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A CRITICAL REVIEW ON COLON TARGETED DRUG DELIVERY SYSTEMS FOR MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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ABSTRACT: Inflammatory bowel disease (IBD) refers to the inflammation of the colon and small intestine of the body, in which Crohn's disease and ulcerative colitis are the principal types of IBD. This article covers most of the information related to a drug delivery system for treatment regarding intestinal diseases more emphasized to inflammatory bowel diseases. Currently, using delivery systems for targeting drugs to colon are osmotic drug delivery system, chronotropic system, pulsinicap system, multiparticulate system, port system, COLAL-Pred system, gas empowered drug delivery system have included in this article. An approach for targeting drugs to the colon is a probiotic approach has also included in this article. These delivery systems are being used to improve the bioavailability of the poorly absorbed drug. The purpose of this review article is to study about techniques employed in colon targeting for the prevention and treatment of IBD.

INTRODUCTION: Novel drug delivery system (NDDS) is an approach of delivering drugs to the desired site in optimal dosage with more patient compliance and safety in comparison to other conventional delivery systems [1]. NDDS can minimize the harmful effects of drugs, increases bioavailability and accumulation at the targeted site due to its control over pharmacokinetics and pharmacodynamic profile of the drug. In addition to this, NDDS are non-immunogenic and non-toxic [2]. This system involves several carriers' (soluble polymers, natural and synthetic polymers, lipoproteins, liposomes, micelles, *etc*.) for proper delivery of drugs to the required zone [3].

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This approach has been used successfully in targeting drugs to the colon site. Colon-specific drug delivery system (CDDS) has become the most selective approach for the local treatment of inflammatory bowel diseases (IBDs). IBD is the condition of chronic inflammation of the gastrointestinal tract that leads to the generation of specific diseases like ulcerative colitis and Crohn's disease. Other types of IBDs include colonic cancer, amoebiasis, and local colonic infections.

This system specifically delivers the drug to the colon site and prevent its degradation at the stomach and small intestine [4, 5]. Protein and peptide drugs generally degrade at gastric pH; the treatment will be more effective by using CDDS to deliver drugs directly to colonic mucosa. These novel approaches may target one or more aspects of gastrointestinal physiology such as colonic microflora, pH, enzymes, *etc*. [6] However, certain drawbacks are associated with this delivery system such as variation of pH in colon region, variation of

gastric emptying time, drug transit due to colonic disease and hindrance due to peristaltic movement [7]. IBD is a pathological immune response due to the attack of microbes. The body starts producing antibodies against microbial antigens; accumulation of T-cells and cell adhesion molecules cause inflammation of the affected organ [8]. The anti-tumor necrosis factor (anti-TNF) antibody therapy had significant success against IBD. There are several drugs approved for treatment of IBDs including infliximab, a first approved drug for induction and maintenance of Crohn's disease; adalimumab, a tumor necrosis factor (TNF-α) antagonist had approved for both Crohn's disease and ulcerative colitis [9]. However, this therapy was not effective in every patient for controlling IBD because the response of drugs decreases with time.

Therefore, it was a need to identify some more suitable disease targets and the discovery of drugs for the treatment of IBD. Recently, it has found that the IBD patients exhibited higher amounts of cytokine oncostatin M (OSM) in the inflamed tissue. OSM is a protein linked to inflammation, OSM receptor (OSMR) responds to OSM that leads to the production of several pro-inflammatory mediators (*e.g.*, interleukins, leukocyte adhesion factor, and chemokines) [10]. Targeting interleukins may be an effective therapy for the treatment of IBD. Specifically, interleukin-6 (IL-6) involves in the pathogenesis of colorectal cancer. The increased amount of IL-6 has found in colonic mucosa and serum of patients with IBD [4]. The objective of the present work was to compile several approaches employing for targeting colon in the treatment IBDs with more emphasis on biodegradable polysaccharides.

Disease Affecting Intestine and Abdominal Problems: There are several diseases affecting colon or large intestine represents a diagnostic problem in patients with abdomen problems. Colon diseases usually occur due to obstruction of our digestive processes such as gas, acidity, irregular bowel movements, constipation, diarrhea, and mild hemorrhoids. Crohn's disease is an ulcerative bowel disease usually associated with granulomatous inflammation [11]. Ulcerative colitis is defined as a chronic disease affecting the mucosa and sub-mucosa of the rectum. It causes bloody diarrhea, severe abdominal pain, and dehydration in its fulminant condition [12]. Amoebiasis is a protozoal disease that affects colon site caused by infection of *Entamoeba histolytica* [13]. Diverticulosis is herniation of mucosa and submucosa, abdominal pain and intermittent bleeding. Its inflammatory form is termed as diverticulitis [14].

Colonic Diseases: Colon is also known as large intestine one of the organs present in the gastrointestinal tract (GIT). It is a hollow tube surrounded by the muscles about 5 feet long and 2.5 inches in diameter [15]. The human large intestine plays an important role in maintaining gastrointestinal homeostasis throughout life. However, the component of microbiota may sometimes become the risk factor for disease in susceptible hosts. The mutualism of host-microbe breaks down during gastrointestinal diversity and inflammatory and metabolic disorders [16]. Colon cancer is the third most common cause of cancer worldwide and the leading cause of deaths for the patients [17].

It is generally considered that several environmental factors such as diet, smoking, and physical activities are responsible for generating colon cancer. Histologically, intestinal type adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma are major subtypes of colorectal cancer [18]. Some colorectal cancer occurs due to germline mutation when cancer cells invading submucosa are termed as malignant polyps. Adenomatous polyposis syndrome (FAP) is associated with mutations in tumor suppressor gene [19].

Inflammatory Bowel Disease: Inflammatory bowel disease (IBD) is a chronic disease characterized by remission and exacerbation tract affecting more than a million people worldwide. The etiology of IBD includes ulcerative colitis and Crohn's disease; factors involving for progression of these diseases include environmental, genetic, and immunoregulatory factors. It is more common to people residing in colder climates like Europe and North America as well as urban population. However, changing lifestyles, dietary habits and environmental factors has been leading incidence of IBD in Asian countries too [20]. IBD fall into the category of autoimmune disease where an

individual's immune system attacks its element in digestive system [21]. These diseases are generally associated with increased morbidity and decreased the quality of life. Few researchers reported that fatigue is associated with IBD due to its effect on the central nervous system interacting with chronic disease pathways like stress-induced changes in corticotropin-releasing hormone (CRH) regulation of the hypothalamic-pituitary axis [22]. Alteration in luminal pH is also responsible for generating IBD. It has reported that reduced intracolonic pH in ulcerative colitis impairs bioavailability of several pH-dependent release formulation such as 5-aminosalicylic acid, sulphasalazine, olsalazine, balsalazide, *etc*. [23] The therapy for IBD has changed with several agents and novel techniques. New targets have been identified by researchers for therapeutic alteration in IBD to restore immune dysregulation and inhibition of proinflammatory mediators. It includes tumor necrosis factor and interleukins such as IL-6, IL-13, IL-17, IL-18, and IL-21. [24]

Drugs Targeting Colon: Intestinal site is suitable for both local and systemic delivery of drugs. The treatment therapy will be more effective if we can deliver drugs directly to the intestine. It will reduce systemic side effects. It also allows oral administration of protein and peptide drugs that are normally inactive in the upper parts of the body [6]. Novel approaches targeting intestinal site includes pressure controlled colonic delivery capsules, osmotic controlled drug delivery and several other techniques that are unique in achieving site specificity and feasibility of production [25]. These novel techniques have overcome preliminary techniques including pH, time-dependent systems, prodrugs and microbially triggered delivery system due to several limitations and low rate of success [26]. The pH of gastrointestinal tract varies from region to region, *i.e*. stomach-1.5, duodenum- 6.1, jejunum- 5.4, ileum- 7.8, rectum- 7 to 8. [27] Drug targeting colon is used for the treatment of diseases like inflammatory bowel disease, amoebiasis, colonic cancer, ulcerative colitis, Crohn's disease, *etc*. [28] Intestinal mucoadhesive drug delivery system increases the residence time of the dosage form at the targeted site and facilitates absorption that contributes to improved therapeutic performance [29]. Drugs showing narrow therapeutic index are highly effective if targeted to the desired site of the GIT [30].

Drugs targeting colon allows to release drug at the desired site and prevents its degradation at stomach as shown in **Fig. 1**. The effective way of targeting drugs to large intestine is to increase release periods or slow release rates by applying thicker layers of enteric coatings. The absorption of the drug at this site is affected by the nature and pH of GIT.

The preliminary methods of targeting drugs to colon are the formation of a prodrug, polymer coatings, coating with a biodegradable polymer, poly-saccharides designed drugs, including novel techniques like pressure-controlled drug delivery systems and osmotic pressure controlled systems [5]. Drugs delivered using this system are more suitable for peptides and protein drugs to achieve reduced dosing frequency, delay drug delivery to attain high concentration and deliver drugs to the region those less hostile metabolically. The colon targeted drug delivery system comprised with certain advantages of reduced side effects in the treatment of colonic diseases, avoid first-pass metabolism, prevents gastric irritation and protects peptide drugs from hydrolysis and enzymatic degradation [31].

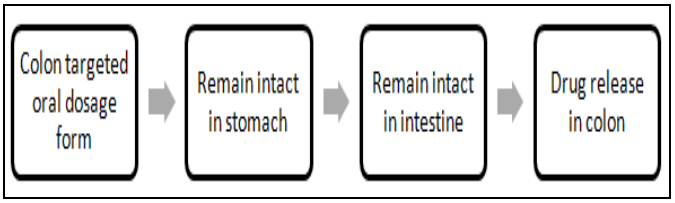

FIG. 1: PATHWAY OF ORAL DRUGS TARGETING COLON

Factors Affecting Drug Absorption: The administer drugs must cross membranes for its pharmacological response through diffusional transfer, and it depends on the chemical nature of the drugs. The membranes are lipophilic containing receptors and carriers' molecules allow passage of drugs through passive diffusion or carrier-mediated transport. Interestingly, the absorption of the drug from the lumen of the gut into systemic circulation needs to cross the epithelial barrier of the intestinal mucosa. Thus, lipid solubility, or the partition coefficient of a drug between the aqueous environment and the lipid phase of the membrane, is one of the most important factors describes its

absorption [32]. The drugs targeting colon should have following properties, *i.e*. the drug should be absorbed at large intestine rather than the stomach and small intestine, it should be compatible with a carrier molecule, it should be stable at alkaline pH, and the drug should have both local and systemic effects [5].

Colon Targeted Drug Delivery Systems: Targeted delivery systems are desirable for the treatment of a range of inflammatory bowel disease and other colon diseases. There are several systems that have been reported for delivery of drugs to the colon. It involves use of formulation components that interact with one or more aspects of gastrointestinal (GI) physiology, such as the difference in the pH along the GI tract, the presence of colonic microflora, and enzymes, to achieve colon targeting. Various novel delivery systems overcome the limitations of conventional systems. However, conventional systems are still using because of their ease and economic value. Here, we will discuss several delivery systems that have been using for targeting drugs to the colon.

Multi-particulate Systems: Multi-particulate systems have a small particle size for easy delivery typically consisting of thousands of spherical particles with a diameter of 0.05-2.00 mm. They reach the colon quickly since pass the gastrointestinal tract more easily. It includes microspheres, pellets, nanoparticles, *etc*. Micro-spheres are prepared using biodegradable components like chitosan, polysaccharides, pectin and guar gum with pH-sensitive polymers. Pellets are small particles or granules produced by agglomeration of fine powders with a binder solution.

Nanoparticles show improved bioavailability due to their increased surface area and thus increased contact with biological surfaces. These particles are taken up by macrophages at the colon and allow remaining at the targeted site for a longer period [6]. The advantages of this system include avoidance of dose dumping, increased bio-availability, faster gastric emptying, improved reproducibility of transit time, a high degree of GIT dispersion, less likely to cause local irritation, improved stability, patient comfort, and compliance. This system is not devoid of certain drawbacks such as low drug loading, high amount of excipients, tedious formulation steps, higher cost of production, *etc*. [33]

Osmotic Drug Delivery: This device delivers drug through an orifice by the generation of osmotic pressure followed by a constant influx of water. It delivers drug through zero order kinetic. It is composed of osmotically active drug core surrounded by the semipermeable membrane. This is further coated with Eudragit S100 an enteric polymer. This coating protects the drug from degradation at the stomach; however, it dissolves in the small intestine and the intestinal fluid enters into tablet core generates osmotic pressure and then finally reaches to the colon, where osmotic pressure core breaks and release drug, *e.g*. OROS-CT [34]. **Fig. 2** exhibits the delivery of drug at colon site using osmotic pressure.

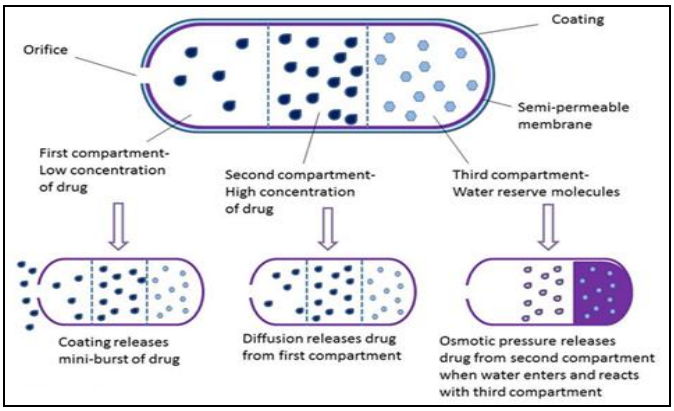

FIG. 2: RELEASE OF DRUG AT COLON THROUGH OSMOTIC PRESSURE

Pulsincap System: It contains a capsule shaped non-disintegrating body and water-soluble cap. The body part fills with drug molecule and sealing with hydrophilic hydrogel, which is covered with a water-soluble cap.

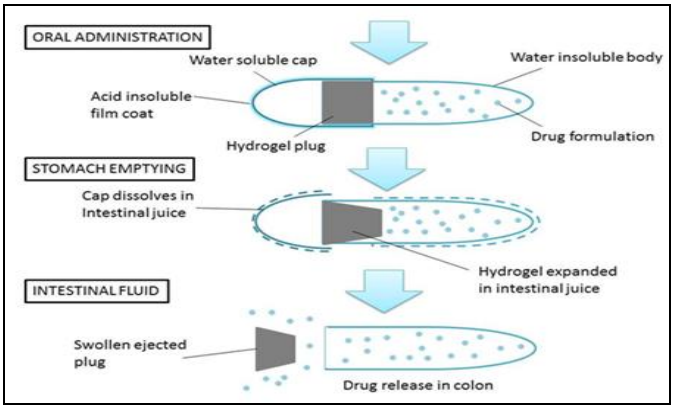

FIG. 3: MECHANISM OF THE PULSINCAP COLON-TARGETED DRUG DELIVERY SYSTEM [6]

The cap drilled to make a hole and sealed with an enteric polymer that gets dissolved into the small intestine and intestinal fluid enter into the capsule due to hydrophilic nature of hydrogel. It absorbs water, starts swelling and then ejects from the body. Drug release duration depends upon the length of hydrogel used [35]. **Fig. 3** shows pulsincap drug releasing mechanism at colon site.

Port System: It is hard gelatin capsule coated with a cellulosic semi-permeable membrane containing drug formulation along with an osmotically active agent and plugged. In an aqueous medium, the semipermeable membrane diffuses water, results in the generation of hydrostatic pressure that ejects plug in the large intestine. The drug release duration or lag time depends upon plug, which gets pushed away by swelling or erosion. The drug release pattern from the port system has shown in **Fig. 4**, where A is Dissolution of capsule's cap leads to immediate release, B is Energy source is activated by controlled permeation of GI fluid, C is Time-release plug is expelled, D is Pulse or sustained release of second dose [36].

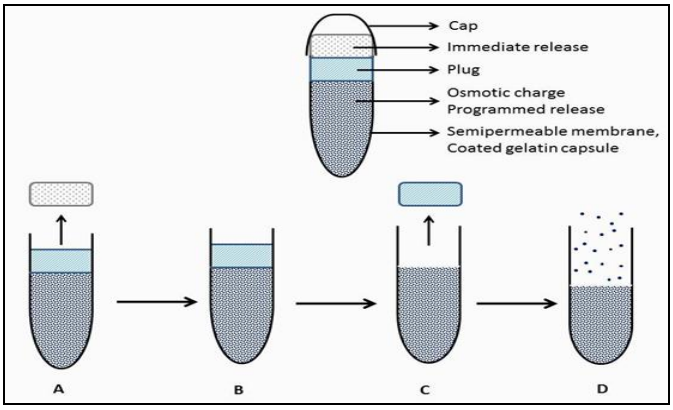

FIG. 4 DRUG RELEASE MECHANISM OF PORT SYSTEM

Gas Empowered Drug Delivery System (GEDD): In this drug delivery system, the proteins and peptides targeted to colon using mucoadhesive polymer polyethylene oxide and trimethylated chitosan (TMC) as penetration enhancer using CO_2 [37]. The drug adhered to the mucous layer due to the mucoadhesive polymer and opens at the tight junctions of the colon because of TMC to promote drug absorption through the paracellular pathway. In GEDD, CO_2 produces a driving force to push the drug to the absorbing membrane and protects the drug from enzymatic and proteolytic degradation [38].

Chronotropic System: This system of drug delivery is beneficial in the treatment of disease affected by circadian rhythms, rheumatoid arthritis, asthma, and hypertension. This system contains hydroxypropylmethylcellulose (HPMC) coated drug-containing core that is responsible for the lag phase in the onset of release. The differences in gastric emptying time can be overcome by using an enteric film. It also helps in releasing drug at the colon site. The thickness and viscosity of HPMC can control the lag time of drug release [35]. A system defining time-dependent release of a capsule is shown in **Fig. 5**.

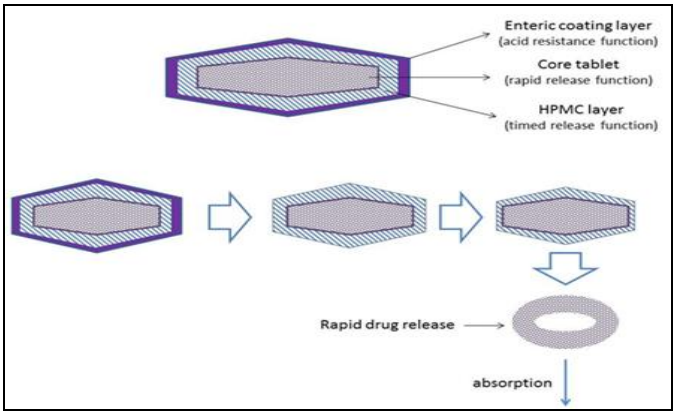

FIG. 5: RELEASE PATTERN OF DRUG FROM CHRONOTROPIC SYSTEM

COLAL-Pred System: This delivery system is specifically designed for the treatment of ulcerative colitis. It is the combination of COLAL (colonic drug delivery system) and prednisolone (an approved generic steroid). This system provides an effective anti-inflammatory treatment for ulcerative colitis whose no competitor products available in the market. COLAL-Pred has a coating, breaks only in the large intestine due to colonic bacteria. It is used in topical delivery of prednisolone in ulcerative colitis [39].

An Approach for Targeting Drug to Colon: Along with delivery system an approach is also used to deliver drug at colon site, *i.e.* probiotic approach. In this approach, the beneficial micro-organism is introduced into the body for the treatment of a particular disease. It promotes a healthy digestive tract and a healthy immune system.

Probiotic Approach: This novel of the approach of colon targeting consists of three components namely probiotic strain (*Bifidobacterium* and

Lactobacillus), microbially digestible carrier and triggering temperature. These strains get active at body temperature and start digesting the carrier and releasing drug at large intestine.

Table 1 shows different diseases for which a probiotic approach can be useful.

TABLE 1: PROBIOTIC MICROBIAL STRAINS USED FOR THE TREATMENT OF GIT DISEASES [40]

Diseases	Strain
Intestinal dysbiosis	*Lactobacillus* strain
Irritable bowel syndrome	*Bifidobacterium infantis*
	Escherichia coli
Traveler's diarrhea	*Lactobacillus* GG
	Lactobacillus plantarum
Crohn's disease	*Escherichia coli*
Colon cancer	*Enterococcus faecium*
Ulcerative colitis	*Lactobacillus acidophilus*
	Escherichia coli
Peptic ulcer disease	*Lactobacillus acidophilus*

Evaluation of Colon Targeted Drugs: Few *in-vitro* and *in-vivo* models are available for evaluation of colon targeted drug release. However, these techniques are not standardized due to its dependence on variable conditions of GIT such as pH, volume, stirring, bacteria, enzyme and other components of food. In vitro models used for drug delivery are:

***In-vitro* Dissolution Test:** Dissolution of colon targeted drugs can be determined as the dissolution method described in United States Pharmacopoeia (USP). It is used to characterize the dissolution pattern of drugs at different pH likely to encounter at various locations in the gastrointestinal tract (GIT). The dissolution of the colon targeted drug is generally evaluated at pH 6.8 to pH 7.4. [5]

***In-vitro* Enzymatic Test:** This test is used to evaluate the effect of drugs in the presence of the enzyme at GIT. The *in-vitro* test is performed to determine the release of drug at a different time interval, which is done outside the body in a buffer medium containing enzymes ezypectinase or dextranase. The degradation of polymer carrier defines the release of drug in particular time [5].

***In-vivo* Evaluation:** *In-vivo* evaluation of drugs targeting colon is determined on animals. Guinea pigs are the animals of choice for experimental IBD model. The following *in-vivo* method is adopted to evaluate colon targeting formulations:

Drug Delivery Index (DDI): It is pharmacokinetic parameter defines the release of oral colon targeted drug. DDI is the relative ration of relative colonic tissue exposure to the drug to the relative amount of drug in the blood, *i.e*. relative systemic exposal to the drug. High drug DDI value indicates better colon drug delivery. It can be determined by the formula given below:

$$DDI = \frac{\text{Relative colonic tissue exposure to the drug}}{\text{The relative amount of drug in the blood}}$$

Gamma Scintigraphy: In this technique, the gamma radiations are used to determine the transit time of dosage form through the GIT and to identify the sites of drug absorption. It is a non-invasive technique of evaluation, where energy is transformed into light scintillation and amplified to give digitalized results. Gamma scintigraphy is also provided the facility of visualization of drug delivery process [41].

DISCUSSION AND CONCLUSION: The colon targeted drug delivery system has been gaining interest in the comparison of other formulations for the treatment of inflammatory bowel diseases in recent years. The drugs like proteins and peptides targeting colon are being explored for its systemic actions in addition to local effects [42]. The oral route is one of the most preferred routes for drug delivery due to its feasibility, patient compliance, and economic value. However, this route has several critical barriers makes the drug delivery less efficient like GI epithelia, high mucus turnover, variable pH range, absorption barrier, first pass metabolism, longer time to achieve a therapeutic level, and rapid luminal enzymatic degradation.

Thus, colon targeted drug delivery system may avoid all these drawbacks of orally giving drugs and delivery it to the specific site. The micro-particulate systems are more efficient for the treatment of IBD than sustained release devices such as tablet and capsules due to their micron size avoids rapid GI transit in the condition of diarrhea [28]. However, osmotic drug delivery has the advantage of zero-order release over an extended period irrespective of the environmental factors [34]. The delivery systems that consist of natural materials and degraded by colonic bacterial enzymes are more likely to be used for colon targeting [26]. However, due to sophistication

concern of colon-specific drug delivery systems, challenges prevail for scientists and researchers to develop validated method can be used routinely in an industry setting for the evaluation of large intestine drug delivery system. The novel materials and technologies are constantly developing and the goal of manufacturing for ideal drug delivery is realizing rapidly. Further, the new molecular targets are needed to identify to increase the drug's effectiveness and reduce side effects.

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