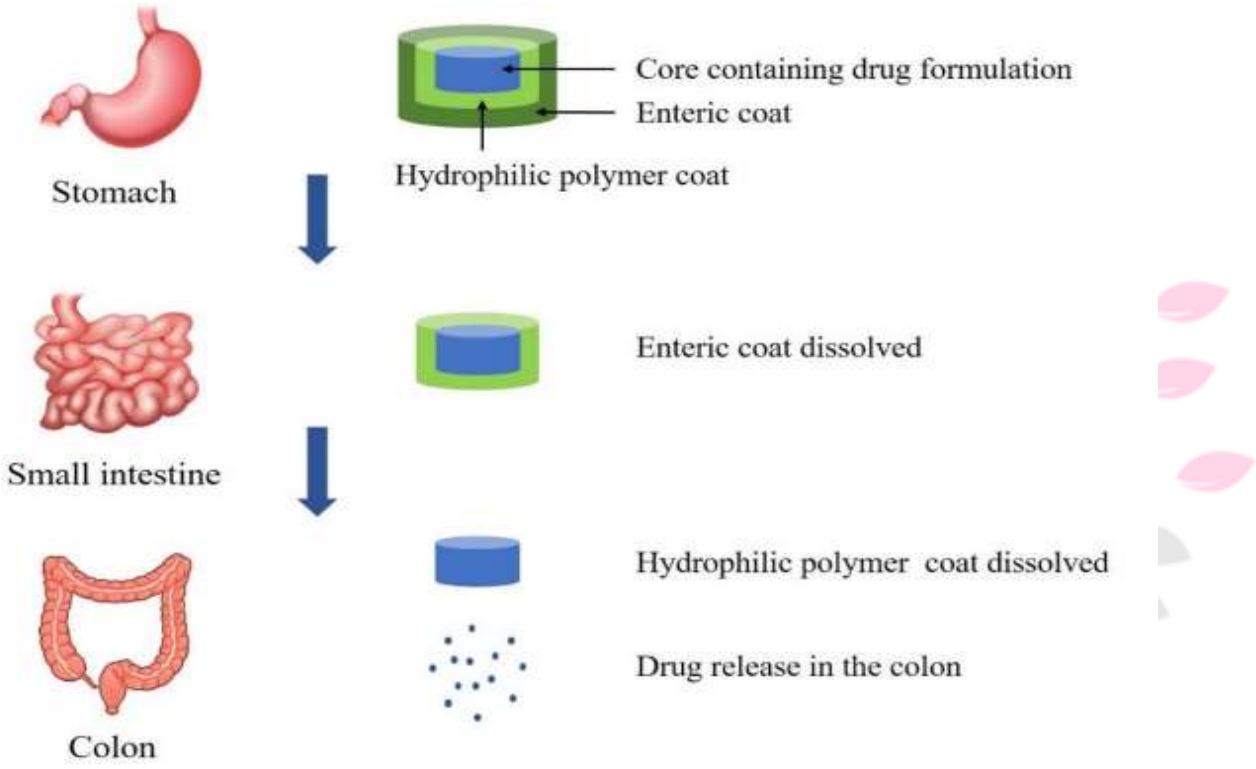

Figure 1. Drug release in the colon from pH-sensitive polymer-based system.

This covalent bilayer system could offer better delivery of the drug to the colon than the tablets coated only by a film of the polymer [49].Using the process of coating the tablet core with low viscous HPMC and Eudragit® L in layers the drug was targeted to the colon. This is usually preferred method which was recently introduced and it uses both time and pH dependence features. During the last decade there has been notable research focus on the application of sophisticated coating strategies for improving the targeting efficiency of pH-sensitive drug delivery systems [50]. Another way used for taking medicines at certain parts of the gastrointestinal tract is gastroresistant shells of capsule [51-52]. Its adv antage of these gastroresistant capsule shells may include: The ability to enclose assorted types of drugs; and able to reduce R&D costs.[53] They used cellulose derivatives and acrylic/methacrylic acid derivatives (Eudragit® L100 and Eudragit® S100) to form various enteric capsule shells for GI tract [54-55]. This may open an additional channel for delivering medication to the colon although the potential of off the shelf enteric capsules for colon selective drug delivery needs further assessment [56].

1.6 Herbal & Novel therapeutics :

Modern medicine has provided a drug delivery system to enhance efficiency of the drugs . The solubility and bioavailability of curcumin raised by reducing its size to nanometer level to pass through the biological membranes .Traditional medicines have been used in treatment of diseases using plant materials. phytochemicals have problems of low solubility in water, low permeability, systemic availability, first-passing.[57] To overcoming these challenges, novel drug delivery can be used as the best alternative.

Conclusion : The purpose of many drug carrier strategies is to get the drug delivered at specific region. into the site of intestinal inflammation active agents. The drug the carries incorporated active agents from the unfavourable conditions of a human body and increasing the therapeutic efficacy. This concept shows how precise drug targeting mechanism is then applied for the treatment . A better drug delivery system, designed to target inflamed tissues, could revolutionize current methods and serve as a breakthrough in advancing this critical field.

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