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Advances in Drug Delivery Approaches for Targeting Colon Cancer

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Abstract:

Colorectal cancer remains an important issue in oncology, requiring innovative strategies to enhance therapeutic effectiveness and minimize systemic toxicity. This comprehensive review looks at recent advancements in drug delivery methods created specifically to treat colon cancer. In the quickly evolving field of targeted drug delivery, we look at a number of cutting-edge methods, including polymeric delivery platforms, prodrug approaches, localised delivery systems, nanoparticle-based systems, and microparticle carriers. Each section examines the benefits, limitations, and potential medical applications of these cutting-edge techniques. The study emphasizes how these new technologies have the ability to address the underlying challenges of traditional medicine delivery as we go through them. This review aims to provide a comprehensive summary of the current situation by integrating the most recent studies. It also highlights areas that warrant further exploration and the potential application of these novel approaches to clinical practice.

Key words : Colorectal cancer, approaches, target drug delivery, biodegradable polymers, stimuli response, etc

1. Introduction:

Colorectal cancer (CRC) is a prevalent and deadly disease that requires constant advancements in therapeutic modalities. Traditional treatment methods, including as radiation, chemotherapy, and surgery, have improved patient outcomes, but they are often limited by systemic toxicity and low efficacy. Targeted medicine distribution is a paradigm-shifting strategy that has the potential to reduce adverse effects and increase treatment accuracy. Because of the unique problems posed by the anatomical and physiological characteristics of the colon, tailored approaches are necessary for treating colorectal cancer (CRC).

This review begins with an overview of the current status of CRC therapy, emphasising the need for more targeted and effective treatments. After recognising the shortcomings of traditional drug delivery techniques, we investigate the rationale for putting new tactics into practice. The next sections explore novel developments in the distribution of medications for colon cancer, specifically focusing on prodrug strategies, polymeric systems, nanotechnology, microparticle carriers, and localised delivery methods. By thoroughly examining each of these

tactics, we want to provide light on how they could improve treatment outcomes.

As we examine the intricacies of these state-of-the-art delivery techniques, it becomes evident that a complete understanding of their benefits and drawbacks is necessary for their successful translation into clinical settings. By supplying data that may guide future research and ultimately contribute to the development of more effective and targeted colon cancer treatments, we seek to further the ongoing discussion in this field.

2. Colon Cancer :

Lung cancer accounts for 11.6% of all cancer cases diagnosed in both sexes, with breast cancer accounting for 11.6 % of cases and prostate cancer for males 7.1%. In terms of mortality, colorectal cancer (CRC) ranks second (9.2%) and is recognised third (6.1%). According to estimates, the overall mortality toll from colon and rectal cancer will rise by 71.5% and 60%, respectively, by 2035 [1]. The degree of economic progress in any country may cause these numbers to vary. As a result, the illness is commonly acknowledged as a sign of the nation's socioeconomic advancement [2]. Dietary habits, body fat percentage, and lifestyle choices all have an impact on the rise in morbidity [3].

There is strong evidence supporting the beneficial effects of physical exercise. Frequent use of alcohol and red and processed meat increases the chance of acquiring the condition [2,4]. In addition to improved social circumstances, the advancement of civilization and economic growth also leads to a shift in eating habits known as the "Westernisation of the Lifestyle." This entails consuming more processed meats, animal fats, refined grains, and sugary foods; it also implies consuming fewer fruits, vegetables, dietary fibres, and physical exercise. Such a lifestyle frequently contributes to the prevalence of overweight or obesity [5]. Numerous ailments that affect society today are linked to being overweight or obese. It has been noted that visceral adiposity has a negative impact on men's CRC prognosis [6]. around 25% of the genetic predisposition. Since colorectal cancer (CRC) often takes years to grow, it is critical to detect the condition at an early stage. Secondary prevention is also crucial, and it is focused on follow-up exams and nutrition prevention based on a balanced diet [7]. We tried to organise the information on colorectal cancer that was accessible in the literature by taking into account all the factors.

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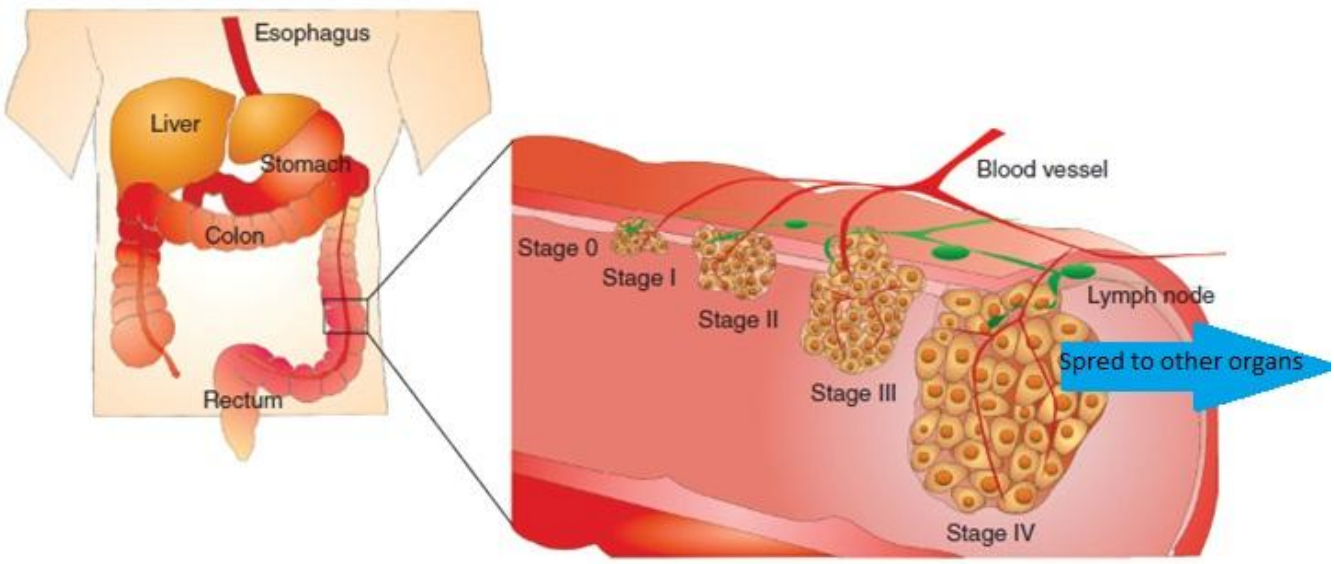

Fig. 1 Stages of colorectal cancer

3. Approaches in Drug Delivery for colon cancer :

3.A Conventional drug delivery

3.A.1 Rectal drug delivery

Rectal preparations (such as enemas, foams, gels, and suppositories) are frequently used to treat constipation, haemorrhoids, discomfort, nausea/vomiting, and colon disorders using 5-ASA [8,9] and corticosteroids [10–12]. Rectal preparations have evolved in recent years from conventional formulations to more sophisticated ones that, depending on the particular application, might encourage systemic absorption as well as local drug retention [14, 15]. In this context, three categories of enemas have been identified: (a) highly hypotonic enemas that cause drug absorption into tissue and circulation; (b) hypertonic enemas that cause bodily fluids to be secreted into the lumen and lead to rapid systemic drug absorption; and (c) moderately hypotonic enemas with ionic compositions resembling faeces that reduce systemic medication absorption but increase local drug bioavailability. In this case, the drug's bioavailability is significantly influenced by the osmolality of rectal preparations. To enhance water absorption, epithelial tissue in the colon actively pumps sodium ions into the lumen. Drugs can therefore be osmotically directed into the epithelium using this fundamental characteristic. This can be accomplished by making rectal formulations less tonic, which creates an osmotic gradient that allows hydrophilic medications and mucus-penetrating nanoparticles to pass through the surface of the epithelial tissue without causing damage [16,17]. For instance, a research comparing three different tenofovir-loaded enemas revealed that the drug concentration was raised by hypotonic sodium-based enemas. in mice's

colon tissues as contrasted to preparations that were isotonic or hypertonic and caused the medication to be absorbed quickly throughout the body [18]. Rectal formulations provide benefits, but some patients find them undesirable because they might increase urge to defecate, induce discomfort from leaks, or create local irritation in the rectum [18]. Consequently, these elements must to be seen as major formulation obstacles that, if solved, would raise the possibility of patient acceptance. The use of thermosensitive polymers, such poloxamers or pluronics, which change from a liquid to a gel phase at body temperature, is one potential remedy for rectal leaking of dosage forms [19]. Thermosensitive gelling might lessen the pain associated with inserting a solid dosage form and enhance drug absorption through mucoadhesion in addition to decreasing rectal leakage. A thermal gelling rectal formulation has not yet been commercialised, although showing promise in many animal investigations and a 1998 human trial [19–22]. This might be because of challenges in attaining high-scale, cost-effective manufacturing.

3.A.2 Coating

3.A.2.1 Biodegradable polymers

The bioenvironment within the human gastrointestinal tract (GIT) is distinguished by the existence of a diverse range of microflora, particularly in the colon, which is abundant in bacteria involved in the reduction of food components or other materials. Pharmaceuticals coated with polymers that exhibit degradation under the action of colonic bacteria may be used to develop colon-targeting medications. These biodegradable polymers, particularly azo polymers, have been investigated for the purpose of releasing a medication taken orally into the colon. In fact, the dosage form doesn't break down in the stomach or small intestine after passing through the gastrointestinal tract (GIT) since there isn't much microbial activity there that would cause the polymer covering to break.

After the azo bonds are reduced and then broken down by the azo reductase enzymes produced by the azo bacteria found in the intestinal microbiota, the medications in the azo polymer coated formulation are expected to be released. This strategy's concept is based on the metabolic activity of azo reductase, which is produced by azo bacteria in the colon. However, other factors, such as the type of food consumed, dietary fermentation precursors, and the coadministration of chemotherapy agents, may also affect the bacterial degradation of polymeric coating. Antibiotic administration can lead to the partial or whole loss of colonic microflora, which has a negative impact on the release of bioactive compounds. An overview of the synthesis and characterization of several azo polymers that have been used for colon targeted drug delivery [23].

3.A.2.2 pH sensitive polymers

The pH range of the stomach is 1-2 during fasting, but it rises when eating. The pH levels in the cecum and the proximal small intestine are respectively 6.4 and 6.5. However, in the ascending colon of healthy individuals, pH levels as low as 5.7 have been recorded. The transverse colon's pH is 6.6, whereas the descending colon's pH is 7.0 [24]. Methacryl resin-based colon targeted drug delivery systems for insulin, prednisolone, quinolones, cyclosporine, salsalazine, beclomethasone

dipropionate, and naproxane have been reported [25]. The idea behind this technique is to coat the tablets, pellets, etc. with different pH-sensitive polymers, which will cause a delayed release and protect the material from stomach fluids[26]. These various polymers release the medication at varied rates based on their varying threshold pH. The preparation of colon medication delivery primarily involves the use of Eudragit L and S, which dissolve at pH values of 6 and 7, respectively [24]. A single unit formulation's low site specificity may result from the pH dropping from the end of the small intestine to the colon, which can cause a number of issues including longer lag periods at the ileocecal junction or rapid elimination through the ascending colon [27]. The dissolving rate of Eudragit® is influenced by a number of formulational parameters, including the combinations of various polymers, the media's pH, the tablets' coating level, and the presence of plasticizers [28].

Depending on the size of the dosage form, such as tablets and granules, and the kind of coating material, the coating specifies the release of bioactives [29]. Targeting the large intestine, eudragit S coated 5-aminosalicylic acid (5-ASA) anti-inflammatory drugs have been employed. Targeting the colon with eudragit L coated 5-ASA has been utilised to treat Crohn's disease and ulcerative colitis [24].

3.A.2.3 Coating with microparticles

Due of the large intestine's confinement of many protozoans, particularly Entamoeba histolytica, significant intracolonic medication concentrations are required [30]. The existing therapies do not achieve this aim since they work on the premise of releasing medications into the upper gastrointestinal tract, where they are absorbed systemically and cause adverse effects. [31] created and assessed a concoction that deviated significantly from the accepted wisdom of traditional medicine. It was made up of tiny silica particles (5–10 μm in diameter) covalently bonded to 2-(4–aminophenoxymethyl)-5–nitro–1–methylimi–dazole, a strong antiamoebic medication. Mice, hamsters, and guinea pigs were given injections of silica-drug particles.

It was discovered that the particles were phagocytosed by trophozoites both in vivo and in vitro, which was followed by a rapid cell death caused by the drug released. After the drug-containing particles were placed in the gut, an analysis of mouse serum showed that no drug was absorbed from the intestine. Particles retrieved from the gut nearly all preserved their antiamoebic action. This innovative antiamebic idea might reduce side effects and dosage frequency while providing luminal treatment for asymptomatic amebiasis..

3.A.3 Polysaccharides base

For colonic targeting, several delivery methods and schemes have been put forth. For them to operate, they often need to take advantage of one or more of the gastrointestinal characteristics such as pH, transit time, pressure, or microflora. Commercialized products include coated systems that make use of the pH differential in the gastrointestinal tract and prodrugs that release when exposed to colonic bacteria. Each strategy has built-in constraints of its own. Many systems in development have not advanced past the bench, while others are too costly or difficult to produce, or they may not have the necessary site-specificity. The practicality of the universal polysaccharide systems and their utilization of the colon's most unique characteristic a profusion of microflora

make them seem to be the most promising. In order to build innovative colontargeted delivery systems based on naturally occurring biodegradable polymers, recent research into the utilisation of the metabolic activity and the colonic milieu in the lower GI tract has proven very valuable. The development of food- and nutraceutical-based formulations for colon-based disorders, such as colorectal cancer, is thought to have enormous promise thanks to these polysaccharide-based encapsulation and targeted delivery methods [32].

Evaluation of the prodrug pectin-ketoprofen (PT-KP), which has the ability to be delivered to the colon specifically, revealed that KP is mostly distributed in the stomach, proximal small intestine, and distal small intestine. However, the colon and cecum are where KP released by PT-KP mostly distributes. As a result, this method implies that the prodrug PT-KP has strong colon targeting properties [33].

3.A.4 PEGylation

The application of poly(ethylene glycol) (PEG) to the surface of nanoparticles results in a hydrophilic surface chemistry that minimises the contact between the intestinal environment and the PEG-functionalized nanoparticles, allowing for nearly unimpeded passage through the disrupted epithelium.[34–36]. PEG is an uncharged, hydrophilic molecule with characteristics that reduce strong interactions with the components of mucus and promote particle translocation across the mucus and mucosa[34]. Specifically, it has been demonstrated that low molecular weight PEG effectively shields the hydrophobic particle core while reducing interpenetration or intermolecular interactions between PEG polymers and the surrounding luminal tissue[35,37]. For colitis-specific medication administration, its hydrophilic surface offers an expedited translocation into the leaky, inflamed intestinal epithelium[37].

PEG-functionalized PLGA nanoparticles (300 nm) and microparticles (3000 nm) have the ability to target inflammatory human intestinal mucosa in vivo. When compared to chitosan- and non-functionalized PLGA particles, surface modification of nanoparticles with PEG showed significantly increased particle translocation and deposition in inflammatory mucosal tissues[37].

3.A.5 Mucoadhesive novel delivery systems

The colon system's mucus interacts with the nano carrier particles by hydrophobic binding, lengthening the nanoparticles' transit duration and retention [38]. By altering their surface, the new carriers' adherence to the colon membranes can be decreased or enhanced [39]. According to some research, the drug's increased bioavailability in the small intestine is due to its attachment to mucus [40–42].

Therefore, by improving the drug's absorption and adherence in the affected area, mucoadhesive innovative delivery methods can improve colon therapy [43, 44]. However, cationic nanoparticles that adhere to the proximal gastrointestinal tract before they reach the colon disrupt this mechanism.

In order to avoid this, the cationic nanocarriers are only deshielded in the colonic area by using a pH-associated release to shield them. To avoid adhesion in the proximal gastrointestinal area, budesonide liposomes rendered with cationic polyethyleneimine were created and coated with Eudragit S100 (an anionic). When the formulation reached the colon, pH caused the

anionic layer to be removed, which allowed the medication to be released. Bioimaging and confocal analysis in the mice in vivo investigations revealed high tissue accumulation and drug release in the colon [45].

3.A.6 Prodrug approach

A prodrug is a parent drug molecule that is pharmacologically inactive and has to undergo biotransformation in vivo in order to liberate the active ingredient from the carrier. For colonic drug administration, the primary targets are enzymes such as azoreductase, galactosidase, xylosidase, nitroreductase, glycosidase, and deaminase[25,46-49]. The three parts of a prodrug targeted drug delivery system are the drug, the carrier, and the targeting moiety. This strategy reduces the amount of active medicine absorbed from the upper GI tract, which has encouraging effects for the colon drug delivery system [28]. Azo bond conjugates, amino acid (polypeptide) conjugates, cyclodextrin conjugates, dextrin conjugates, polymeric conjugates, glycoside conjugates, glucuronide conjugates, and sulphate conjugates are among the many carriers and materials employed in the development of colon drug delivery systems [26].

3.A.6.1 Covalent linkage of drug carrier

It entails the creation of a covalent bond between the medication and carrier such that, in the stomach and small intestine, the moiety is retained after oral administration.

This method primarily entails the creation of prodrugs, which are pharmacologically inactive derivatives of parent drug molecules that must release the active ingredient by enzymatic or spontaneous change in the biological milieu. Prodrugs that are formed have better delivery qualities than their parent drug molecules. Prodrug formation, which transforms into the parent drug molecule once it enters the colon, can solve the issue of some medications' instability in the harsh environment of the upper gastrointestinal tract.

3.A.6.1.1 Azo bond conjugates

A diverse and mostly stable collection of microorganisms, many of which have physiological activities and are essential to both health and sickness, make up the intestinal microflora. The natural microflora of the body performs a multitude of metabolic functions, such as reducing the amounts of nitro and azo groups in environmental and medicinal compounds, in addition to shielding the patient from potentially harmful bacteria colonising their digestive tract [50–52].

Sulphasalazine was first introduced to treat anti-inflammatory diseases and rheumatoid arthritis. Chemically speaking, it is salicylazosulphapyridine (SASP), in which an azo bond binds sulfapyridine to a salicylate radical [53]. Orally administered sulphasalazine mostly passes through the colon undigested, with only a little amount being absorbed from the small intestine. There, the colonic bacteria break it at the azo bond, releasing 5-ASA and sulphapyridine (SP). Nonetheless, sulphapyridine appears to be accountable for the majority of sulphasalazine's adverse effects, leading to the emergence of several novel treatments for inflammatory bowel disease.

3.A.6.1.2 Glycoside conjugates

A novel colon focused medication delivery method is based on the specific glycosidase activity of the colonic microbiota and steroid

glycosides. Because they are hydrophilic, drug

glycosides are not well absorbed from the small intestine. When a glycoside of this kind enters the colon, bacterial glycosidases can break it, releasing the medicine so that the colonic mucosa can absorb it free.

D-galactosidase, L-arabinofuranosidase, and D-xylopyranosidase are the main glycosidases found in human faeces [54]. Since these enzymes are found at the brush edge, it is not too difficult to reach the substrate. Numerous chemicals are discovered as glycosides in the kingdom of plants. Certain medications function as glycon and can create glycosides when they are conjugated to certain sugar moieties. These glycosides are hydrophilic and bulky, which prevents them from passing through the cellular membrane when consumed [55].

3.A.6.1.3 Glucuronide conjugates

One of the main processes for the inactivation and clearance of many medications is the conjugation of glucuronide and sulphate. However, the lower GIT's bacteria release glucuronidase, which the gut may use to deglucuronidate a number of medications[56]. Glucuronide prodrugs would be predicted to be preferable for colon focused drug delivery since the deglucuronidation mechanism releases the active drug and facilitates its reabsorption.

The effects of naloxone, nalmefene, and its glucuronide conjugates on the gastrointestinal system and other aspects of brain-mediated withdrawal were assessed in rats that were opiate-dependent. Nalmefene glucuronide was ineffective when applied subcutaneously, while nalmefene hydrochloride increased tail skin temperature in a dose-dependent manner.[57,58].

3.A.6.1.4 Cyclodextrin conjugates

Cyclodextrins (CyDs) are cyclic oligosaccharides made up of six to eight glucose units joined by α-1,4 glucosidic linkages. They are used to enhance the solubility, stability, and bioavailability of medications. These compounds prefer to form inclusion complexes with different drug molecules because their surface is somewhat hydrophilic and their inside is relatively lipophilic [59–63]. Although they are known to be very poorly absorbed in the small intestine and stomach and to be very poorly hydrolyzed, they are instead fermented into tiny saccharides by colonic bacteria and absorbed in the large intestine [64–66].
Through the creation of inclusion complexes, CyDs' bioadaptability and multifunctional qualities enable them to mitigate the unwanted aspects of therapeutic molecules in a variety of delivery methods. While hydrophobic CyDs can slow the release rate of water-soluble pharmaceuticals, hydrophilic and ionizable CyDs can act as effective drug carriers in immediate release and delayed release formulations, respectively, in an oral drug delivery system. Molecular encapsulation in conjunction with other carrier materials will become a useful and important tool in the enhancement of medication formulation, as CyDs have the ability to extend the function of pharmaceutical additives. Furthermore, the capacity of the drug carrier to deliver a medicine to a specific location is its most desired feature;

CyD-containing drug conjugates can be

flexible way to create a novel class of colon-targeting prodrugs. A research conducted on healthy human volunteers has demonstrated that β CyDs are entirely broken down by the microbiota in the colon but only partially digested in the small intestine. The majority of human-isolated bacterial strains have the ability to break down CyDs. Their capacity to grow on cyclodextrins by using them as their only carbon source and their ability to stimulate cyclodextrinase activity after as little as 2-4 hours of exposure to cyclodextrins are proof of this. This medication's characteristic may be used to create colon-targeted drug delivery systems. Enantioselective hydrolysis of many CyDs conjugates has been reported [67–69].

3.A.6.1.5 Dextran conjugates

After the preparation of dextran ester prodrug, in vitro release analysis demonstrated that naproxan release from the prodrug was several times more in caecum homogenates compared to control medium or pig small intestinal homogenates [70, 71]. Harboe et al. [72] evaluated the naproxan bioavailability in pigs following oral administration of a dextran T-70-naproxan ester prodrug. The conjugate's average absorption percentage was 91% when compared to the oral solution of an equal dosage of naproxan. It was determined that a number of characteristics of the prodrug suggested that naproxan was liberated from the prodrug before systemic absorption and that the action of one or more gastrointestinal tract enzyme systems was required for drug activation. The conjugate's plasma concentration time curves in rabbits were shown to have an initial lag time of around two to three hours, while naproxan was found in plasma as soon as the drug component perse was administered orally. The qualitative evaluation of the prodrug distribution along the GIT was conducted using HPLC examination of conjugated and free naproxan in different segments of the GIT, following conjugate administration. It was inferred from these tests that drug regeneration functioned well in the colon below the ileum.

3.A.6.1.6 Amino-acid conjugates

Amino acids and proteins have less membrane permeability because of the hydrophilic nature of polar groups like -NH2 and -COOH, which are found in proteins and their building blocks, or amino acids. Drug molecules have been conjugated to these polar amino acids to create a variety of prodrugs [73–76]. Tyrosine, glycine, methionine, and glutamic acid were conjugated to SA, which is a non-essential amino acid. It was discovered that the microbes of the intestinal flora of dogs and rabbits metabolised salicyluric acid, which is the glycine conjugate of SA, into SA. The prodrug was shown to be inappropriate for delivering medication to the colon since it was absorbed into the systemic circulation from the upper GIT. To create salicylic glutamic acid conjugates, Nakamura et al. increased the hydrophilicity and chain length of the carrier amino acid and decreased the conjugate's membrane permeability. With little absorption and degradation in the upper gastrointestinal tract, this combination demonstrated excellent outcomes and was shown to be appropriate for colon-targeted SA administration.

3.A.6.2.Polymeric prodrugs

Azo-linked polymeric prodrugs of 5-ASA were made and assessed in an environment mimicking the microbiota of the human gut. In

vitro tests were conducted on polyamides with azo groups present in their backbone, either in a reductive buffer or in the bioreactor medium. It was shown that reduction for the hydrophobic polymer ends at the hydrazine stage, whereas reduction for the hydrophilic homologue proceeds to the amine production stage. Depending on the polymer's makeup, the drug's release concentration may be similar to that of prodrugs with low molecular weight [77].

3.A.7 Embedding in matrices

The polymer matrix contains embedded medicinal molecules. For the medication to be released from its entrapment, the polymers utilised in this approach must be able to degrade in the colon.

3.A.7.1 Redox sensitive polymers

Drug delivery formulations that respond to changes in redox potential have the potential to be a useful treatment for ulcerative colitis and colorectal cancer [78,79]. Reactive oxygen species (ROS) that are inflammatory and cause excessive production are linked to oxidative stress in ulcerative colitis [80]. Delivery to the colon that is infected can thus be accomplished through the development of innovative methods that are degraded by ROS. Additionally, the research found that adding ROS scavenger radicals of nitroxide to redox nanoparticles prevented colitis in mice [81]. Redox nanoparticles were also shown to accumulate in the tissues of [80] and to be capable of suppressing colon cancer. Although these systems seem like a cutting-edge method for delivering medication to colonised areas, they are also linked to instability and early drug release. As a result, the drug delivery system's therapeutic efficacy is reduced. Several stimulus responses can be employed as a strategy to address these problems.

3.A.7.2 Bioadhesive systems

For best therapeutic results, oral administration of some medications need a high local concentration in the large intestine. Low intracolonic drug concentration is caused by dosage form dissolution and concurrent absorption from the upper gastrointestinal tract, and drug absorption produces adverse effects. The process by which a dosage form stays in touch with a specific organ for an extended amount of time is called bioadhesion. If the medication has a longer residence time, it will either have a higher local concentration or, in the case of poorly absorbable medicines, better absorption qualities. The development of colonic medication delivery devices can use this tactic.

As materials for bioadhesive systems, a variety of polymers, such as polycarbophils, polyurethanes, polyethylene oxide, and polypropyline oxide copolymers, have been studied [82,83]. Colic drug delivery devices have been shown to operate better and have a longer mean residence duration when bioadhesion is used [84, 85]. Numerous studies have proven in vitro bioadhesion, and there aren't many data on in vivo bioadhesion research [86, 87].

3.A.7.3 Biodegradable matrices

Because monosaccharides are resistant to the digesting action of gastrointestinal enzymes, their polymer keeps its integrity. In the physiological milieu of the stomach and small intestine, polysaccharide matrices are thought to stay intact. However, once they enter the colon, bacterial polysaccharidases begin to operate on

them, causing the matrices to degrade. Because it consists of polymers with a large number of derivatizable groups, a wide range of molecular weights, diverse chemical compositions, and, for the most part, low toxicity and biodegradability but high stability, this family of naturally occurring polymers has appeal in the field of drug administration.

The fact that these materials are already authorised to be used as pharmaceutical excipients is their best feature. Many polysaccharides have been studied for use in colon focused drug delivery systems, including amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, and locust bean gum. The choice of an appropriate biodegradable polysaccharide is crucial in the creation of polysaccharide derivatives for colon focused medication delivery. These polysaccharides need to be rendered water insoluble by hydrophobic derivatization or crosslinking since they are typically soluble in water. An ideal ratio of the hydrophobic and hydrophilic components, as well as the quantity of free hydroxy groups inside the polymeric molecule, are crucial. general characteristics of the polysaccharides in the colon targeting drug delivery [88].

3.A.7.4 Hydrogel approach

medication-containing hydrogels have also been found to be employed as oral colon medication delivery systems. Numerous studies demonstrate the great potential of this approach. distinct researches have reported on distinct types of CDDS based on hydrogel.

These come in three varieties: hydrogels that are cross-linked by azo, alcohol, or aldehyde. By combining azo crosslinking agents with pH-sensitive monomers, azo hydrogels generated colon specificity. By cross-linking polymerization of N-substituted (meth)acrylamides, N-tert-butylacrylamide, and acrylic acid with 4,4'-di (methacryloylamino) azobenzene [46] and N-N'-methylene bisacrylamide [89], one may achieve this synthetic method for colon targeting. Using the identical polymeric precursor and related copolymer with side chains terminating in NH2 groups, the hydrogels were also made by polymer–polymer reaction[46]. From the aldehyde family, glutaraldehyde was discovered to be a good model option for cross-linking different polymer systems. They experimented with various glutaraldehyde concentrations and determined the best one to regulate guar gum swelling. It has been demonstrated that these cross-linked hydrogel systems are advantageous for colon-specific drug delivery methods. Many tests have demonstrated the unique cross-linking ability of poly vinyl alcohol. According to Orient et al.'s research, succinyl, adipoyl, and sebacoyl chloride were cross-linked using PVA to create hydrogel foamy polymers [26].

3.A.8 Particulate delivery systems

It has been demonstrated that shrinking medication delivery vehicles to the nanoscale can lengthen colonic residency times in inflammatory gastrointestinal areas and offer further advantages for IBD treatment. By causing an epithelial enhanced permeability and retention (eEPR) effect, this size reduction permits more effective and targeted delivery of active molecules into the colitis tissue [90,91]. It also permits immune cells, which are highly concentrated in the inflammatory areas, to preferentially absorb the nanoparticles. It is also feasible to prevent diarrhoea, a frequent sign of

colon illnesses, from rapidly eliminating carriers by decreasing the width of the particles [93].

3.A.8.1Micoroparticlulate system

the possibility of microparticle absorption into human IBD patients' rectal mucosa and discovered a clear buildup of microparticles in cases of active IBD, but only negligible amounts of nanoparticles were observed in these patients' mucosa. They showed that the inflammatory mucosal wall was the site of microparticle accumulation and bioadhesion; however, there was no evidence of these particles being absorbed through the epithelial barrier. On the other hand, it is possible that the nanoparticles caused systemic absorption because they were translocated to the serosal compartment of IBD patients. According to the findings, human intestinal lesions may be treated locally without the need for nanoparticles. It is unknown why there is a difference in particle size between trials conducted on humans and animals, but it might have significant implications for how human IBD is treated in the future. It should be highlighted that although there was statistically significant accumulation of particles in ulcerated regions, the overall percentage of particles that penetrated the mucosa was comparatively low in the study [94].

3.A.8.2 Multiparticulate approach

Pellets, granules, and microparticle formulations are examples of the multi-particulate method that has been tested for colon administration. Using guar gum, researchers created a biodegradable colon-targeted multi-particulate device. In that investigation, aqueous guar gum slurry was used to coat the drug-loaded pellets. Following in vitro testing, the drug released with a 4.5-hour lag time when an enzyme was present, and an increased lag time when an enzyme was absent, indicating the presence of an enzyme-triggered mechanism for colonic release. Colon targeting has also been done using multi-particulate systems [95].

3.A.8.3 Nanoparticulate system

For colon targeting, nanoparticle size colloidal carriers made of synthetic or natural polymers have also been studied. Orally given nanoparticles have been demonstrated to improve the solubility, permeability, and bioavailability of many drug types while acting as carriers for them [96]. Moreover, the administration of peptide and protein medications has been studied using nanoparticles [97]. Studies have also been conducted on the application of nanoparticles for bioadhesion reasons. The huge specific surface area of nanoparticles suggests that they have a significant potential for interaction with biological surfaces. Bioadhesion can be produced by binding nanoparticles with diverse molecules since the contact is nonspecific. The surface of the nanoparticle must exhibit free functional groups, such as carboxylic or amine residues, in order for covalent bonding to occur [98].

Because nanodelivery methods are easily absorbed by inflammatory tissue and cells, they are able to evade fast carrier removal. Since conventional formulations are often made to encourage localised drug deposition in the GI tract, they do not offer this benefit. The local concentration of IBD therapies is increased by preferential accumulation in inflammatory tissue. In the gastrointestinal system, nanoparticles often internalise into the GI tract's epithelial cells by endocytosis or paracellular transport. M cells—specialized, differentiated epithelial

cells—play a major role in the transcytosis-mediated absorption of nanoparticles in inflammatory bowel disease (IBD). Persorption through openings or pores at the tips of the villous membranes can also result in the translocation of nanoparticles [99–101].

Particle size determines this accumulation, with smaller particle sizes having a greater impact. the impact of particle size on deposition in the colon's inflammation in the rat model of colitis caused by trinitrobenzene sulfonic acid (TNBS).[102]

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Surface charge-dependent nano-delivery systems, Apart from particle size, very little is known about how the physicochemical characteristics of drug carriers affect adherence to inflamed intestinal tissue. The impact of surface charge on colonic targeting, in particular, has been the subject of contradictory research, much of which has been based on ex vivo tissue binding tests or in vivo investigations after rectal delivery. Changing the surface charge of nano-delivery systems can affect how the nanocarriers interact electrostatically with GI tract components and, in theory, should give sick tissue selectivity. However, it should be mentioned that during GI transit, these nanoparticles may attach to other substances that change charge through electrostatic interactions (such as soluble mucins and bile acids). Therefore, in order to precisely localise medication delivery to sick colitis tissue, further pharmacological techniques are probably required, in addition to surface charge.

3.A.8.3.1 Positively charged nano-delivery systems

Numerous investigations have demonstrated that the cationic surface of nanoparticles significantly affects the deposition pattern and treatment efficacy in inflammatory bowel disease [103,104]. Because of the interaction between the negatively charged intestinal mucosa and the positively charged nanocarrier, cationic nano-delivery systems stick to the mucosal surface within inflammatory tissue[105]. Due to the many sulphate and sialic acid residues that replace their carbohydrates, colonic mucins have a negative charge[106, 107]. Since adhesion to the mucosa facilitates improved interaction with the mucosal surface for cellular absorption and drug release, it can be advantageous for GI tract targeting. When intestinal motility is elevated, as is frequently the case in IBD, it can also lessen the clearance of nanocarriers[103, 108].

Mucoadhesion is a viable tactic to improve targeting and retention of drug delivery systems in colitis since Crohn's disease is also associated with an increase in mucus production, which results in a thicker mucus layer in places that are more ulcerated[91, 106]. The effectiveness of rectally delivered clodronate-loaded nanoparticles (120 nm) incorporating cationic polymethacrylate (Eudragit RS) in the TNBS and OXA models of colitis provides evidence in favour of mucoadhesive nano-delivery methods. Clodronate by itself was not useful in experimental colitis treatment; but, when combined with cationic nanoparticles, it was possible to reduce the inflammatory response in both colitis models. It's interesting to note that instead of penetrating the mucus layer and adhering to the inflamed mucosa for uptake into epithelial cells or immune cells, the immobilisation of Eudragit RS nanoparticles in the mucus may have increased their therapeutic potential. Mucin interaction not only increased the danger of premature drug release through an ion exchange mechanism, but also hindered the transport of cationic nanoparticles through the mucus layer.[109]

3.A.8.3.2 Negatively charged nano-delivery systems

Thanks to anionic nano-delivery systems' ability to interact electrostatically with the more highly concentrated positively charged proteins in inflammatory areas, they are specifically engineered to cling to inflamed tissue. IBD patients' inflammatory colon sections have been found to contain elevated levels of transferrin and eosinophil cationic protein, in particular[110–112]. But first, the medication delivery system would have to break through the thicker layer of mucus covering the inflammatory regions in order to get to the inflamed tissue. Because they can more easily penetrate the mucus layer due to their smaller size, smaller particles tend to attach to the mucus layer better regardless of surface charge [102, 113]. Anionic nanoparticles exhibit less electrostatic interaction with mucus, which allows them to interdiffuse across the mucus network instead of immobilising as cationic nanoparticles do when they bond to the mucus. Negatively charged liposomes adhered to inflamed tissue more preferentially than neutral or cationic liposomes, with a 2-fold higher adherence than neutral or cationic liposomes, according to an ex vivo comparison of cationic, anionic, and neutral multilamellar liposomes (800 ± 50 nm) on inflamed tissue from the dinitrobenzene sulfonic acid (DNBS)-induced colitis model[114].

The concentration of DSPG used in the liposomal formulation, and therefore the negative charge density, determined the adhesion of negatively charged liposomes. There was no discernible binding of neutral or cationic particles to the inflammatory intestinal regions.; Nonetheless, compared to neutral or anionic liposomes, three times as many cationic liposomes attached to the healthy colonic mucosa. On the other hand, Lautenschlager et al. [37] evaluated the negatively charged poly(lactic-co-glycolic acid) (PLGA) nanoparticles' capacity to target inflamed human intestinal mucosa ex vivo. These nanoparticles had a size of 300 nm. Compared to positively charged chitosan functionalized nanoparticles, these anionic nanoparticles stuck to the tissue surface and shown similar bioadhesion to both inflammatory (9.4% ± 5.2%) and healthy tissue (7.4% ± 6.3%). Note that these two studies looked at the specificity of nanoparticle binding in ex vivo settings, which might not be the same as an in vivo setting for inflammatory bowel disease.

Anionic nano-delivery devices in inflammatory bowel disease have demonstrated encouraging outcomes in vivo. For instance, Beloqui et al. [93] found that, after oral gavage, anionic nano structured lipid carriers (NLCs) containing 200 nm of budesonide markedly decreased inflammation in the dextran-sulfate (DSS)-induced colitis model. Second generation solid lipid nanoparticles (SLN) with enhanced stability and drug loading capability are referred to as NLCs [115].

3.A.8.3.3 Plant based nano systems

Colon disease therapy has already demonstrated the great potential of synthetic nanotechnology-based technologies. but carry a danger of harmful consequences if used over an extended period of time. Moreover, their large-scale manufacture may be technically challenging and costly for medicinal studies [116]. Therefore, less expensive and harmless natural plants may be used to synthesise nanoparticles, which would help overcome the limitations of these synthetic ones. Direct administration of natural drugs is frequently linked with low levels of bioavailability, absorption, and solubility

[117].Nanotechnology can be used to enhance the medicinal and physicochemical properties of a natural source by decreasing the particle size, which increases the solubility of weakly miscible medications [118].

Plant-based nanosystems are constructed using several bioactive components, including proteins, lipids, and miRNA. In a published work, ginger extract nanoparticles with a negative surface charge and a particle size of 230 nm were created. These particles include large concentrations of proteins, lipids, miRNAs, and bioactive ingredients. The outcomes of the in vivo investigations showed that toxicity was not seen, intestinal repair was enhanced, colitis was lessened, and chronic colitis was prevented [119]. Other research using grape extract exosomes and broccoli extract nanoparticles in mice also demonstrated protective effects against colitis [120, 121]. When the lipids in the nanovectors made from ginger were put back together to create nanoparticles, they demonstrated high biocompatibility. These nano-vectors contained doxorubicin and were coupled with folic acid. Compared to free doxorubicin, they were able to stop the growth of colon-26 tumours in mice when tested in in vivo investigations [122].These answers suggest using plant-based nanosystems for effective and safe colon targeting.

3.B Modified release

3.B.1 Delayed release

For the colon-targeted administration of metronidazole, a drug delivery system with pH-sensitive properties and selective enzyme biodegradability was designed [123]. Pectin microspheres were made using the method of emulsion dehydration. Using the oil-in-oil solvent evaporation process, Eudragit(R) S-100 was applied to these microspheres. The in vivo investigations also included measuring the medication concentration in different GIT segments at various time points, demonstrating the formulation's potential for colon targeting. Therefore, it may be said that colon-specific medication administration can be achieved using Eudragit coated pectin microspheres.

Creating pH-sensitive polymeric nanoparticles of the natural anti-cancer drug curcumin to treat colon cancer. These nanoparticles increase curcumin's bioavailability while also lowering the dosage needed since they are specifically targeted to the colon [124]. Since the polymer degrades at colonic pH to produce selective colonic release of the entrapped medication, Eudragit S100 was used to aid in targeting. The formulation of the nanoparticles was done using the solvent emulsion evaporation process. The combined effect of three independent factors on the mesalamine tablet with compression coating. [125]

3.B.2 Sustained release systems

It is recognised that pH-dependent drug delivery systems intended for colon targeting should release the drug in the caecum first, and then in a way dictated by the delivery system in order to guarantee optimal therapeutic efficacy. Instead of releasing the drug in the stomach and small intestine. For instance, the delivery system has to guarantee the drug's prolonged release in the colon, as opposed to its instantaneous release, if the maximum portion of the colon is impacted. Once the delivery device reaches the colon, sustained release of the medicine is frequently advantageous. If the medicine is released all at once and immediately, High amounts of the locally released medication may produce local

irritations since they affect on both healthy and inflammatory tissues.

There are two types of sustained release dosage forms for colon targeting: single-unit and multiple-unit dosage forms. Single-unit dosage forms consist of matrix tablets covered with pH-dependent polymers and prepared with extended-release polymers. The core matrix tablet delivers the medication continuously into the colon when the coating dissolves in the upper intestine. The multiple-unit dose forms are made up of several single-unit dosage forms that are included in tablets or capsules and have the shape of pellets, granules, or microspheres. Every particle in the tablet or capsule acts as a separate unit when it disperses to release its contents.

3.B.3 Controlled release

The creation of oral sustained release medications in the 1940s and early 1950s served as the impetus for the field of controlled release science. Initially, the controlled release of fertiliser in the 1970s and marine antifoulants in the 1950s were developed with a single purpose in the field of soul science. The advancements in pharmacology and pharmacokinetics have elucidated the significance of medication release rate in ascertaining the efficaciousness of therapeutic interventions. This serves as the impetus for the creation of controlled release.

The dose formulations with modified release are brand-new. Rhozes creates mucilage-coated tablets for the first time about 900 A.D. The tenth century saw a widespread adoption of this technology by European nations, who produced tablets coated in gold, silver, and pearl, which altered the rates of medication release. developments in coating technology in the late 1800s, including enteric and sugar coating for pills and tablets. About 1938, the second medication was added to the sugar coating layer after the additional coating evolved to the enteric coating of tablets. Nonetheless, Lipowski was granted the first patent for an oral sustained release preparation; his formulation included tiny coated beads that released the medication gradually and continuously. Blythe subsequently improved this concept and introduced the first commercially available continuous release product in 1952. Over the last 30 years, more attention has been dedicated to this sector due to the growing complexity involved in the marketing of new drugs and the recognition of the many benefits of controlled release drug delivery systems (CRDDS). These days, oral controlled drug administration is one of the most popular methods for delivering medications, especially those with short biological half-lives and high water solubility. In addition to oral administration, several drug delivery methods such as transdermal, ophthalmic, vaginal, and parenteral are used [126].

3.B.3.1 Single mechanism controlled

3.B.3.1.1 Probiotic approach

The probiotic method is among the most recent strategies for colon targeting. Three elements—the probiotic strain, the microbially digestable carrier, and the triggering temperature—are ideal for this strategy. Inactive microflora such as Lactobacillus species and Bifidobacterium are examples of probiotic strains. These strains become active at body temperature, begin to break down the carrier, and eventually release the medication where it is wanted. The reason this method works so well for colon medication delivery is that these characteristics are unique to the colon. This method of encapsulating diclofencac sodium in matrix tablets with guar gum was used by Ghosh et al. They were successful because the probiotic-containing formulation showed a better medication release than the drug in the carrier alone [127].

3.B.3.1.2 Time dependent approach

The fundamental idea behind this strategy is that the medication is released from the dosage form at the site of action at the appropriate time and in the appropriate amount following a predefined lag period [128]. Because the amount of time needed for the formulation to reach the stomach was not anticipated, both big single-unit formulations and tiny multiple-unit formulations require three to four hours to travel through the small intestine. This duration is independent of the particle size, density, or content of the meal [129]. The ideal formulation would not be impacted by individual variations in the small intestine's pH, the stomach's pH, or the presence of anaerobic bacteria in the colon at the delivery site[130]. This formulation consists of three parts: an inner semipermeable polymer membrane with a plasticizer that allows water inflow but inhibits drug outward diffusion; an outer enteric coating that dissolves above pH 5.5; and a central core containing a drug and swelling excipients [131]. The solid dosage form in this approach is coated with various sets of polymers, and the thickness of the outer layer controls how long it takes for the polymer to disperse in an aqueous environment.

A time-dependent strategy was used in the development of the diclofencac sodium (DS) colon drug delivery system. This involved coating diclofencac sodium tablets with PEG 400 acting as a channelling agent, ethyl cellulose in ethanol solution cooling diethyl phthalate as a plasticizer. The thickness of the ethycellulose coating layer was the main factor influencing the lag time of DS release. The lag time of DS release is lengthened by increasing the coating layer's thickness [128].

3.B.3.1.3 Microbial triggered approach

This method's fundamental idea is that the colon's microorganisms will break down the coated polymers on the drug delivery system, releasing the medication into the colonic area [132,133]. The colon's microflora, which ranges from 1011 to 1012 CFU/ml, is mostly made up of anaerobic bacteria such as Ruminococcus, Bacteroides, Bifidobacterium, Eubacteria, Clostridium, and Enterococci[134].This strategy differs from the probiotic strategy in that the probiotic strategy provides microorganisms from outside sources to support the internal flora. The colon's bacterial enzymes have an alternate substrate in the form of polysaccharides. Since many of these polymers are already found in human diets or are employed as excipients in medication formulations, they are widely accepted to be safe. Numerous polysaccharides, including chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose, sodium alginate, and locust bean gum, have already been investigated for their potential as colon-specific drug carrier systems [135,136].

3.B.3.1.4 Osmotic controlled drug delivery

Alza Corporation unveiled OROS-CT, a cutting-edge controlled drug delivery technology that targets the medication locally to the colon. A single osmotic unit or up to six push pull units, each measuring 4 mm in diameter and housed inside a hard gelatin capsule, are both included in the OROS-CT system. In this technique, the drug layer and the osmotic push layer are encircled by a semipermeable membrane. An

aperture is drilled through the membrane next to the drug layer. After the OROS-CT was ingested in the gelatin capsule, the push-pull unit was dissolved. The push-pull mechanism of the impermeable medication's enteric coating inhibits the drug's absorption in an acidic

environment, therefore there is no drug release in the stomach. The medication's coating dissolves in the push pull unit's small intestine at pH values higher than 7, causing the osmotic push compartment to expand from water absorption and solidify into a gel inside the drug compartment. By increasing the osmotic push unit's size and regulating the flow of water across the semi-permeable membrane, that gel was liberated. In order to avoid medication administration in the small intestine, this push-pull device was created for the treatment of ulcerative colitis with a 3–4 hour post-gastric delay.

The medicine may be delivered into the colon via OROS-CT units for a maximum of 24 hours, during which time it can maintain a steady release rate for four hours. This was a novel approach to administering the medication to the colon, and several stability tests and in-vitro/in-vivo assessments could be carried out in CDDS [137].

3.B.3.1.5 Pressure controlled drug delivery system

The propulsion of intestinal contents is caused by the peristalsis of the intestines and the contraction of the stomach. The colon's increased luminal pressure conditions are caused by these peristaltic motions. Based on the aforementioned principle, a pressure-controlled medication delivery device was designed. The pressure's duration and intensity change in response to the visceral organs' muscles contracting [130, 131]. It is made up of suppositories in the form of capsules covered in a water-insoluble polymer, such as ethyl cellulose (EC). Because the capsule's basis liquefies at body temperature, when taken orally, they act like balloons made of ethyl cellulose [24, 46].

The ethyl cellulose membrane's thickness is a critical factor in the capsule's breakdown. The capsule's density and size may also have an impact on the system. The ideal capsule wall thickness ranges from 35 to 60 μm. Due to the colon's re-absorption of water, the luminal material in the colon is more viscous than in the small intestine. As a result, medication dissolution in the colon may be a challenge for colon-specific oral drug delivery systems. Three to five hours were seen to elapse between the administration of the pressure-controlled capsule and the onset of drug absorption in the human volunteer. Additionally, it was discovered that capsule breakdown occurs when luminal pressure increases [28,47-49,129].

3.B.3.1.6 pH controlled

To prepare pH-sensitive matrix pellets for colon-targeted drug administration, extrusion spheronization and pelletization have been employed [138]. The quantities of Eudragit® S, citric acid, and spheronizing time were the three independent variables that the authors examined in relation to pellet size, shape (roundness and aspect ratio), and drug release using a central composite design.

Using ibuprofen as a model medication and enteric polymers Eudragit® S and Aqoat AS-HF, Nykanen et al. [139] developed site-specific drug release systems for the colon or the lower portion of the small intestine. The

purpose of this work was to determine whether adding organic acids as excipients may affect the pace at which drugs released from enteric matrix granules. It was determined that while the addition of an organic acid to a formulation slowed the model drug's release in vitro, there

was no discernible difference in the in vivo experiments.

3.B.3.1.7 Enzyme controlled systems

Because of the distinct enzymatic capabilities of the colonic microflora, the microbially controlled method is the most advantageous and promising of all the colon targeting strategies. It makes more targeted treatment possible, regardless of GI tract pH fluctuations [28]. The majority of colonic bacteria are anaerobic, and they release enzymes that may break down substrates like proteins and carbohydrates that are not broken down in the upper gastrointestinal tract [29]. The colon contains the following enzymes:

3.B.3.1.7.1 Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.,

3.B.3.1 .7.2 Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucoronidase sulfatase etc.,

Compared to previous techniques, the use of biodegradable polymers for colon specific medication administration appears to be a more site-specific strategy due to the presence of biodegradable enzymes exclusively in the colon. When the medication reaches the colon, these polymers are able to transport it there while protecting it from the conditions of the stomach and small intestine. Their molecular weight decreases as a result of enzymatic or polymer breakdown, microorganism absorption, or polymer breakdown. Targeting prodrug delivery may be done in three different ways: 1) by targeting a specific enzyme; 2) by targeting a specific membrane transporter; and 3) by using systems based on polysaccharides [30].

3.B.3.2 Multiple mechanisms controlled

As previously mentioned, formulation techniques that depend on a single physiological signal (pH, transit duration, or microbial enzymes) for the administration of colonic drugs may exhibit significant inter- and intra-patient variability in their targeting efficacy [143]. Therefore, it has been demonstrated in recent years that the strategy of integrating drug release mechanisms based on many physiological stimuli is more dependable [144]. These combination or multifaceted systems can be categorised as sequential or parallel trigger systems based on their architecture. The drug release mechanism of a sequential trigger system unfolds layer by layer, starting from the outermost layer and working its way into the centre, using several matrices divided into distinct layers [145].

In this way, drug release depends on the physiological stimulus activating each layer in turn. A parallel system, in juxtaposition, involves many drug release mechanisms operating concurrently. Independent trigger mechanisms are usually activated simultaneously in parallel systems by combining them into a single layer [144]. This means that drug release should still happen via the other routes even if one fails owing to physiological variability (for example, failing to reach a pH-mediated dissolving threshold or be metabolised by intestinal flora). Parallel systems therefore stand as the most dependable approach to the creation of novel colon-targeted medications. In terms of colonic drug

administration, multistimulus coatings for tablets, capsules, and pellets have had the most translational success to yet [144, 146]. Oral nanomedicines tuned to many stimuli may have

potential, but these systems are uncommon and have not yet shown meaningful outcomes in human trials [147–150]. It is essential to take oral material safety into account while creating new targeted formulations. The US Food and Drug Administration (FDA) has generally recognised as safe a number of materials currently used for colonic delivery, such as polysaccharides for pH-triggered release, Eudragit® polymers for microbiota-triggered release, and hydroxypropyl methylcellulose (HPMC) for time-triggered release [151]. A number of indication-specific factors, including the drug to be administered, the condition to be treated, and any pathophysiological consequences that could change the GI environment, will determine which colon-targeting approach is best for new medications. Systems that depend on physiological cues that are changed in particular illness states can be something developers want to stay away from. For example, time-triggered combination systems and microbiota may be less effective in treating Clostridium difficile infections linked to antibiotics. Due to the likelihood of colonic dysbiosis and shortened gastrointestinal transit times in these individuals, coatings could not be completely broken down by bacteria or experience long enough lag periods to allow for colonic drug release [152].

3.B.3.2.1 pH- and microbiota-triggered combination systems

3.B.3.2.1.1 Phloral®

The first dual triggered colonic medication delivery device to be commercially launched was the Phloral® system. Comprising a uniform blend of Eudragit® S and resistant starch (amylose and amylopectin), it is a single layer coating system [153,154]. The two parts work in tandem with each other and can offset each other's activity if one of the trigger mechanisms malfunctions because of their separate trigger mechanisms [144]. The Eudragit® S mechanism in this system makes sure that the tablet's integrity is preserved during its passage through the small intestine and stomach. It also controls the swelling of the starch by acting as a structural agent. In contrast, resistant starch acts as a substrate for the microbiota in the colon, offering a backup plan for initiating medication release in the event that Eudragit® S's essential pH threshold is not reached. Regardless of the patients' eating condition, Phloral® technology has in fact demonstrated good effects in the treatment of inflammatory bowel disease [144,155]. Additionally, Phloral® has been effectively used to treat obesity [157] and Clostridium difficile infection [156].

3.B.3.2.1.2 OPTICORE™

A combination method called Shot, which stands for OPTImised COlonic RElease, was created lately with the goal of quickly releasing medications in the ileocolonic area, which has larger fluid volumes than the mid-to distal colon [158,159]. The foundation of the system consists of two coating layers: the base layer is made up of a buffering salt and a neutral enteric polymer called Eudragit® S. An outer Phloral® coat then encircles this layer [159]. Since the base layer is alkaline, it could be necessary to add an extra HPMC layer to the formulation of acidic medications in order to separate them from the alkaline base layer. By speeding up the

Phloral® coating's disintegration, the OPTICORE™ technology produces rapid ileocolonic medication release. The formulation dissolves the enteric base layer and allows

luminal fluid to reach the distal GI tract through holes in the Phloral® coating. The Eudragit® S component of Phloral® dissolves quickly as a result of this dissolution, which also causes a rise in pH, buffer capacity, and ionic strength at the inner surface of the remaining Phloral® layer [160–162]. Because the OPTICORETM device can administer 5-ASA to the region of colonic inflammation selectively, it has shown to be a successful therapy for IBD to date [146]. AsacolTM 1600 mg, a commercial therapy for IBD licenced in Europe following successful completion of Phase III clinical studies, has OPTICORETM as its colon-targeting mechanism [163]. Notably, the multi-stimuli system makes it possible to provide 1.6 g of 5-ASA orally, the greatest amount of medication ever approved for oral administration, by colonic delivery. Since 5-ASA is acidic, OPTICORE^{TM}'s base layer buffering helps to speed up breakdown via the Phloral® layer, causing a quicker colonic release. Having access to such high dosages of 5-ASA lessens the amount of medicine that patients must take. Another acidic medication, metronidazole benzoate, has been studied for use in the treatment of *Clostridium difficile* infection using the OPTICORE^{TM} technology through ileocolonic administration [164].

3.B.3.2.2 pH- and time-triggered combination systems

Although they are less frequent, various pH- and time-dependent parallel systems have been studied. One such instance is the coating of 5-ASA pellets with or without inulin by combining two enteric polymers (Eudragit® S and L) with a time-dependent polymer (Eudragit® RS) [165]. The combination was examined at various ratios and coating thicknesses; in vitro investigations revealed that the 16:64:20 w/w ratio of Eudragit® S:L:RS at 15% coating thickness was optimal for colon-targeted medication delivery. The coated pellets exhibited noticeably superior therapeutic effects than the Pentasa product (pH-only triggered) in a rat model of ulcerative cornea. It should be highlighted that there was no discernible therapeutic difference between the inulin-containing and non-inulin-containing pellets, indicating that the extra therapeutic advantage was provided by the combination as well as the time- and pH-triggered mechanisms. Using a separate method, tablets of flurbiprofen were compress-coated with both Eudragit® S100 and sodium alginate (SA) [166]. In contrast to using SA alone, the pH-dependent polymer in the coating inhibited drug release and prevented SA from swelling in the stomach area when tested in healthy individuals. This led to a greater concentration of the medication in the colon. These results were supported by in vivo X-ray imaging, which also demonstrated that the tablets' structural integrity was maintained during their passage to the colon.

3.B.3.2.3 Microbiota- and time-triggered combination systems

Although colonic drug delivery triggers that are time- and microbiota-dependent have been thoroughly studied, it is uncommon for these triggers to work in tandem as parallel processes [167]. Microbiota-sensitive triggers that are often utilised include resistant starch, guar gum, pectin, and chitosan. Time-dependent processes can be of the reservoir, capsular, or osmotic types; the best studied of these uses reservoir

systems that employ diffusive or erodible polymers, as HPMC [143]. Utilising the GI swelling of HPMC and the microbial digestion of pectin, the combination of pectin and HPMC

(80:20 ratio) for tablet coating is an example of a parallel system [168]. The coating was demonstrated to consistently transport cargo to the ascending or transverse colons of six human subjects in good health during a pilot trial. In another study, the release of paracetamol from injection-molded capsule shells containing high-amylose starch and HPMC was examined using both in vitro and ex vivo models [169]. The quick drug release in the colonic environment is caused by the microbiota's efficient metabolism of starch, while the presence of HPMC allows for a time-controlled drug release as it swells. It has been proposed that the polymer ratios, shell thickness, and shape might all be adjusted to optimise medication delivery. Based on the ability to customise dosage form shape to enable indication-specific medication release, these findings may serve as a model for the development of novel pharmaceuticals that might benefit from release in certain colonic areas.

3.B.3.2.4 pH-, microbiota- and time-triggered combination systems

A novel colon-targeted medication delivery system combining three separate trigger mechanisms was proposed by Moutaharrik et al. in a recent study [170]. An inner, swellable, time-dependent cellulose derivative (HPMC, or hydroxypropyl cellulose, HPC) makes up the two layers of this coating, which are encircled by a combination of a pH-dependent polymer (Eudragit® S) and a microbiota-triggered polysaccharide (high-amylose starch, Amylo N460). In vitro and ex vivo models of the cellulose derivatives Eudragit® S and Amylo N460 demonstrated consistent colon-targeting efficacy, indicating the effectiveness of this first instance of a triple colon-targeting mechanism. In light of these positive first findings, the system's further development in in vivo models seems promising.

3.C. Targeted drug delivery systems

Both the surface and the size of the nanoparticle have an impact on the drug's accumulation in the colon's diseased region. By interacting with certain receptors or antigens that are overexpressed by immunological and colonic cells during ulcerative colitis or colorectal cancer, the medication can be specifically targeted to the affected region. Therefore, ligands such as antibodies, mannose, lectin, hyaluronic acid, and folic acid can be coupled with the surface of the nanocarriers for active targeting at the location of the illness [171]. These ligands enable the nanocarriers to bind to the precise adhesion molecule, protein, or receptor at the illness site, improving the internalisation and cell-specific adherence of the nanoparticles.
This results in a decrease in side effects and an increase in effectiveness since the medicine accumulates highly at the target location. PLGA nanoparticles conjugated with aptamer and loaded with apigenin were developed for the treatment of colorectal cancer [172]. The aptamer on the surface of the nanoparticles targets the biomarker agent (adhesion cell of epithelial) overexpressed on the cell surface of colorectal cancer. The in vivo trials' findings showed improved effectiveness, little cytotoxicity, and significant colon accumulation. Similarly, tripeptide-based PLGA and hyaluronic acid nanoparticles have been demonstrated to mitigate colitis [173].

3.C.1 Active Targeting

To get the necessary biofate for this type of targeting, the carriers are modified. The following categories can be used to further

group active targeting: [174] First order targeting, or organ compartmentalization, Second order targeting is the term for cellular targeting. Third-order targeting is the term for intracellular targeting.

3.C.1.1 Organ compartmentalization

Dissemination of the drug-carrier combination can occasionally be restricted to a chosen region, tissue, or organ's capillary network. It is possible for lymphatics, multiple holes, peritoneal holes, lungs, cerebral ventricles, joints, eyes, and other structures to undergo this kind of vectoring. Tissue macrophages remove liposomes less than 150 nm, but automatic lung filtration rapidly removes liposomes larger than 10 μm[174].

3.C.1.2 Cellular targeting

Cellular or second order targeting is the process of directing the medicine towards a certain cell type, such as cancer cells, while blocking its distribution to healthy cells [174].

3.C.1.3 Intracellular targeting

It entails vectoring the medication to the targeted cells' predetermined intracellular locations. Examples of intracellular targeting include drug delivery to the nucleolus, ligand-mediated drug complex entrance into a cell by endocytosis, and lysosomal carrier disintegration followed by intracellular drug release[174].

3.C.2 Passive Targeting

Drug transfer via systemic flow is typically shown as a passive process. The body's typical response to a drug's or drug-vector complex's physicochemical properties causes drug vectoring at a predetermined place. It gathers at the target place by taking advantage of the vector's typical biodissemination course[174].

3.C.3 Dual Targeting

The dual targeting idea selects a drug vectoring agent type that possesses anticancer action in addition to the drug. In this way, the entrapped anticancer medicine and the entrapping carrier work together to have an anticancer impact[174].

3.C.4 Physical Targeting

Physical targeting refers to specific medication delivery that is planned and verified at the external level with the use of physical tools. The bio-environment's characteristics are either used to direct the transporter to a certain location or to cause a specific arrival of its material. An example would be temperature-sensitive liposomes that were created and directed towards cancerous cells. The drug is delivered to the tumour site by serum segments, usually lipoproteins, which causes the encapsulated drug to release when phase transitions.[174]

3.C.5 Double Targeting

A suitable balance between management of the location and the period of medication release is optimised in the twofold targeting strategy.

First, the drug is released locally at the designated locations, and the spatial selectivity is amplified to increase the selectivity. Consequently, double targeting is defined as the combining of two notions into one, making it dual[174].

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3.C.6 Inverse Targeting

This idea is known as inverse targeting as it is used to avoid the reticuloendothelial system's passive absorption of colloidal transporters, which results in the aversion of a carrier's biodistribution propensity. By infusing a significant volume of blank colloidal carriers or macromolecules, this type of targeting is achieved. This results in the RES being blocked, which compromises the host defence mechanism. Altering the vectors' surface charge, hydrophilicity, surface stiffness, orientation, and size to correspond with the desired biofate is another suitable strategy[174].

3.C.7 Combination Targeting

Combination targeting is made up of polymers, transporters, and targeting substances with certain structures that may help deliver drugs to pre-targeted locations. For instance, proteins and peptides can be combined with certain polymers, such polysaccharides, to change them in a way that modifies their physical characteristics and makes them appropriate for targeting to specific organs, compartments, or tissues[174].

3.C.8 Receptor or Ligand targeting

Different ligands (such as antibodies, folic acid, peptides, and hyaluronic acids) are used by the ligand/receptor framework based on certain particular receptors/proteins at the targeted region. It offers site specificity and improves GIT stability in conjunction with pH-dependent systems. Conjugated liposomes, as opposed to unconjugated liposomes, demonstrated increased internalisation of cellular activity when prepared using the anti-transferrin receptor (Harel et al., 175). In addition, compared to the normal mucosa, anti-transferrin receptor coupled liposomes exhibited a higher dispersion inside the inflammatory mucosa, resulting in a more pronounced aggregation at the inflammation site. Additionally, Zhang et al. [176] created a curcumin-based self-micro emulsifying drug delivery framework that was adjusted by folate to increase the drug's solubility for colon delivery. Their findings confirmed that this delivery method may efficiently enter the colon and release the medication quickly. Hyaluronic acid-conjugated PEGylated multi-walled carbon nanotubes with gemcitabine (GEM/HAPEG-MWCNTs) were developed by Prajapati et al. [177] with the specific goal of directly targeting colon cancer. The exterior layer of PEGylated Multi-Walled Carbon Nanotubes (MWCNTs) was conjugated to hyaluronic acid. Based on enhanced proliferative activity, this approach showed promising results for viable colon malignant development. Planning dosage forms is becoming more and more difficult these days due to the extensive use of innovation in measuring structures to manage various angles.

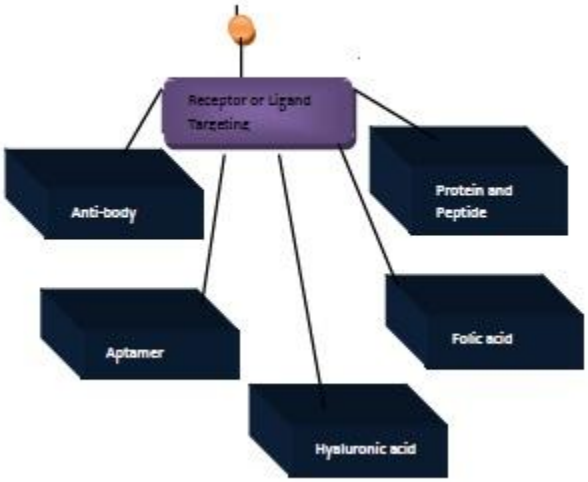

Fig. 2 Receptor or Ligand Targeting

3.C.8.1 Protein and peptide targeting [178]

Research integrating contributions from gastroenterologists, polymer and material scientists, pharmaceutical scientists, technologists, and polymer and material scientists is necessary for targeted distribution to the gastrointestinal system. Drugs with systemic activity as well as those that operate locally must be delivered through the intestines [179, 180]. Oral administration of peptides is of special interest, and it is thought that the colon might offer an optimal absorption location for these molecules. We will critically evaluate the many targeting techniques that pharmaceutical scientists can use to deliver medication to particular sites in the gastrointestinal system. Since many of the delivery issues are similar to those in the delivery of pharmaceuticals, delivery methods and targeting agents that are being developed for medication delivery may also be used for vaccination distribution. This study included recent advancements in the creation of oral antigen formulations [181–183].

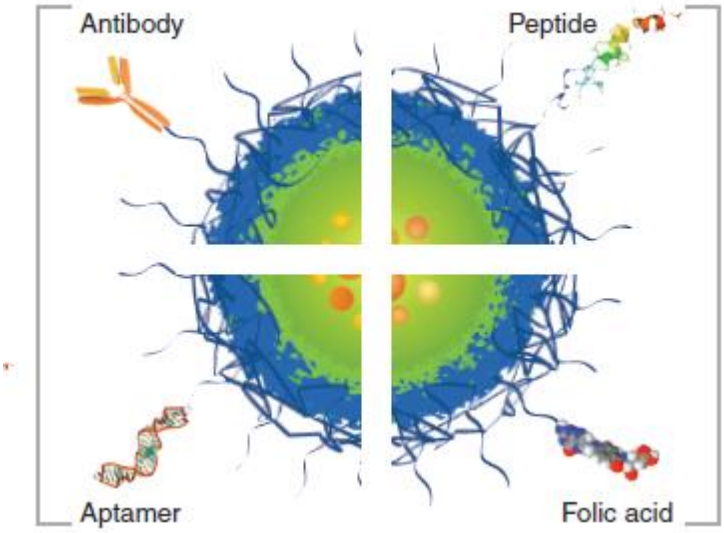

Fig. 3 Ligand Binding Sites

3.D Integrated drug delivery system

3.D.1 COLAL-PRED system

Alizyme developed COLAL-PRED, a unique gastrointestinal medication, to treat ulcerative colitis (US). Prednisolone sodium metasulfobenzoate, an authorised generic steroid, and Alizyme's proprietary colonic drug delivery technology, COLAL, have been combined to cause it. It is a UC medication that effectively reduces inflammation without having the negative effects associated with steroids.

There aren't any rival goods with the similar product characteristics either on the market or in development right now. A "safe steroid" medication with COLAL-PRED's profile would be a huge improvement in UC treatment. The coating on COLAL-PRED is only broken down by locally present bacteria in the colon. This minimises steroid-related adverse effects by delivering prednisolone topically to the colon without causing considerable systemic exposure [46].

3.D.2 PULSINCAP System

R.R. Scherer International Corporation, located in Michigan, US, developed this method specifically to target capsules that are insoluble in water. This formulation has a swellable hydrogel plug in the seal coat that encloses the drug reservoir inside the capsule body. When the capsule comes into touch with the dissolving fluid at a specific lag time, swelling occurs and the medicine releases quickly. The hydrogel plug was designed using a variety of polymers with varying grades and viscosities, such as polymethyl methacrylate, hydroxyl propyl methyl cellulose, poly vinyl acetate, and polyethylene oxide. The length and site of insertion of the plug, which was examined in human volunteers, determined the lag time of the Pulcinicap capsule [137].

3.D.3 Chronotropic system

With this method, a medicine is released after a predetermined lag period and is surrounded by a soluble barrier layer made of a hydrophilic polymer HPMC-coated drug reservoir in the core. The coating thickness and viscosity grade of the HPMC regulated the coating of additional enteric coating film outside that layer to overcome the variability of stomach emptying and the drug's lag time [137].

3.D.4 Time clock system

In this method, the solid dosage form is coated using an aqueous dispersion. To enhance adherence to the core, a water soluble polymer is added to a hydrophobic surfactant layer in this coating. When the system comes into touch with dissolving fluid, it redisperses and becomes rehydrated as a result. The lag time in this method might be adjusted by adjusting the coating material's thickness proportionately. The impact on the lag time may vary between high- and low-calorie meals, according to research conducted with gamma scintigraphy. The drug release had a mean lag time of 5.5 and 5.7 hours, respectively [137].

3.D.5 PORT system

Therapeutic System Research Laboratory, located in Arm Arbour, Michigan, USA,

invented this approach. It uses an osmotically active agent and an insoluble drug plug covered in a semi-permeable capsule membrane. A method for administering methylphenidate to school-age children has demonstrated a strong in-vitro and in-vivo association for treating attention deficit hyperactivity disorder in humans (ADHD). [46]

3.D.6 CODES^{TM}

The purpose of this technique was to prevent viscero-colonic issues related to pH or time. A combination of pH-dependent and microbially driven CDDS is called CODESTM. It was created using a special triggered mechanism employing lactulose for site-specific release in the colon. The composition of this system consists of lactulose in the core, an acid soluble coat of Eudragit E, and an enteric substance, Eudragit L, applied on top. The outermost layer of Eudragit L shields the final pill from dissolving in stomach contents, while the inner layer of Eudragit shields the mixture as it travels through the small intestine's alkaline pH. The breakdown of lactulose is initiated by microbes as soon as the tablet reaches the colon. The pH of the environment around the system decreases as polysaccharides (lactulose) breakdown into monosaccharides (organic acids), which facilitates the dissolution of the acid-soluble coating and subsequent medication release [46].

3.D.7 Pulsatile colon delivery

Pulsatile drug delivery systems (PDDS) fall into two categories: time-controlled and site-specific. The gastro intestinal tract's environment, including its pH, enzyme content, and pressure, affects how drugs are released from site-specific systems. Time-controlled DDS, on the other hand, don't depend on the biological environment. Only the system has control over the release of the medicine. Release-controlling layers are placed on top of drug-containing cores to produce time-controlled pulsatile delivery. [184, 185]

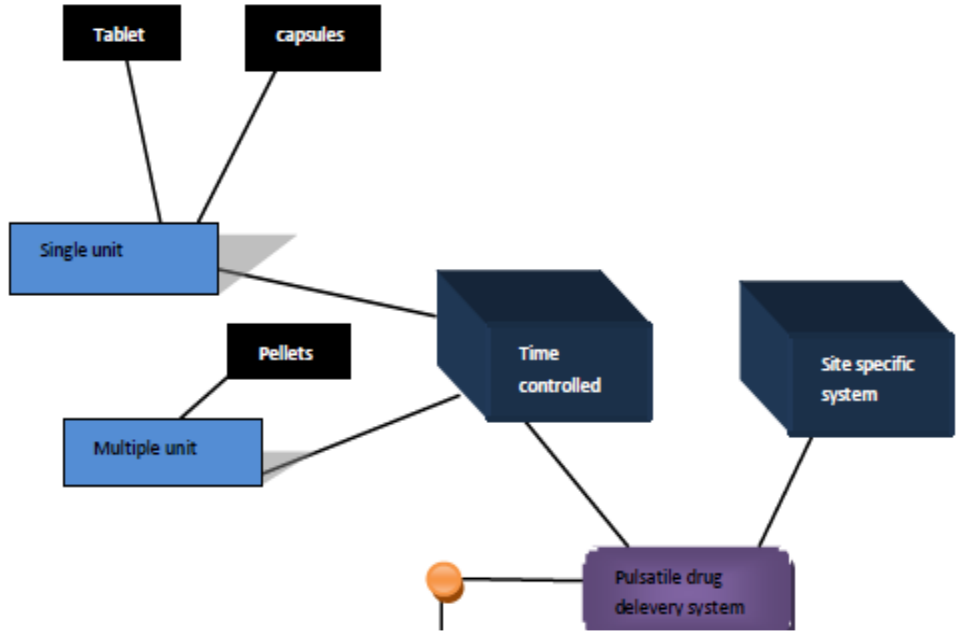

Fig. 4 Pulsetile Drug Delevery System

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4. Challenges and Future Directions:

Preserving the formulation during its transit through the stomach and about six metres of the small intestine is the most significant obstacle in the oral colon specific medication delivery strategy. Researchers discovered a number of fresh ways that serve as a cure for earlier ones after investigating the shortcomings of numerous tactics. Currently, a number of strategies have been researched to achieve colon site specificity. When creating a colon-specific medication delivery system, choosing an appropriate carrier and/or coating system is a crucial step.

The preclinical and clinical stages of numerous current promising formulations are now underway, and after meeting the FDA's stringent safety and effectiveness requirements for patients, they may eventually find their way onto the market, providing a bright future for colon medication delivery. The implementation of methods or procedures to ascertain the disease's molecular expression profile from patients and categorise them based on their

genetic makeup, the disease's stage of development, and potential target molecules will be a problem in the future. Everything mentioned above will help ensure that the most potent medications are administered logically and in precisely targeted formulations.

5. Conclusion:

The field of colonic drug administration is experiencing a period of exciting advancements in understanding the distinct physiology of the colon, as well as efficient formulation techniques and medications. oral intestinal medication administration, providing chances for more effective local illness therapy or targeted regulation of newly identified systemic targets. Subsequent investigations may build on these formulation techniques to create formulations that are indication-specific, with drug release triggers that are tailored to certain patient populations or based on pathophysiology. The development of physiologically appropriate instruments for evaluating the PK of rectal formulations and the standardisation of in vitro and in vivo models for PK evaluation of oral colon-targeted medications represent more areas of potential. Lastly, in order to encourage others to embrace these techniques, additional research demonstrating how cutting-edge technologies may be used to shorten the time and cost needed to produce colon-targeted medications would be helpful. Recent developments in the design and development of colon-targeted medications provide significant opportunities for the translation of safer and more effective therapies into clinical practice.

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