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A Review on Colon Drug Delivery

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ABSTRACT

Colon-targeted drug delivery systems have attracted a lot of interest as potential vehicles for the local treatment of colonic diseases with fewer systemic side effects as well as for the improved oral delivery of many therapeutics susceptible to enzymatic and acidic degradation in the upper gastrointestinal tract. [1]The significance of colonic drug delivery as a noninvasive delivery method for macromolecules is highlighted by recent growth in the worldwide pharmaceutical industry for biologics and rising desire for a more patient-friendly drug administration system. Because they are painless and self-administerable, colon-targeted drug delivery devices for macromolecules can offer therapeutic advantages such as improved patient compliance and lower costs. Therefore, a variety of techniques can be used to achieve more effective colonic medication administration for local or systemic pharmacological effects [2]

Keywords: Colon; noninvasive drug delivery; Inflammatory bowel diseases; colorectal cancer; protein

INTRODUCTION

In other words, neither drug release nor absorption should take place in the stomach or small intestine, and neither the bioactive agent nor the dissolution site should be degraded. Instead, the drug should only be released and absorbed once the system reaches the colon. The colon specific drug delivery system (CDDS) is helpful for treating diseases of the colon and large intestine, such as ulcerative colitis, diarrhoea, and colon cancer, as well as for oral delivery of proteins and peptide drugs (which are broken down by digestive enzymes in the stomach and small intestine) [3]. if the peptide is protected The colon can be used for both local and systemic medication administration ration. Topical therapy of inflammatory bowel disease is possible with local administration. However, treatment can be significantly more effective if the medications are delivered directly to the colon, reducing systemic adverse effects.[4]

Local treatment of bowel disorders such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic distribution of protein and peptide medications is extremely desirable with targeted drug delivery into the colon. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon, which means that drug release and absorption should not occur in the stomach or small intestine, and the bioactive agent should not be degraded in either dissolution site, but only released and absorbed once the system reaches the colon. The colon is thought to be an appropriate absorption location for peptides and protein medicines because to the following factors: I reduced diversity and intensityAmong all the administration methods investigated for the creation of controlled release systems, the oral route has received the most attention and success. This is owing, in part, to the convenience of administration, as well as the fact that gastrointestinal physiology allows for greater dosage form design flexibility than most other routes. The scientific framework required for the development of a successful oral controlled drug delivery dosage form includes an understanding of three components of the system, such as the medication's physiochemical properties. gastrointestinal anatomy and physiology, as well as dosage form characteristics Controlled drug delivery system that delivers the drug continuously for a defined amount of time with predictable and reproducible kinetics and a known mechanism of release."

Need of Colon Targeted Drug Delivery System

Reduced dosage and less adverse effects across the body to allow for direct treatment of the condition. A formulation tailored to the colon could be utilised to increase medication distribution. It should be regarded as helpful in the treatment of colon diseases. Both local and systemic drug distribution could take place in the colon. A topical medicine is used to treat irritable bowel illness, including Crohn's disease and ulcerative colitis. Sulphasalazine and glucocorticoids are frequently used to treat inflammatory disorders If drugs were particularly targeted to the colon, a variety of other significant colon illnesses, such as colorectal cancer, may be treated more successfully. Therapeutic drugs, such as those that are polar and/or susceptible to enzymatic and chemical breakdown in the upper GI tract, which is greatly controlled by hepatic metabolism. [5]

Approaches to Colon Target Drug Delivery

Main Methods for Drug Delivery to the Colon:

Colon Drug Delivery using pH-Sensitive Polymer Coating:

The pH-dependent CTDDS profit from the well accepted notion that the pH of the human GIT gradually increases from the stomach (pH 1-2, which rises to 4 during digestion), small intestine (pH 6-7) at the point of digestion, and the distal ileum (pH 7-8). When opposed to capsules or pellets, the release of the active ingredient is delayed by the coating of tablets with pH-sensitive polymers, which also shields the ingredient from stomach acid. Lower pH levels are maintained in the stomach and proximal small intestine by the polymers used for colon targeting. The most popular method for assessing how well pharmacological agents work in the gastrointestinal tract is gamma scintigraphy.

Delayed-Release Drug Delivery to Colon:

This technology is based on the notion that the medication will release at the selected time and location following a predetermined lag period. The colon targeted drug delivery system's lag time is considered acceptable. Medication delivery time to the colon is influenced by the coated polymer or polymer blend. The colon inflow time of the dose form cannot be properly predicted because everyone's gastric emptying rate differs. Polymers used in this delayed-type system include Microcrystalline Cellulose (MC), Hydroxyl Propyl Methyl Cellulose (HPMC), Hydroxyl Propyl Methyl Cellulose Acetate Succinate, Hydroxyl Ethyl Cellulose (HEC), Ethyl Cellulose (EC), Lactose/Bionic acid, and others. The following are the system's drawbacks:[6]

• Gastric emptying time varies significantly between subjects or is affected by the type and amount of food consumed.

• The drug's gastrointestinal transit is influenced by peristaltic movements or contractions in the stomach.

• This effect is most noticeable in IBD, diarrhoea, and ulcerative colitis.

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Prodrug Approach:

Microbially Triggered Drug Delivery: The technique is based on the notion that the polymers coated on the dosage form disintegrate due to the colon's flora[7] The microflora in the colon is complex, and it is responsible for the fermentation of intestinal substrates such polysaccharides. These microorganisms create enzymes that metabolise substrates such as polysaccharides, carbohydrates, and proteins,leading in digestive escape in the upper GIT. Pectin is used in high quantities to prevent medication from being released from dosage forms. When combined with chitosan and HPMC, it was proven to be especially useful in limiting medicine release in the stomach and efficiently releasing the drug in the colon. Microbiologically degradable Prodrugs are pharmacologically inactive substances that transform either spontaneously or enzymatically.

A. Azo-Polymeric Prodrugs: This novel strategy to colonic administration makes use of a variety of polymers as drug carriers. Sub synthetic polymers are used to join drugs and polymers with an azo group, commonly known as azo linkage. The polymer crosslinking with an azo aromatic group when coated protects the drug against degradation in the upper GIT, as does the release of these azo bonds in the colon, where the azo bonds were broken. Segmented polyurethane-coated budesonide pellets are an example of an azo polymer-based drug delivery method.[8]

Approach Based on Polysaccharides:

Because of their ease of availability, abundance, and low cost, naturally occurring polysaccharides are extensively employed for drug targeting. They are ultra-stable, non-toxic, gel-forming, biodegradable, and hydrophilic. Natural polymers originating from plants, microbes, animals, and algae, such as chitosan, pectin, chondroitin sulphate, and alginates, are used in novel medicinal dosage forms

Innovative Approach:

Drug-Delivery System Under Pressure:

The colon endures higher pressures than the small intestine as a result of peristalsis. Ethyl cellulose, which is insoluble in water, is used to make pressure-controlled colon-delivery capsules. Drug release occurs in such systems as a result of pressure in the colon lumen and the disintegration of water-insoluble polymer capsules.[9]

The ethylcellulose membrane thickness is the most important element

Introducing a New Colon Targeted Delivery System:

With this approach, problems with pH and time-dependent drug delivery systems are reduced. Bacteria in the intestine break down pH-sensitive polymers and polysaccharides. This method employs a three-layer coated core tablet with polymer coatings. Eudragit-L polymer is used for the exterior coating. The coating dissolves as the tablet travels through the pyloric and duodenal valves, revealing the next coating, which is comprised of Eudragit E. This layer liberates the lactulose from the internal core. The unrestricted lactuse dissolves the Eudragit E layer, which is transformed into short-chain fatty acids and lowers the pH of the surrounding environment. The drug is revealed as a result of Eudragit E breakdown. Other polysaccharides are used, such as manitol and maltose.

OsmoticallyControlled Colon Targeted Drug Delivery System:

This system consists of osmotic units that are enclosed in a firm gelatin capsule and can be used individually or in a combination of five to six push-pull units. The outer layer of these push-pull units is an enteric impermeable membrane, while the inner layer is a semi-permeable membrane. The internal or central section of the drug layer and the push layer make up the push-pull. The semi-permeablemembrane, which consists of an opening through which

drug contents are ejected over time, is the next layer to the drug. Following administration of the capsule, the body encapsulating the push-pull units dissolves immediately. [10]

Pulsincap System:

Port System:

The formulation is put into capsules in this system. The capsule's plug is in charge of managing the drug's release. To seal the drug's contents, swellable hydrogels are used. As the capsule comes into touch with the dissolution fluid, it swells, and the plug is pushed off after the lag time, allowing the medicine to be released. Hydrogel plugs contain the polymers hydroxyl propyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polymethyl methacrylate.

In this configuration, the capsule body is encased in a semi-permeable membrane. An insoluble plug comprising osmotically active chemicals and drug formulation is contained within the capsule body. When the semi-permeable membrane comes into contact with the dissolution fluid, it allows fluid to flow into the capsule, resulting in an increase in pressure in the capsule body and drug release as a result of the plug expelling. The medication is administered at regular intervals, with a time lag between each.[11]

Azo Hydrogels:

The colon specificity in the hydrogel is achieved through the use of pH-sensitive monomers and azo cross-linking agents. As they pass through the GIT, these hydrogels expand as the pH rises. The swelling of the hydrogel, which slices the cross-links in the hydrogel's network, causes the release of medications trapped in the hydrogel. Cross-linking N-tart-butyl acrylamide, N-substituted (meth) acrylamides, and acrylic acid with 4, 4-di methacryloylamino azobenzene yields these hydrogels. Polymer-polymer interaction with corresponding copolymer including side chains terminating in NH2groups, as well as cross-linking polymeric precursors using the same polymeric precursor. [12]

Multi-particulate System:

Multi-particulate systems provide several advantages, including decreased local irritation and systemic toxicity, as well as increased bioavailability. Multi-particulate processes include the generation of pellets, microparticles, granules, and nanoparticles. Because multi-particulate systems allow medicine to reach the colon fast and stay there for an extended period of time, they are preferredover single-unit dose forms such as tablets. Because of their small/fine size, these systems

FACTORS TO BE CONSIDERED IN THE DESIGN OF COLON-SPECIFIC DRUG DELIVERY SYSTEM

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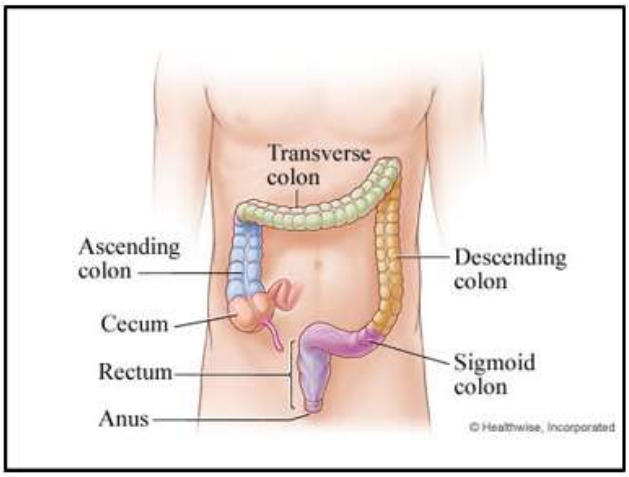


Fig.1: Anatomy of Colon.

pH in the Colon:

The pH of the gastrointestinal tract varies both within and between subjects. Diet, disease state, and food intake all have an impact on the pH of the gastrointestinal fluid. The variation in pH along the gastrointestinal tract has been used to deliver drugs to the colon. The gastrointestinal tract has a pH gradient, with values ranging from 1.2 in the stomach to 6.6 in the proximal small intestine and peaking at about 7.5 in the distal small intestine. Historically, utilising pH sensitive enteric coatings, the pH differential between the stomach and small intestine has been used to transport medications to the small intestine. The presence of short chain fatty acids as a result of polysaccharide fermentation by bacteria

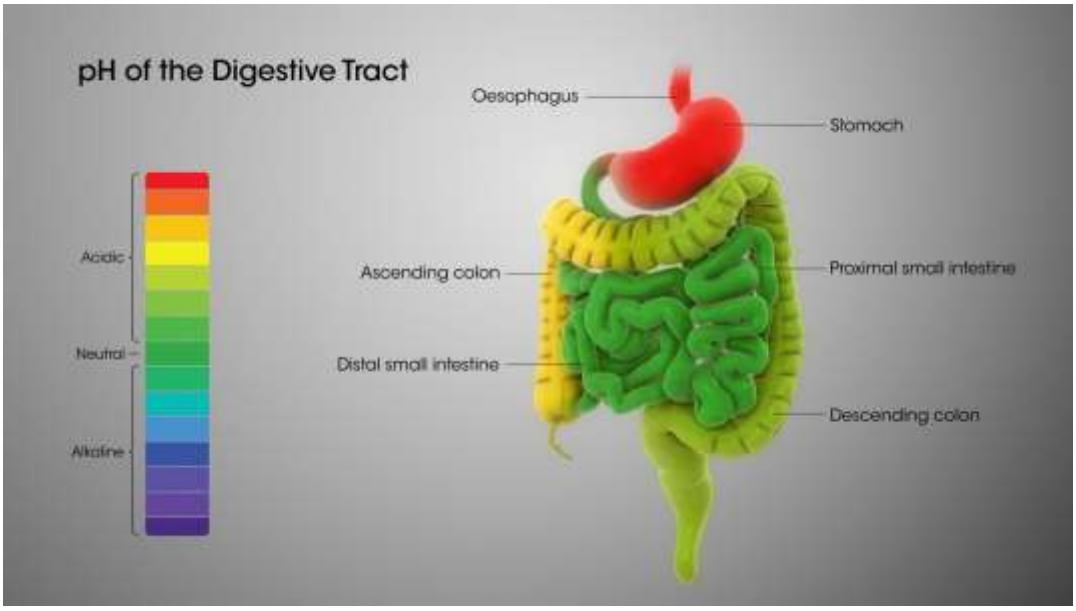


Fig2. PH in the colon

The pace of stomach emptying of dosage forms varies substantially depending on whether the individual is fed or fasted, as well as the size and density of the dosage form. When an oral dose form reaches the colon is influenced by the pace of stomach emptying and the small intestine transit time. The movement of materials through the colon is slow and irregular, influenced by a number of factors such as food, dietary fibre content, mobility, stress, disease, and medications. In healthy young and adult males, dosage forms such as capsules and tablets transit through the colon in roughly 20-30 hours, though it can take anything from a few hours to more than two days. The consequences of disorders that have an impact on colonic health.[14]

Colonic Micro Flora and their Enzymes:

Intestinal enzymes induce drug release in diverse locations of the GIT. These enzymes are often produced by the colon's extensive gut bacteria. These enzymes are used to disrupt bindings between an inert carrier and an active substance (e.g., drug release from a pro drug) as well as to break down coatings/matrices. Over 400 bacterial species have been identified, with 20-30% of them belonging to the genus Bactericides.. [15]

In the upper section of the GIT, the bacterium concentration is 1011- 1012 CFU/ml. Bifidobacterium, Eubacterium, Bactericides

NEED FOR COLON TARGETED DRUG DELIVERY

• Targeted medicine delivery to the colon may provide direct treatment at the illness site, lower dose, and fewer systemic side effects.

• Peptide and protein medications can be administered orally using site-specific or targeted drug delivery methods.

• A colon-specific formulation could also be employed to extend medication delivery.

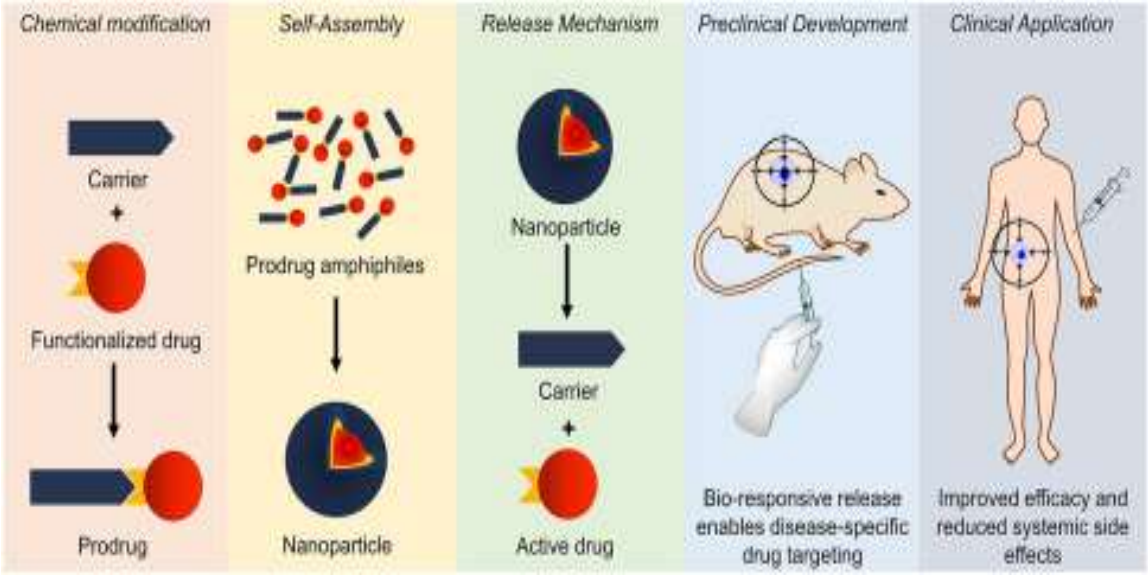
• The colon is a place for topical, local, or systemic drug delivery, as in the treatment of bowel disease, ulcerative colitis, or Crohan's disease. Glucocorticoids and sulphasalazine are commonly used to treat inflammatory disorders.[16]

• By focusing medications to the colon, a variety of other important disorders of the colon, such as colorectal cancer, may be treated more efficiently.• Formulations that are substantially influenced by hepatic metabolism, are polar, or are vulnerable to chemical and enzymatic deterioration

TARGETED DRUG DELIVERY

Traditional pro drug design is a non-specific chemical technique used to mask unfavourable pharmacological properties such as low bioavailability, limited site specificity, and chemical instability. Targeted pro drug design, on the other hand, is a unique approach to medication delivery that is both targeted and efficient. Pro drugs that target a specific enzyme, membrane transporter, or both have the potential to be used as a drug delivery strategy in cancer treatment. Developing a strategy to target specific enzyme or carrier substrate specificity in order to overcome a variety of unwanted pharmacological properties demands detailed knowledge of a specific enzyme or carrier system, including its molecular and functional properties.

Glycoside derivatives are hydrophilic and poorly absorbed from the small intestine; but, once in the colon, they can be successfully released by bacterial glycosidase to release the free medicine, which increases absorption by the colonic mucosa. Dexamethasone glucoside, a glycosidic prodrug, appeared to be a better choice, with around 60% of the prodrug reaching the caecum as free steroids and the parent drug being absorbed in the small intestine

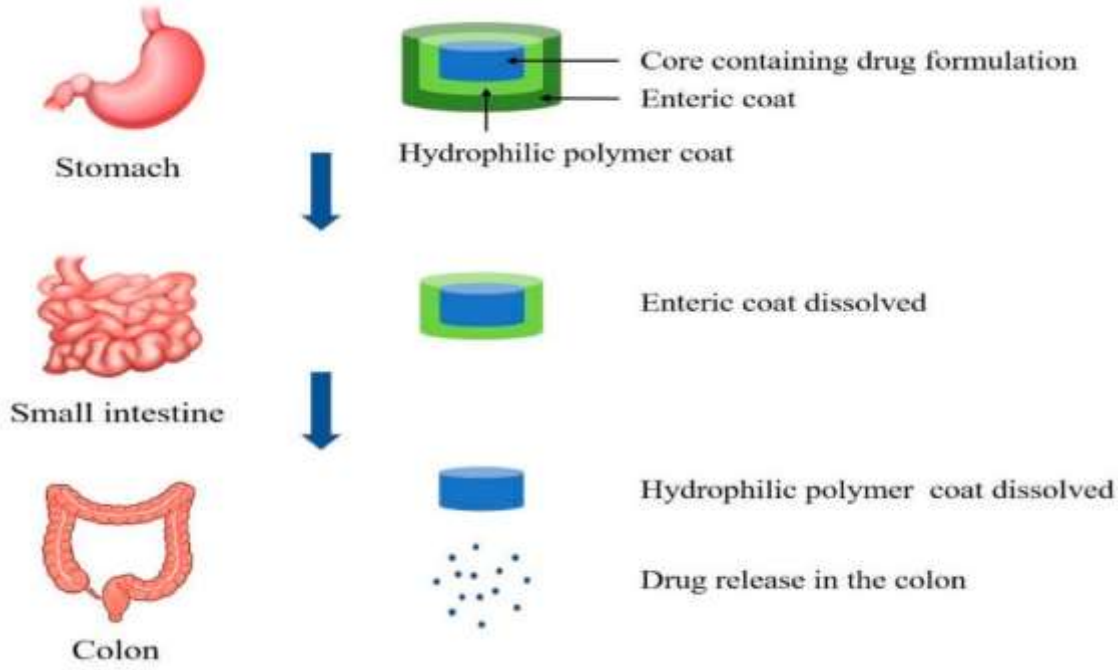


Targeting specific membrane transporters: When free steroids were administered orally, they were almost entirely absorbed in the smallintestine, with only 1% reaching the colon. Azo compounds have been employed for colontargeting in the form of hydrogels as a coating medium for coating the drug cores and as prodrugs. Sulphasalazine, a medicine used to treat rheumatoid arthritis, was later revealed to offer potential in the treatment of IBD. In this molecule, anazo is linked between 5- amino salicylic acid and sulphapyridine.[17]

Polysaccharide-based systems: Polysaccharide matrices are expected to survive in the physiological environment of the stomach and small intestine because they are resistant to GI enzyme digestion. When they enter the colon, bacterial polysaccharide acts on them, inducing matrix collapse. The natural polysaccharide family has appeal in the field of drug delivery because it is composed of polymers with a significant number of derivitizable groups, a wide range of molecular weight, changing chemical composition, and the lowest toxicity and biodegradability while maintaining excellent stability. Pectin is a polysaccharide that contains D-galactose and D-arabinose on one side and 1,4 D-galactouronic acid and 1,2 D-Rhamnose on the other. The use of an innovative colonic medication delivery method.[18]

Fig 4.tablet and capsule

Fig .5: Drug release in the colon from pH-sensitive polymer-based system.



Because Zen is resistant to low pH settings, it could be employed as a carrier for controlled-release solid dispersion systems delivering poorly water soluble medications to the colon. A single-layer film coating of tablets using biopolymer Zein in conjunction with Kollicoat® MAE 100P recently exhibited outstanding potential for blocking drug release in the upper GI tract for delayed drug release in the colon. The coating component ratio and coating layer thickness have a substantial impact on the performance of coated tablets for colonic drug administration. In recent years, new coating technology has been widely pursued in order to improve the targeting efficacy of pH-dependent delivery systems. ColoPulse technology, for example, is a pH-responsive coating system that includes a super-disintegrant in the coating matrix to accelerate disintegration.[19]

These liposomes demonstrated excellent stability at acidic and neutral pHs, with minimal drug leakage, boosting sorafenib systemic exposure in rats. Solid lipid nanoparticles are a superior solution for drug protection, trapping efficiency, and boosting the amount of drug released at specified locations. The lipid matrix of solid lipid nanoparticles degrades slowly, allowing for extended drug release.[20]

Nano/Microparticles pH-dependent polymeric nanoparticles made of polymers have been shown in multiple studies to be successful as colonic drug delivery systems. Metallic et al. delivered curcumin nanoparticles to the colon using a pH-sensitive hydrolyzed polyacrylamide-grafted-xanthan gum (PAAm-g-XG). The amount of medication released from PAAm-g-XG-modified nanoparticles was minor in acidic conditions (pH 1.2 and 4.5), but it was faster and higher at pH 7.2..

ANTIBODIES

Harel et al created anti-transferrin receptor antibody-conjugated liposomes and discovered that the conjugated liposomes were more effective in cellular internalisation than the unconjugated liposomes. Furthermore, anti-transferrin receptor antibody-conjugated liposomes dispersed preferentially to inflamed mucosa rather than normal mucosa, resulting in much higher accumulation (more than 4-fold higher) at the site of inflammation than normal mucosa. Xiao et al. created nanoparticles with single-chain CD98 antibodies on their surface for IBD therapy (scCD98-functionalized). CD98 is a heterodimer neutral amino acid transporter that is overexpressed in intestinal macrophages and colonic epithelial cells in colitis rats. CD98-overexpressed cells were particularly fond of scCD98-functionalized nanoparticles.[21]In animals with colitis, scCD98-functionalized nanoparticles expressing CD98 siRNA (siCD98) reduced CD98 expression levels and colitis severity. [22-23]

PEPTIDES

Peptide is gaining popularity as a potential medication delivery ligand. Peptides have several advantages, including biocompatibility, cost-effectiveness, chemical variety, and stimulus responsiveness. Furthermore, peptide ligands have significantly higher binding affinity and specificity than small molecule ligands due to their large binding surfaces with receptors. Peptide ligands are also valuable because of their ease of synthesis using automated solid-phase peptide synthesis equipment and their availability for high-throughput screening.[24]Furthermore, by changing peptide sequences, metabolic instability induced by proteases can be avoided, allowing peptide ligands to be employed in customised drug delivery systems. Peptide-conjugated drug delivery systems, in particular, are being studied as a potential method for tumor-targeted medication delivery. [25]

DESIGN OF ELECTRONIC DEVICE-ASSISTED FORMULATION

The evaluation of medication absorption across the GI tract in vivo is essential for the development of colon-specific drug delivery devices. As a result, a quick and simple approach for precisely and reliably assessing drug release qualities along the GI tract to determine whether the tested formulation is valid for modified drug release is critical.[26] In this approach, the use of electronics presents a fresh means of integrating data from many sources. The IntelliCap® gadget is the world's first intelligent electronic medication delivery and monitoring device, integrating controlled drug delivery, patient monitoring, and real-time wireless communication. Caregivers will be able to track the capsule's transit through the GI tract because it features real-time wireless data capture. In the case of formulation design,[27]

CONCLUSION

Drug administration and absorption have become increasingly important in the colonic portion of the GIT. Treatment targeting to the diseased colon has the advantages of reducing systemic adverse effects, lowering medicine doses, only giving the drug when needed, and maintaining the drug as close to the target site as possible in its intact form.

All colon medicine administration strategies enable for the treatment of local colon problems as well as systemic absorption of poorly absorbed pharmaceuticals. The wide range of pH levels and enzymes found in the gastrointestinal tract, which the dosage form must travel through before reaching the target region, hampers formulation reliability, delivery efficiency, and colon targeting.

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