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Review Article

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Approach on Colon-Targeted Drug Delivery Systems

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Abstract Colon-specific drug delivery systems (CDDS) can be used to treat a variety of colon-related issues, including ulcerative colitis, colon cancer, Crohn's disease, irritable bowel syndrome, and chronic pancreatitis. Many medications used to treat conditions other than colon problems may also be absorbed systemically through the colon. If drugs like proteins and peptides—which are known to disintegrate in the excessive gastric pH—are transported to the colon intact, colonic mucosa can ingest them and absorb them systemically. The intended delivery mechanism must particularly target the colon when administering medications for therapeutic purposes. Colon-targeted medication delivery systems have been developed using a variety of formulation strategies. In order to accomplish colon targeting, these methods use formulation ingredients that interact with one or more features of gastrointestinal (GI) physiology, such as the pH differential along the GI tract, the presence of colonic bacteria, and enzymes. This article emphasizes the factors affecting colon-specific medication delivery, colonic bioavailability, and CDDS limits. Also, the study offers an organized discussion of different traditional as well as comparatively more recent formulation approaches/technologies currently used for the production of CDDS.

Keywords colon targeting drug delivery system, various parameters that affect colon delivery,

1. Introduction

Recently, a lot of research has focused on colon-targeted medicine delivery since it may improve the treatment of colonic local ailments while reducing systemic adverse effects. A few conditions that affect the colon are irritable bowel syndrome (IBS), Crohn's disease (CD), and ulcerative colitis (UC). These disorders are commonly treated with sulfasalazine, hydrocortisone, metronidazole, and other drugs. Because these medications are delivered directly to the colon rather than first being digested in the upper gastrointestinal (GI) tract, a larger concentration of the medication can reach the colon with less systemic absorption.

The colon is a prime location for medication delivery since the colonic contents have a longer retention duration (up to 5 days) and the colonic mucosa is known to aid in the absorption of various pharmaceuticals. Oral or rectal administration of a medication is two ways it can reach the colon. The most convenient delivery method for colon-specific distribution is oral dose forms. Oral dose forms also offer more manufacturing and design flexibility, better patient compliance, reasonably safe administration, and a lack of sterile preparation requirements. Targeting a medicine to particular areas within the colon is difficult with direct rectal delivery of active pharmaceutical ingredients. Also, according on their spreading ability and retention period, different rectal dose forms have varying degrees of drug distribution.

The effectiveness of a colon-specific drug delivery system (CDDS) depends on the various parameters like physico-chemical characteristics of the medication, the kind of delivery system, any other parameters that may affect the GI transit time, and the level of interaction between the drug and the GI tract. To prevent the medication from being released in the stomach and small intestine, oral CDDS is crucial. In order to delay the release of the drug until the system reaches the colon, many ways were used to produce a CDDS, with some showing greater effectiveness than others. To increase therapeutic effectiveness, lower drug doses, and achieve low systemic absorption levels that result in fewer adverse effects, several number of drug delivery systems have been developed that release medications, particularly in the large intestine.

Many proteins and peptides that are broken down in the stomach and small intestine because there are so many digestive enzymes are also sent to the colon for systemic absorption and increased therapeutic effectiveness. Researchers are continuously working to create fresh strategies for medication targeting, but there are still several number of obstacles to overcome before they can successfully target pharmaceuticals to the colon.

2. Some targeting approaches of colon drug delivery system (CDDS)

2.1 Sustained release systems

One can categorize sustained-release dosage forms for colon targeting as single-unit dosage forms or multiple-unit dosage forms.

Matrix tablets with extended-release polymers coated with pH-dependent polymers are the preferred form factor for single-unit dose forms. The core matrix tablet delivers the medication continuously in the colon once the coating dissolves in the upper intestine. The multiple-unit dose forms are made up of several single-unit dosage forms that are contained within a capsule or tablet. These single-unit dosage forms can be in the shape of pellets, granules, or microspheres. Each particle acts as a single-unit dose form when the tablet or capsule disperses to release its contents.

2.2 Microbially activated systems

There are more than hundreds of different kinds of bacteria in the intestinal fluid, and non-starch polysaccharides constitute one of their main sources of sustenance. The colon contains a much greater variety and quantity of bacterial species than the stomach or small intestine.

Hence, site-specific medication administration could be accomplished by using drug delivery devices coated or manufactured with such polysaccharides that act as food for the bacterial population present in the colonic fluid. The changing pH conditions of various people might not have an impact on such systems. Many polysaccharides have been researched for site-specific delivery in the colon based on this theory.

According to a cytotoxicity investigation, the microspheres outlasted the free drug's cytotoxic action on the HT-29 colon cancer lines (10). For the colon's targeting of 5-Fluorouracil, Paharia et al. created eudragit-coated pectin microspheres and assessed the drug's in vitro release in digestive fluids. In an acidic medium, the release rate was substantially slower but increased quickly at pH 7.4. An organ distribution investigation in albino rats demonstrated the microspheres' colon-targeting capability. Sinha et al. created 5-Fluorouracil quickly disintegrating core tablets and then compression coated them with a mixture of xantham gum and guar gum in varied amounts. They next tested the tablets' ability to release the medication in simulated colonic media containing 2% and 4% of rat caecal contents.Diltiazem hydrochloride was used as the model medicine, and Ravi et al. constructed tablets utilising chitosan and guar gum as carriers. The tablets were then coated with inulin as the inner coat and shellac as the outer coat. According to in-vitro release trials, the tablets released the most amount of medication in the colon while controlling release in the stomach and small intestine.

They also came to the conclusion that chitosan was an appropriate carrier for colon targeting.

2.3 pH dependent systems

pH-dependent systems are produced mainly with the help of pH-sensitive coating polymers which are insoluble in acidic pH but soluble in alkaline pH. Examples that are significant include shellac, cellulose acetate phthalate, and

eudragits. For colon-specific drug delivery, Sinha et al.32 investigated several coating polymers, including eudragit S100, cellulose acetate phthalate, shellac, and ethyl cellulose. Comparative dissolving results showed that a 3% m/m layer of shellac was the most effective polymer for delivering drugs to the colon (3). To improve coating formulations for colonic drug delivery, Akhgari et al. investigated the effects of the ratio of Eudragit S100: Eudragit L100 and the coating level on indomethacin release from pellets.

2.4 Pressure-controlled systems

The membrane containing the drug opens up under the increased luminal pressure in the colon, and the pressure-regulated systems are designed to withstand the luminal pressure in the upper sections of the gastrointestinal tract. The membrane's thickness can be adjusted, which will change how quickly the membrane collapses (2). To increase the bioavailability of glycyrrhizin in solution, Shibata et al. created pressure-controlled colon delivery capsules (PCDCs). Eight different types of glycyrrhizin solutions were created and then encapsulated inside PCDCs. In beagle dogs, the capsules were tested in-vivo. Labrasol, a component of self-emulsifying drug delivery systems, was found to significantly increase the bioavailability of glycyrrhizin in the colon.

2.5 Osmotic-controlled systems

Drug release may be influenced by formulation elements such as the core component(solubility)'s and osmotic pressure, the delivery orifice's size, and the membrane's type that regulates the release rate. In their most basic configuration, these devices consist of an inner core containing a drug, maybe in the presence of a cosmogenic, encircled by a semi-permeable membrane that has an opening for regulated drug release. The semi-permeable membrane allows water to pass through when the system comes into touch with digestive fluids. Depending on the size of the hole and the solubility of the drug, the drug within the core generates a saturated solution that is then delivered via the orifice in a regulated manner.

Drugs with a modest solubility can be administered using such systems. Push-pull devices can be utilized for medications with a wide range of solubility. Such systems have two layers that are covered with a semi-permeable membrane that is semi-permeable. Polymeric osmotic agents make up the inner compartment, whereas drug core and osmogents make up the outer compartment. The inner compartment's polymers swell when water is ingested through the membrane and enters the system, forcing the medicine through the membrane's aperture. In addition to being able to be employed for systemic medication action, OROS-CT (Alza Corp.) was created for targeted delivery to the colon. It comes in a firm gelatin capsule with one or perhaps five or six push-pull, enteric-coated delivery methods.

2.6 Colonic Luminal Contents' Viscosity

The colonic luminal contents' viscosity is higher than that of the upper GIT contents due to a higher water-absorbing capacity, which makes it difficult for CDDS to dissolve. Also, when the contents go from the ascending colon to the descending colon, their viscosity gradually rises, reducing the amount of medication that dissolves and the amount of mucosal absorption. The drug's ability to reach the colon's disease-causing bacteria is also influenced by viscosity. It has been demonstrated that the viscosity of colonic contents influences the movement of bacteria in the colon.

2.7 Formulation Elements

The physicochemical characteristics of the medications, the dose, and the dosage form parameters are all formulation factors that affect colonic drug delivery and bioavailability. Because there is only 1–44 ml of colonic fluid available for dissolution, a drug's solubility and dosage play crucial roles in colonic bioavailability. Although budesonide (dosage, 9 mg), a highly strong medication, has reduced water solubility, it is effectively absorbed in the colon and is used to treat UC (33). Mesalamine has a substantially better solubility than budesonide (3.64 mg/ml vs. 0.24 mg/ml), but it also has a significantly higher dose (4.8 g daily), which acts as a rate-limiting factor for its absorption through the colon.Covalently attaching a medication formulation to a carrier is another technique to help

it stay intact as it travels through the stomach and small intestine. Drugs can attach to molecules known as carriers, including cyclodextrin, glucuronide, dextran, and amino acids. An azo bond may also be used to connect it to a carrier. Colonic bacteria or enzymes break down each of these linkages. By using sodium alginate (Na-Alg) and hydroxypropyl methylcellulose (HPMC) as carriers, matrix, enteric-coated, and compression-coated tablets containing curcumin were successfully delivered to the colon, according to research by Modasiya et al.[19]

2.8 Recent Approaches

A novel colon-specific medication delivery system known as CODES TM was recently created by Liu et al.37 Colonic microorganisms in conjunction with pH-sensitive polymer coatings cause this system's drug release. The core tablet is covered in an acid-soluble Eudragit E coating, which is then covered in an outer layer of enteric polymer and a barrier layer of hydroxypropyl methyl-cellulose. The main and secondary coats' opposed polymers cannot interact with one another because of the barrier layer. The CODES TM stayed intact in the stomach, according to gamma scintigraphy experiments, but the enteric and barrier coats disintegrated in the small intestine where the pH is higher than 6.The acid-soluble eudragit E covering shields the core in the small intestine, but once it reaches the colon, the core's polysaccharide dissolves and diffuses through the coating, where it is broken down by bacteria and transformed into organic acids. This lowers the pH around the system just enough to cause the acid-soluble coating to disintegrate and the release of the medicine.

Comparative research has been done to gauge the effectiveness of targeted medicine delivery methods. Takaya et al.23 conducted this investigation to determine the association between the drug's in vitro release and in vivo absorption using three different colon delivery devices. The three systems were eudragit S-coated tablets for solid preparations, pressure-controlled colon delivery capsules for liquids, and time-controlled colon delivery capsules for liquids. The drug release from eudragit S-coated tablets was shown to be the most delayed of all preparations in vitro dissolving testing. However, in vivo tests revealed that colon administration capsules had higher systemic availability than eudragit-coated tablets.

3. Traditional method for implementing colonic delivery

There are various methods which help in implementing the colonic drug delivery.some of are:

3.1 Biodegradable Delivery Systems Particular to the Colon

There are many different anaerobic bacteria species are present in the colon, and they get their energy by digesting undigested substrates like polymers. These colon-specific organisms include Bacteroides, Eubacteria, Clostridium, Enterococci, etc and they produce several enzymes like glucuronidase, xylosidase, nitroreductase, and azoreductase to ferment these polymers . This seems to be a more viable method for colon-specific administration because these enzymes are localized to the colon. Chemically altering the polymers utilized in CDDS creation has the potential to affect how much of them are degraded by enzymes. For instance, Roos et al.34 created a hydrogel of bovine serum albumin using the acetyl derivative of guar gum. They discovered that the degree of substitution had an impact on the rate of hydrolysis for AcGGM modified by -mannose (DS). The fact that the hydrolysis rate dropped as DS rose suggests that the side chain constrained the enzyme. Contrarily, the addition of -mannose greatly increased BSA release; after 8 hours, 95% of the BSA was released in the presence of this enzyme, compared to 60% in the absence. The most extensively studied class of substances employed as prodrugs, azo-aromatic polymers are vulnerable to azoreductase breakdown t o prevent peptidases from breaking down drug molecules like peptides in the stomach and small intestine while still allowing for drug release in the colon, they can be employed to coat the drug molecules.

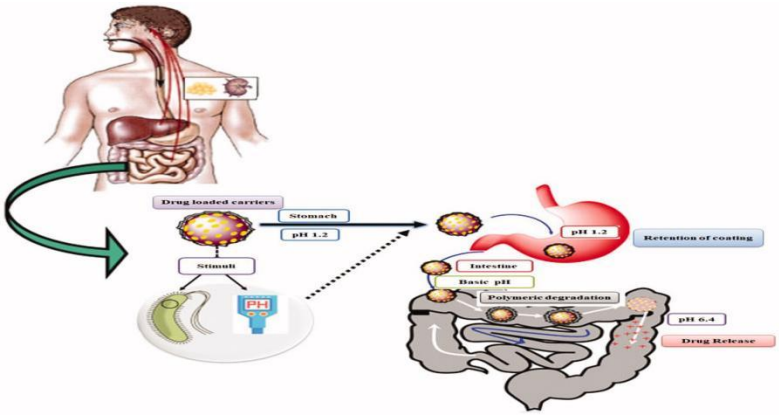

Figure 1: Diagrammatic representation of Biodegredable polymer action in Colon drug delivery system.

3.2 Systems with Many Particles

In a multi-particulate system that Beckert et al.33 created and tested, the drug's basic formulation was made up of two different kinds of pellets. Pellet A, the first kind of pellet, had an outside polymer that only degraded at a pH higher than 5.5 and an inside polymer coating that allowed the medicine to be delivered constantly. Pellet B's polymer coating prevented more than 20% of the medication from dissolving after six hours at pH 6.8. At pH 7.2, however, more than 50% of the medication was released in the same time frame. Hence, it was determined that the combination of these two types of pellets with their polymer coatings held promise for the targeted delivery of drugs to the colon.

3.3 Colon Targeting with Coatings

Enteric-soluble polymers can dissolve at greater pH levels in the intestine than they can in the stomach's acidic environment. For their application as coatings in formulations intended to transport active pharmacological components, especially to the colon,some polymers have undergone substantial research. This purpose has frequently been served by polymers based on poly-ethacrylate, which has a specific pH value at which it dissolves. To create a coating with an optimal dissolving rate, these polymers have been combined in various ratios. Furthermore, coatings made of these polymers are intended to be quite thick in order to delay their decomposition and offer a regulated or prolonged release of the medicine.

Acid-soluble polymers have also been researched as prospective ingredients for colon-targeted formulations in addition to enteric-soluble polymers. In people with IBS, the pH of the proximal large intestine drops. For instance, a healthy person's colonic pH ranges from 6.4 to 7.0, but someone with UC may only have it between 2.3 to 4.7. (71). Dexamethasone minitablets were created by Leopold et al.36 and coated with the acid-soluble polymer Eudragit® E. It was discovered that this coating quickly disintegrated in buffers with a pH range of 2.0 to 5.0, allowing the medicine to be released in 10 to 50 minutes. Yet, the makeup of the drug core and the thickness of the coating both had an impact on how much the drug's release was postponed in the pH 6.8 buffer.

The percentage carbonate content in the ASS marble sample is presented in Fig 4. This result revealed high carbonate content (72.4 wt.%) for ASS sample. This suggests that ASS sample is carbonated.

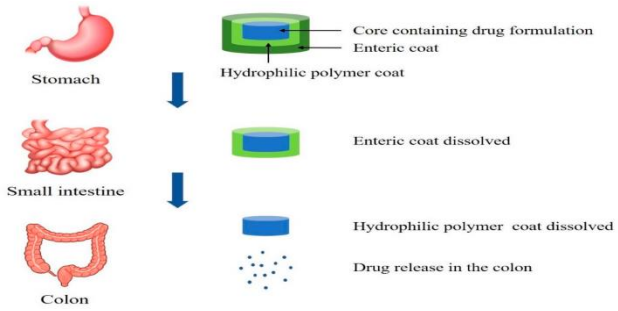

Figure 2: Diagrammatic representation of the enteric-coated colon-targeted drug delivery system

3.4 Bio-adhesive System

With the help of bioadhesive devices, poorly absorbable medications can stay in contact with an organ—in this example, the colon—for an extended period of time. Polycarbophil, polyurethanes, and polyethylene oxide are a few of the polymers that have been investigated as bioadhesive components for these systems. To target the delivery of metronidazole to the colon, Ahmad et al.35 created a bio-adhesive microsphere (BAM) using the starch from Assam Bora rice (48). It was discovered that these bio-adhesive microspheres had a longer retention duration in the colon and contributed to a greater rate of medication absorption there.

4. Conclusion

A key tactic for more efficient local therapy of colonic disorders like IBD and colorectal cancer is colon-targeted medication delivery. In terms of safety, effectiveness, and patient compliance, it may offer numerous advantages over traditional dose forms. Moreover, colon-targeted delivery methods can increase the systemic exposure of medicines that are enzyme- and/or acid-labile, including macromolecules. In terms of safety, efficacy, and patient compliance, colon-specific medication delivery devices provide patients with significant therapeutic benefits. The successful formulation of a drug delivery system for the colon depends on several number of variables, including the medication's physicochemical properties, formulation and process variables, and GI physiological parameters. The formulation strategies used to address these issues primarily center on a specific method of drug delivery, such as bypassing the complex pH environment of the upper GIT with the dosage form, obstructing drug release and absorption in the upper GIT, and releasing the drug in the colon for absorption. It seems that the key to the development of colon-specific drug delivery systems is a combination of conventional and novel ways to ensure a balance between efficiency, target-specificity, cost, and patient compliance.

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