International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 512-518 www.ijprajournal.com ISSN: 2249-7781

A Review On Colon Targeted Drug Delivery System.

Dr.Shendge Sir, Pooja Shinde,Vaishnavi Pathare.

Date Of Submission: 01-04-2021 Date Of Acceptance: 14-04-2021

ABSTRACT: Recently colonic drug delivery has gained more scope for delivery of drug for the treatment of local diseases associated with colon and systemic delivery of therapeutic peptides and proteins. Treatment could be more effective if it is possible for drug to be directly delivered to colon. This article focuses on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery. This article also discusses precedence & limitations of the different approaches & evaluation for site specific drug delivery to colon.

Key Words: Colon specific drug delivery system, Advantages, Approaches.

I. INTRODUCTION:

The aim of the targeted drug delivery system is to provide a desired drug concentration in the body by delivering a therapeutic amount of drug to a targeted site. It is suitable and required for the drugs having instability, low solubility, short half-life, high volume of distribution, poor absorption, low specificity, and therapeutic index. Targeting may provide maximum therapeutic activity. Meanwhile, it can also minimize adverse effects, the toxicity of potent drugs by reducing dose. The oral route is the most convenient and important method for administration of drugs for systemic effect.

In addition, less pain, reduced risk of cross-infection, needlestick injuries, patient acceptance and ease of administration made it more preferred. Nearly 50% of the drug delivery systems available in the market are oral drug delivery systems. Apart of these advantages, the oral route is not suitable to the administration of the drug for lower gastrointestinal (GI) diseases; this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract.

To overcome this difficulty, colon-specific drug delivery systems have been broadly analyze during the last two decades. By definition, a colonic delivery refers to delivery of drugs accurately into the lower GI tract (by avoiding the drug release in upper GIT), which occurs primarily in the large intestine. Rectal administration is another route used for colon targeting, but it shows less compliance (uncomfortable) and becomes difficult to reach the colon. Conventional dosage forms that are used in the prevention of colon diseases (ulcerative colitis, crohn's diseases, amoebiasis) are failing as an improper amount of drug reaches site of action. Conventional dosage form affords the drug to be absorbed from the upper part of GIT, i.e., stomach. This action of conventional dosage form has a serious drawback for colonic localized delivery. Thus, for efficient and safe therapy, the drug is needed to be preserve from upper hostile environment [3, 5, 6].

Site-specific delivery into the colon is not only needed for local treatment of a variety of colon diseases, like ulcerative colitis, Chron's diseases, amoebiasis, colon cancer, but also systemic delivery of proteins and peptides this is because of less diversity and intensity of digestive enzymes and less proteolytic activity of colon mucosa than that observed in the small intestine. Beside the colon diseases, this system is also helpful in the treatment of asthma, angina and rheumatoid arthritis for taking advantage of chronotherapeutic drug delivery and for delivery of steroids [7].

Some factors to be considered for successful colonic drug delivery, including the properties of the drug, the type of delivery system and its interaction with healthy or disease gut. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make it most promising site for drug delivery. The absorption enhancers are sub characterized into categories of chelating agents, non-steroidal anti-inflammatory agents, surfactants (mostly as mixed micelles), phenothiazenes and a general class of molecules which include fatty acids, acylcarnitiveacyl amino acids and dicarboxylicacid.

Advantages:

- Ideal site for the delivery of active agents to cure the colon diseases.

International Journal of Pharmaceutical Research and Applications
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- Smaller drug quantities should be required for local treatment.
- Less side effects and drug interactions occurs.
- Dosage frequency is less so, cost effective.
- The long retention time of colon, improved bioavailability of poorly absorbed drug molecules (up to 5 days).
- Reduce gastric irritation caused by many drugs by preventing their absorption in upper GIT (g., NSAIDS).
- Bypass initial first pass metabolism.
- Extended daytime or night time activity.
- Limitation and challenges [4, 9]
- Hard accessibility of the colon because of its location at the distal part of the alimentary canal.
- The drug may bind non-specifically to intestinal contents cause reduce drugs bioavailability.
- Metabolic degradation of the drug by resident microflora could also affect colonic performance.
- Restrict drug transport across the mucosa and into the systemic circulation due to lower surface area and relative tight junctions in the colon.
- Lack of an appropriate dissolution testing method to evaluate the dosage form in-vitro.

The GIT (alimentary canal) is a muscular, digestive tube that extends from mouth to anus, having functions to digest dietary food, to absorb nutrients, electrolytes, and fluids, and to prevent the absorption of potentially harmful substances as shown in **Fig. 1**.

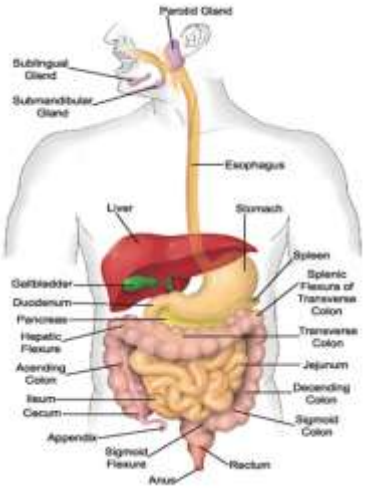

FIG 1: COLON ANATOMY

Why Colon Targeted Drug Delivery Needed?

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

FACTORS TO BE CONSIDERED IN THE DESIGN OF COLON-

SPECIFIC DRUG DELIVERY SYSTEM Anatomy and Physiology of Colon The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long[6] (Table 1). The colon is upper five feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter [7]. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal (Figure 1) [8]. The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

pH in the Colon :

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery[9]. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Table 1.). The pH

International Journal of Pharmaceutical Research and Applications
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difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

Transit of material in the colon.

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors such as diet, dietary fiber content, mobility, stress, disease and drugs. In healthy young and adult males, dosage forms such as capsules and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur. Diseases affecting colonic transit have important implications for drug delivery: diarrheoa increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant.

Colonic Microflora And Their Enzymes:

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut micro flora residing in high number in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus Bacteroides[10, 11]. The upper region of the GIT has very small number of bacteria and predominantly consists of Grampositive facultative bacteria. The concentration of bacteria in the human colon is 1011 - 1012 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptostreptococcus, peptococcus, Ruminococcusclostridiums[12] .

CRITERIA FOR SELECTION OF DRUG FOR COLONIC DRUG DELIVERY:

Drug candidate Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used in treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery [13] . Drug carrier The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule[14]. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems[15] .

Approaches For Colonic Drug Delivery :

A. Covalent Linkage of Drug with Carrier Prodrug approaches[18] :

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

B. Azo bond conjugate:

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. The use of these azo compounds for colontargeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrug. In the latter approach the drug is attached via an azo bond to a carrier[19] . This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora.Sulphasalazine, used for the treatment of IBD has an azo bond between 5-ASA and sulphapyridine (SP). In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier SP[19]

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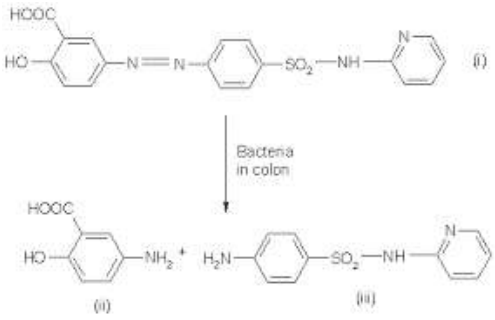
Figure 3. Hydrolysis of Sulphasalazine (i) into 5-aminosalicylic acid (ii) &sulfapyridine (iii)



C. Approaches to deliver intact molecule to colon pH dependent approach[25] :

This approach utilizes the existence of pH gradient in the git that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.

Coating of the drug core with pH sensitive polymers (Table 4): The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles.The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction.The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatincapsules.The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter- and intraindividual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0(attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system. Problem of premature drug release can be overcome by the use of Eudragit FS.

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS:

The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastro luminal pH and enzyme population.

pH and time dependent systems[28] : One of the simplest approaches for designing pH dependent multiparticulate colon specific delivery system is to formulate enteric coated granules. Most commonly used pH-dependent coating polymers for oral delivery are methacrylic acid copolymers, Eudragit L100 and Eudragit S100, which dissolve at pH 6.0 and 7.0 respectively. The combination of these two polymers in various ratios makes it possible to manipulate drug release within 6.0-7.0 pH range. Incorporation of organic acid in both the enteric coated granules as well as the tablet matrix retarded the in vitro release and in vivo absorption of the drug because of the prolongation in disintegration time of the core system due to the presence of the acid. In another approach, 5-fluorouracil granular matrices were designed for release of the drug in the descending colon in a controlled fashion for the treatment of colorectal carcinoma. The Glyceryl plmitostearate matrices (retardant material) coated by Eudragit S100 and were then covered by a layer of chitosan HCl and loaded inside HPMC capsules coated with 30 D. Upon hydration, the capsule shell dissolves and the chitosan layer forms a gel (internal pH of 4.5), which generates an acidic environment around the Eudragit film so that it does not dissolve in the ascending colon. In the ascending colon, the chitosan HCl gel is degraded by the colonic micro flora, thereby exposing the Eudragit film to the colonic environment. But since the ascending colon is weakly acidic where pH is less than 7.0, the film coat still remains intact. However, on arrival in the descending colon where pH is greater than 7, the Eudragit film coat dissolves and the drug is released in a controlled fashion from the matrices.It is accepted that a colonic delivery system which is based only on GI transit time or pH of the GI tract would not be reliable because of the inherent

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variability of pH and emptying times from the GI tract. Figure 10. Structure of multiple unit colon specific tablet developed Micro particulate systems: In the treatment of IBD, sustained release devices like pellets, capsules or tablets have less efficiency due to diarrhea, a symptom of IBD that enhances their elimination and reduces the total time available for drug release. It has been shown that drug carrier systems with a size larger than 200 µm would be subjected to speedy bowel evacuation due to diarrhea, resulting in a decreased GI transit time and decreased efficiency. Therefore, a multiparticulate system in the micron size range could be a useful option in the design of a suitable dosage form for IBD.

Typical formulation: Eudragit P-4135 F, a new pH-sensitive polymer was used to prepare micro particles of tacrolimus, an immunosuppressant drug, for colonic delivery. The use of Eudragit P-4135 F in the microencapsulation of 5-fluorouracil for the treatment of colorectal cancer has been reported. Eudragit P-4135 F belongs to the pH-sensitive Eudragit group of polyacrylates and possesses a dissolution threshold pH slightly above 7.2. This is very useful as ulcerative colitis mainly affects the distal parts of the colon and an early drug loss towards the non-inflamed tissue would be undesirable. Eudragit P-4135 F might prove a useful alternative for systems intended for targeting to the distal colon.It is reported that biodegradable microspheres could be efficiently taken up by macrophages. Therefore, the direct uptake of antiinflammatory agents loaded microspheres by macrophages would have a superior immunosuppressive effect and be more useful for treatment of patients with IBD.

Micro particulates in the delivery of peptides: The colon has always attracted attention as a potential site for the systemic absorption of peptide drugs on account of its lower proteolytic enzyme activity compared to the upper GI tract.

Formulation 1: A system consisting of insulin encapsulated by polyacrylates wherein the coating was meant to dissolve only in the colon

Formulation 2: A terpolymer of styrene and hydroxyethyl methacrylate cross-linked with a difunctional azo- compound has also been reported for the delivery of insulin. The system depends on cleavage of azo bond by colonic microflora resulting in degradation of polymer and release of insulin. Nanoparticulate systems: Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability. Nanoparticles have also been investigated for the delivery of protein and peptide drugs.For colonic pathologies, it was shown that nanoparticles tend to accumulate at the site of inflammation in IBD. This is because in case of colitis, a strong cellular immune response occurs in the inflamed regions due to increased presence of neutrophils, Natural Killer cells, macrophages and so on. It has been reported that microspheres and nanoparticles could be efficiently taken up by these macrophages. This results in accumulation of the particulate carrier system resulting in prolonged residence time in the desired area. However, an important area of concern is to prevent loss of Nanoparticle in the early transit through GI tract in order to optimize therapeutic efficacy. Moreover, particle uptake by Payer's patches and/or enzymatic degradation may cause the release of entrapped drug leading to systemic drug absorption and side effects. In order to overcome this problem, drug loaded nanoparticles were entrapped into pH sensitive microspheres, which serve to deliver the incorporated nanoparticle to their site of action, thereby preventing an early drug leakage. The use of nanoparticles for bioadhesion purposes has also been investigated. Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion can be induced by binding nanoparticles with different molecules. For covalent attachment, the nanoparticle surface has to show free functional groups, such as carboxylic or amine residues.

II. EVALUATION :

In Vitro Evaluation:

No standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should posses the in vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and other components of food. Generally these conditions are influenced by the diet and physical stress and these factors make it difficult to design a slandered in vitro model.

In vitro model used for CDDS are:

In vitro dissolution test: Dissolution of controlled-release formulations used for colonspecific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic in vivo conditions such as those relating to pH, bacterial environment and

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Volume 6, Issue 2 Mar-Apr 2021, pp: 512-518 www.ijprajournal.com ISSN: 2249-7781

mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon- specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. Entericcoated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. In vitro test for intactness of coatings and carriers in simulated conditions of stomach and intestineDrug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time)

In vitro enzymatic test: For this there are 2 tests: 1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (Streptococcus faccium or B.ovatus) amount of drug released at different time intervals determined. 2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier. In Vivo Evaluation A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Eg. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host. Clinical Evaluation Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

High frequency capsule: Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator.Release of drug & radiotracer triggered by an impulse, the release is monitored in different parts of GIT by radiological localization.It checks the absorption properties of drug in colon.

Gammascintigraphy: By means of gammascintigraphic imaging, information can be obtained regarding time of arrival of a colonspecific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gammascintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharma coscintigraphy).

III. CONCLUSION:

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colonspecific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

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