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Formulation And Evaluation Of Colon Targeted Drug Delivery System.

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ABSTRACT

Colon-specific drug delivery systems (CDDS) are ideal for the treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, and colon cancer, among other conditions. In addition, the colon may be a location for systemic absorption of a variety of medications used to treat non-colonic illnesses. If transported to the colon intact, drugs such as proteins and peptides that are known to disintegrate at high stomach pH can be absorbed systemically by the colonic mucosa. It is critical that the developed delivery system properly targets the medications into the colon in order to obtain good treatment effects.In the development of colon-targeted medication delivery systems; several formulation techniques have been investigated. To accomplish colon targeting, these methods entail the use of formulation components that interact with one or more features of GI physiology, such as the differential in pH throughout the GI tract, the presence of colonic bacteria, and enzymes.

Keywords: Colon-specific drug delivery systems (CDDS), Crohn's disease (CD), ulcerative colitis (UC), and irritable bowel syndrome (IBS), Polymer Coated Drug Delivery, γ–Scintigraphy , Drug Delivery Index (DDI)

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INTRODUCTION

Due to its potential to enhance treatment of local disorders affecting the colon while avoiding systemic adverse effects, colon-targeted medication delivery has been the subject of several investigations in recent years. Crohn's disease (CD), ulcerative colitis (UC), and irritable bowel syndrome (IBS) are some of the diseases that affect the colon. Sulfasalazine, dexamethasone, hydrocortisone, metronidazole, prednisolone, and other medications are commonly used to treat these conditions [1].The colon is believed to be a suitable site for absorption of peptides and proteinous drugs for following reasons: (i) Less diversity and strength of digestive enzymes. (ii) The proteolytic activity of colon mucosa is comparatively very less than that of small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradationn in the duodenum and jejunum. The release of drug molecules in the ileum or colon leads to greater systemic bioavailability. (iii) Thecolon has a long residence time and is extremely responsive towards absorption enhancers [2].

General consideration before formulation of drug for Colon Targeted Drug Delivery System: before formulating colon targeted drugs one has to consider following points:

Anatomical/Physiological Consideration: The colon (ascending, transverse, and descending) is formed by the human large intestine, with a little distal portion constituting the rectum. The colon is 2–3 inches in diameter, with a mucus-lined lumen. The colon's physiology is distinct from that of other parts of the gastrointestinal tract (GIT). Furthermore, the ascending, transverse, descending, and sigmoidal colons have different physiology and physical features of the colonic contents. Furthermore, the flow of food and dosage forms across the colon varies, which might pose a problem in the development of colonic medication delivery systems [3].

Intestinal-Colonic Transit Time: The intestinal-colonic transit time plays an important role in the performance of CDDS and the colonic bioavailability of drugs. The transit times are also influenced by colonic disease states. Patients with Ulcerative colitis are known to have shorter colonic times (~24 h) compared to healthy subjects (~52 h) .Similarly, patients with Inflammatory Bowel disesease (IBD), the orocecal transit time was delayed. The transit of dosage forms generally depends on the time of administration, presence/absence of food, and the type of dosage form [4].

Colonic Fluid Volume: The typical human food intake is about 1.5 kg per day, with the majority of that being undigested proteins, carbs, and lipids. The bacteria enzymes in the colon may use these dietary components as a substrate. The colon has a high water-absorbing capacity, absorbing up to 90% of the water that enters it. The amount of colonic fluid is estimated to be between 1 and 44 ml, with an average value of around 13 ml [5, 6].

Viscosity of Colonic Luminal Contents: The viscosity of colonic luminal contents is greater than upper GIT contents due to a larger water-absorbing capacity, posing a difficulty for CDDS disintegration. Furthermore, when the contents go from the ascending to the descending colon, the viscosity of the contents rises, resulting in decreased medication solubility and mucosal absorption. The drug's penetration into the disease-causing bacteria in the colon is also influenced by its viscosity. The viscosity of colonic contents has been proven to affect the movement of bacteria in the colon [7, 8].

Colonic pH: The pH varies significantly between different regions of the GIT. For example, the pH of gastrointestinal contents can be as low as 1 to 2 in the stomach and rise to 7.5 in the distal small intestine [9]. The pH then declines from the end of the small intestine to the colon and gradually increases once again in the colon [10]. The pH of the colon may be influenced by a carbohydrate rich diet. This is due to the fermentation of polysaccharides by colonic bacteria and subsequent formation of short chain fatty acids. Similarly, polysaccharide-based drugs may also alter colonic pH. Laxative drugs like lactulose are known to be fermented by colonic bacteria to produce lactic acid and reduce colonic pH. Gastrointestinal disease states such as UC have also been found to influence the colonic pH. The pH of the colon affects the pharmacokinetic and pharmacodynamic behavior of a CDDS by influencing the solubility of drugs in the colonic fluid. Moreover, if one or more components of the dosage form are pH-sensitive, for example, a pH-sensitive coating membrane, the effect of colonic pH is even more pronounced on the drug release[11-13].

Colonic Enzymes and Metabolism: Over 400 distinct species of aerobic and anaerobic microbes, such as Escherichia coli and Clostridium species have been found in the colon. Several hydrolytic and reductive metabolising enzymes are found in these bacteria. The metabolism of xenobiotics (e.g., pharmaceuticals) and other biomolecules (e.g., bile acid), as well as the deactivation of toxic metabolites and carbohydrate and protein fermentation, are all catalysed by colonic enzymes. Polysaccharides including chitosan, guar gum, pectin, and others are often included in colon-targeted dosage forms as rate-controlling components.

Formulation Approaches For Formulation Of Drug For Colon Targeted Drug Delivery

pH Sensitive Polymer Coated Drug Delivery to the Colon: During fasting, the pH in the stomach is between 1 and 2, but it rises after eating. The proximal small intestine has a pH of around 6.5, whereas the distal small intestine has a pH of about 7.5. The pH drops dramatically from the ileum to the colon. In the cecum, the pH is at 6.4. In healthy participants, however, pH levels as low as 5.7 have been reported in the ascending colon. The transverse colon has a pH of 6.6, whereas the descending colon has a pH of 7.0. The use of pH-dependent polymers is based on these pH variations.The polymers used in colon specific drug delivery that are pH sensitive are insoluble at low pH levels but become progressively soluble as pH rises. Although a pH-dependent polymer can protect a formulation in the stomach and proximal small intestine, it may disintegrate in the lower small intestine, resulting in poor site-specificity. The drop in pH from the small intestine to the colon can cause issues, such as long lag durations at the ileo-cecal junction or fast transit through the ascending colon, both of which can lead to poor site-specificity in enteric-coated single-unit formulations [14-16].

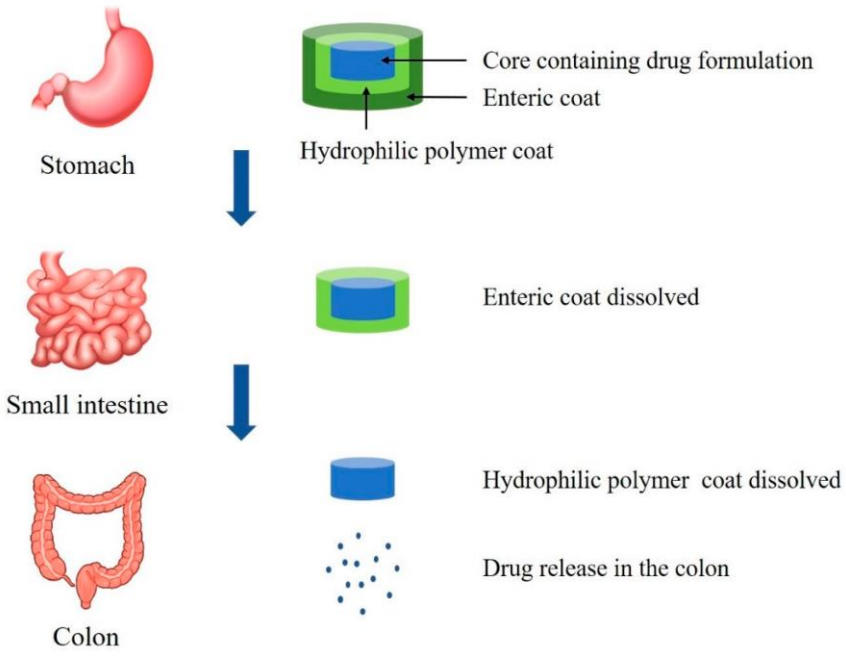

Figure 1: pH Sensitive Polymer Coated Drug Delivery to the Colon [18].

Delayed (Time Controlled Release System) Release Drug Delivery to Colon: Sustained or delayed release dose forms are examples of time controlled release systems (TCRS). However, colon arrival time of dose forms cannot be correctly anticipated in these systems due to possibly considerable variability in stomach emptying time of dosage forms in people, resulting in low colonical availability. By extending the lag period to around 5 to 6 hours, the dosage forms might be used as colon targeting dosage forms.

Microbially Triggered Drug Delivery to Colon: The microflora of the colon ranges from 1011 to 1012 CFU/mL [17], with anaerobic bacteria such as bacteroides bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria, and ruminococcus being the most common. This large microflora meets its energy requirements by digesting a variety of substrates that have been left undigested in the small intestine, such as di- and tri-saccharides, polysaccharides, and other carbohydrates. .The microflora generates a wide range of enzymes for this fermentation, including glucoronidase, xylosidase,

arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.

Prodrug approach: The term "prodrug" refers to a drug that is inactive until it is converted or metabolised by the body. [17] A covalent bond is created between the medication and the carrier, allowing the drug to reach the colon without being absorbed from the upper section of the GIT. In comparison to the stomach and small intestine, medication release in the colon is induced by increased activity of particular enzymes**.**

Prodrug types used in CDDS	***Examples***
Azo bond conjugate	Sulfasalazine , sulphapyridine , flurbiprofen etc.
Glucuronide conjugate	Glucuronidase
Cyclodextrin conjugates	Ibuprofen prodrugs of α- , β-and γ-Cyclodextrins
Dextran conjugates	Dextran ester prodrugs of metronidazole , Dextran ester prodrugs of dexamethasone and methyl prednisolone.
Amino-acid conjugates	Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid

Table 1: Types of Produgs used in CDDS

.5. Pressure controlled drug delivery system (PCDCS): The colon is subjected to higher pressures than the small intestine as a result of peristalsis. Takaya et al. (1995) created pressure-controlled colon administration capsules made from an insoluble in water ethyl cellulose. In such systems, drug release happens as a result of the breakdown of a water-insoluble polymer in the colon lumen as a result of force per unit area. The most essential aspect in the formulation's breakdown is the thickness of the ethyl cellulose membrane. The mechanism seems to be influenced by capsule size and compactness as well. The viscosity of luminal material in the colon is greater than in the stomach due to water reabsorption from the colon [19, 20].

Hydrogels: The inclusion of pH-sensitive monomers as well as cross-linking agents in the hydrogel structure gives the expression colon specificity. As the pH of these hydrogels rises in the GIT, their swelling capacity rises as well, peaking at pH 7.4. The drug contained in the hydrogel is released as the hydrogen network degrades due to the breakage of cross-ties. They are made by cross-linking Nsubstituted (meth) acryl amides, N-tert-butylacrylamide, and acrylic acid with 4,4'-di (methacryloylamino) azobenzene, 4,4'-di (Nmethacryloyl-6-aminohexanoylamino) or 3,3',5,5'-tetrabromo-4,4, 4',4'- (methacryloylamino).

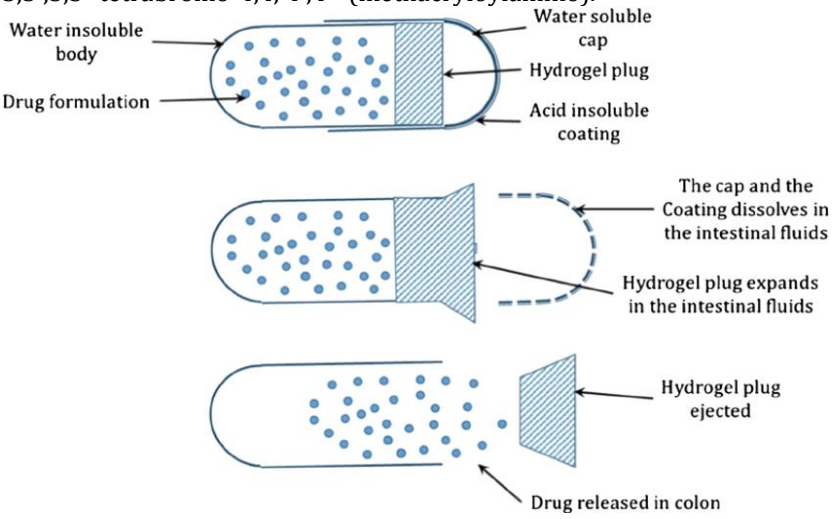

Figure 2: Schematic representation of the mechanism of the hydrogel colon-targeted drug delivery system [1].

Microspheres: For effective treatment of colorectal cancer, cross-linked guar gum microspheres carrying methotrexate were produced and described for their local release in the colon. Glutaraldehyde was

utilised as a cross-linking agent in this procedure, and guar gum microspheres were created via an emulsification process. According to in vitro and in vivo tests, methotrexate-laden cross-linked guar gum microspheres transported the majority of the loaded pharmaceuticals to the colon (79%) while regular drug suspensions only delivered 23% of their whole dosage to the target region.Colon-specific 5-fluorouracil microspheres have been produced and are used to treat colon cancer. Using a modified emulsification process in liquid paraffin and calcium chloride as a cross-linking agent, core microspheres of alginate were created. To inhibit drug release in the stomach and small intestine areas, the core microspheres were coated with Eudragit S-100 using a solvent evaporation process. The results showed that this approach has a lot of potential for delivering 5-fluorouracil to the colon [23].

Nanoparticles: Nanoparticles are predicted to be used as medication carriers in the administration of oral peptides. Polymeric nanoparticles offer the benefit of preserving protein and peptide medications from chemical and enzymatic breakdown in the GI tract, hence enhancing their stability and absorption across the intestinal epithelium, as well as preventing drug release. To generate polymeric nanoparticles, a variety of processes such as polymerization, nanoprecipitation, and inverse microemulsion can be used; however, most of these procedures involve the use of organic solvents, heat, and rapid agitation, which-may be hazardous to peptide and protein therapeutics [24].

Liposomes: Liposomes are hydrated phospholipid-based bilayered closed vesicular structures. Because of their alternating hydrophilic and hydrophobic nature, liposomes may entrap molecules of various solubilities. However, the physicochemical makeup of the vesicle is linked to significant alteration or tailoring of the fundamental liposomal structure of hydrated phospholipid bilayer. Liposomes' adaptability is extremely valuable in a variety of applications; including radiography, cosmetology, and vaccineology.Liposomes ranging in size from 25 millimetres to several micrometres are often propagated in aqueous media. There are several nomenclatures for designating liposome subclasses based on vesicle manufacturing process or structural features. Liposomes are classified as large unilamellar vesicles (LUV), small unilamellar vesicles (SUV), and big multilamellar vesicles or multivesicular vesicles based on their size and number of lamellae. As liposomal nanocarriers for drug and antigen administration, SUVs with low particle sizes in the nm range are of interest [25].

Evaluation Of CDDS: Different methods of in vitro and in vivo release studies, which reveal the success rate of different designs of colon drug delivery systems, are used to evaluate drug release in the colonic area from different CDDS. Different assessment approaches are suggested depending on the manner of preparation. An effective colon-specific drug delivery system is one that maintains its integrity in the stomach and small intestine's physiological milieu while releasing the medication in the colon.

In-vivo dissolution test: Controlled-release formulations used for colon specific drug delivery are typically complicated to dissolve, and the dissolving methods outlined in the USP cannot adequately match in vivo circumstances like as pH, bacterial environment, and mixing forces. . CDDS dissolution tests can be performed using the traditional basket method. Dissolution studies of a colon-specific formulation in several fluids replicating pH values and times anticipated to occur at various places in the colon. There has been research on the gastrointestinal tract. The media that was picked pH 1.2, for example, was used to replicate gastric fluid, whereas pH 6.8 was used to represent stomach acid. pH 7.2 was used to replicate the jejunal portion of the small intestine section of the ileum CDDS capsules with an enteric coating have been developed In three buffers, a gradient dissolution research was conducted.The capsules were tested for two hours at pH 1.2 and subsequently for one hour at pH 4.0 pH 6.8 was reached, followed by pH 7.4 .

In-vitro enzymatic test: Incubate the carrier drug system in a fermenter with bacteria-friendly media (strectococcus faccium and B. Ovatus). The amount of medicine released at various intervals is calculated. Drug release studies are carried out in buffer media containing enzymes (ezypectinase, dextranase), or in the cecal contents of guinea pigs or rabbits. The quantity of medicine released in a given period is calculated, which is related to the rate of polymer carrier breakdown.

In-vivo tests [26, 27] : Dogs, guinea pigs, rats, and pigs are utilised to test medication transport to the colon since their anatomic and physiological circumstances, as well as the microorganisms of the human GIT, are similar. A relative model for colonic disorders should be considered while picking a model for evaluating a CDDS. Guinea pigs are a frequent experimental model for IBD. In the GIT of rats and rabbits, the distribution of azoreductase and glucouronidase activity is similar to that of humans. A unique paradigm has been presented for the quick evaluation of CDDS.The human foetal intestine is transplanted

into a subcutaneous tullel on the back of thymic nude mice in this model, which bascularizes, develops, and is capable of establishing a mucosal immune system from the host within four weeks.

Drug Delivery Index (DDI) and Clinical Evaluation of Colon Specific Drug Delivery Systems: DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. 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.

γ–Scintigraphy: With growing complexity in the design of novel drug delivery systems (including colon-specific delivery systems) and associated fabrication process, it is critical to understand the in vivo performance of those delivery systems and demonstrate that the system functions in vivo in accordance with the proposed rationale. In most cases, conventional pharmacokinetic evaluation may not generate sufficient information to elucidate the intended rationale of system design. γ-Scintigraphy is an imaging modality, which enables the in vivo performance of drug delivery systems to be visualized under normal physiological conditions in a non-invasive manner. Since first employed to investigate the functionality of tablets and capsules in vivo more than two decades ago . γ-scintigraphy has become an established technique and extensively used to monitor the performance of novel drug delivery systems within human GI tract. The underlying principles of γ-scintigraphy and its applications in pharmaceutical research and development are available in the literature. Through γ-scintigraphy imaging, the following information regarding the performance of a colon-specific delivery system within human GI tract can be obtained: the location as a function of time, the time and location of both initial and complete system disintegration, the extent of dispersion, the colon arrival time, stomach residence and small intestine transit times.

CONCLUSION

In recent years, the colon has emerged as the ideal target location for medication delivery in the gastrointestinal system. CDDS has significant therapeutic benefits for both systemic and local therapy. Prodrugs, pH, time-dependent systems, and microbially triggered drug delivery systems are four basic techniques for colon targeted drug delivery that have been proposed for CDDS. The first three methods are not suitable for CDDS. New CDDS techniques have been developed that are more specialised. Colon specificity is more likely to be obtained with methods that use natural materials that are destroyed by colonic bacterial enzymes.It was also determined that many testing methods are required to identify drug release and justify system objective for conducting in vitro evaluation of a colon specific drug delivery system. There are challenges for pharmaceutical scientists to train and validate a dissolution method that incorporates the physiological features of the colon and can even be used routinely in an industrial setting for the evaluation of CDDS, depending on the sophistication of colon-specific drug delivery systems and the uncertainty of current dissolution methods in establishing possible in vitro/in vivo correlation.

REFERENCES

[1] S Amidon, J Brown and V Dave. AAPS Pharm Sci Tech 2015;16(4):731-741.
[2] Ahmed S. Drug Dev Ind Pharm 2005;31:465-70
[3] Coupe AJ, Davis SS, Wilding IR. Pharm Res 1991;8(3):360–4.
[4] Hebden JM, Blackshaw PE, Perkins AC, Wilson CG, Spiller RC. Aliment Pharmacol Ther. 2000;14(2):155–61.
[5] Christl SU, Scheppach W. Scand J Gastroenterol Suppl 1997;222:20–4.
[6] Sandle GI. Gut 1998;43(2):294–9.
[7] Shameem M, Katori N, Aoyagi N, Kojima S. Pharm Res 1995;12(7):1049–54.
[8] Pijper A, Discombe G. J Pathol Bacteriol 1946;58(3):325–42.
[9] Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Gut 1988;29(8):1035–41.
[10] Fallingborg J, Christensen LA, Ingeman-Nielsen M, Jacobsen BA, Abildgaard K, Rasmussen HH. Aliment Pharmacol Ther 1989;3(6):605–13.
[11] Macfarlane GT, Gibson GR, Cummings JH. J Appl Bacteriol 1992;72(1):57–64.
[12] Bown RL, Gibson JA, Sladen GE, Hicks B, Dawson AM. Gut 1974;15(12):999–1004.
[13] Nugent SG, Kumar D, Rampton DS, Evans DF. Gut 2001;48(4):571–7.
[14] Bussemer T, Otto I, Bodmeier R. Crit Rev Ther Drug Carrier Syst 2001;18(5):433-458.

[15] Ashord M, Fell JT, Attwood D, Sharma H, Woodhead P. J Control Release 1993;26:213-220 .
[16] Fukui E, Miyamura N, Kobayashi M. J Control Rel 200; 70:97-107.
[17] Cole E, Scott R, Connor A, Wilding I, Petereit HU, Schminke C, et al. Int J Pharm 2002;231:83-95.
[18] S Lee, R Bajracharya, J Min, J Han, B Park and H Han. Pharmaceutics 2020;12(1):68.
[19] Fukui E, Miyamura N, Verma K, Kobayashi M. Int J Pharm 2000;204:7-15.
[20] Gazzaniga A, Iamartino P, Maffino G, Sangalli ME. Int J Pharm 1994;108:77-83.
[21] Kothawade PD. J Sci Technol 2011;2:33-56.
[22] Nanoparticle for colon specific drug delivery system. 3rd International conference on Nanotech and Expo, Las Vegas, USA; 2013.
[23] Choudhury PK, Panigrahi TK, Murthy PN, Tripathy NK, Behera S, Panigrahi R. Web Center Pharm Sci 2012;3:1-20
[24] Kothawade PD. J Sci Technol 2011;2:33-56.
[25] Onuigbo EB, Okore VC, Esimone CO, Ngene A, Attama AA. Avian Pathol 2012; 41:355-60.
[26] Alpsten M, Ekenved G, Soelvell L. Acta Pharm Suec 1976;13:107–22.
[27] Casey DL, Beihn RM, Digenis GA, Shambu MB. J Pharm Sci 1976;65:1412–3.