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A Review on Colon Drug Delivery

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ABSTRACT

Colon targeted drug delivery systems have gained a great deal of attention as potential carriers for the local treatment of colonic diseases with reduced systemic side effects and also for the enhanced oral delivery of various the therapeutics vulnerable to acidic and enzymatic degradation in the upper gastrointestinal tract. In recent years, the global pharmaceutical market for biologics has grown, and increasing demand for a more patient-friendly drug administration system highlights the importance of colonic drug delivery as a noninvasive delivery approach for macromolecules. Colon-targeted drug delivery systems for macromolecules can provide therapeutic benefits including better patient compliance (because they are pain-free and can be self-administered) and lower costs. Therefore, to achieve more efficient colonic drug delivery for local or systemic drug effects, various strategies have been explored including pH-dependent systems, enzyme-triggered systems, receptor-mediated systems, and magnetically-driven systems. In this review, recent advancements in various approaches for designing colon targeted drug delivery systems and their pharmaceutical applications are covered with a particular emphasis on formulation technologies

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

INTRODUCTION

Drug delivery to the colon should be capable of protecting the drug en route to the colon, i.e., drug release and absorption should not occur in the stomach or small intestine, and neither the bioactive agent nor the dissolution site should be degraded, but only once the system reaches the colon should the drug be released and absorbed. The colon specific drug delivery system (CDDS) is useful not only for the oral delivery of proteins and peptide drugs (which are degraded by stomach and small intestine digestive enzymes), but also for the delivery of low molecular weight compounds that are used to treat diseases of the colon and large intestine, such as ulcerative colitis, diarrhoea, and colon cancer [1]. If the peptide can be shielded from acid and enzymes in the stomach and upper intestine, clinically significant bioavailability can be attained. Because the colon has a high water absorption capacity and the contents of the colon are viscous and poorly mixed, most medications are not readily available to the absorptive membrane. The human colon is home to around 400 different bacteria species, with a density of up to 1010 bacteria per gram of colonic contents. azo reduction and enzymatic cleavage, i.e. glycosides, are two reactions carried out by these gut flora[2].

These metabolic pathways could be responsible for the metabolism of a variety of medications, and they could also be used to transfer peptide-based macromolecules like insulin to the colon by oral administration. A medication delivery system for the colon is required to enable direct treatment at the disease site, reduced dose, and fewer systemic side effects. To extend drug distribution, a colon-specific formulation could be used. In the treatment of colon disorders, it should be considered useful. The colon is a potential venue for both local and systemic medication delivery. Irritable bowel disease, such as ulcerative colitis or Crohn's disease, is treated with a topical medication. Glucocorticoids and Sulphasalazine are commonly used to treat inflammatory disorders. A number of other important colon disorders, such as colorectal cancer, could be treated more effectively if medications were specifically targeted to the colon. Drugs that are polar and/or sensitive to chemical and enzymatic breakdown in the upper GI tract, which is heavily influenced by hepatic metabolism, such as therapeutic proteins and peptides, can also be delivered using colonic formulations [3].

NEED OF COLON TARGETED DRUG DELIVERY SYSTEM

Reduced dose and fewer systemic side effects to enable direct treatment at the illness location. To extend drug distribution, a colon-specific formulation could be used. In the treatment of colon disorders, it should be considered useful. The colon is a potential venue for both local and systemic medication delivery. Irritable bowel disease, such as ulcerative colitis or Crohn's disease, is treated with a topical medication. Glucocorticoids and Sulphasalazine are commonly used to treat inflammatory disorders[4]. A number of other important colon disorders, such as colorectal cancer, could be treated more effectively if medications were specifically targeted to the colon. Drugs that are polar and/or sensitive to chemical and enzymatic breakdown in the upper GI tract, which is heavily influenced by hepatic metabolism, such as therapeutic proteins and peptides, can also be delivered using colonic formulations [5].

APPROACHES TO COLON TARGET DRUG DELIVERY

3.1. Primary Approaches for Colon Targeted Drug Delivery:

3.1.1 pH-Sensitive Polymer Coated Drug Delivery to Colon:

The pH-dependent CTDDS take advantage of the widely held belief that the pH of the human GIT rises gradually 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). The use of pH-sensitive polymers to coat tablets delays the release of the active drug when compared to capsules or pellets, and protects the active drug from gastric juice. The polymers employed for colon targeting maintain lower pH levels in the stomach and proximal section of the small intestine. Gamma scintigraphy is the most widely used approach for evaluating the gastrointestinal performance of pharmacological dose forms. [6]

3.1.2. Delayed-Release Drug Delivery to Colon:

This technology is based on the idea that after a predetermined lag period, the medicine will release at the chosen time and location. The lag time of the colon targeted medication delivery system5 is regarded acceptable. The coated polymer or mixture of polymers affects the time it takes for medications to reach the colon. Because the gastric emptying rate varies from person to person, the colon influx time of the dose form cannot be anticipated precisely. [7]

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 are polymers employed in this delayed-type system.

The disadvantages of this system are:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- The gastrointestinal transit of the drug is influenced by peristaltic movements or contractions that occur in the stomach.
- This influence is mainly observed in IBD, diarrhea, ulcerative colitis type diseases.

3.1.3 Microbially Triggered Drug Delivery :

The technique works on the idea that the microflora of the colon causes the polymers coated on the dosage form to degrade. The microflora in the colon is complex, and it is responsible for the fermentation of substrates such polysaccharides found in the intestine. These micro flora produce a wide range of enzymes, which metabolise substrates such as polysaccharides, carbohydrates, and proteins, resulting in digestion escape in the upper GIT.To control the drug release from the dosage form pectin is used in large quantitiesif used alone but it was used in combination with chitosan and HPMC it was found very useful to control the drug release in the stomach and very efficiently releasing the drug in the colon. The microbial degradable polymers are pectin, dextran, chitosan, inulin, lactulose, guar gum, cyclodextrin, alginates, amylose and locust bean gum. The Microbial triggered drug delivery includes mainly the three approaches mentioned below[8].

A. Prodrug Approach:

Prodrugs are pharmacologically inert compounds that spontaneously or enzymatically transition into active forms in vivo to release the active drug. The covalent connection between the drug and its carrier exists in this approach, it remains intact in the upper GIT, and it breaks in the colon, allowing the medication to be released. A variety of pharmacological connections with hydrophobic moieties such as glucose, cellulose, amino acids, glucoronic acid, and galactose, among others, have been developed that are susceptible to hydrolysis in the colon. Chemical linkage in the prodrug technique has a significant constraint in that the formation of the functional group plays a critical role in its design and presence on the drug moiety. 5-ASA17 is an example of a prodrug that was discovered to be stable in the upper GIT and digested by cercal to release 5-ASA and is linked to glycine via an amide bond[6,7,8].

B. Azo-Polymeric Prodrugs:

This innovative approach for colonic delivery employs several polymers as drug carriers. Drugs and polymers are designed by connection with an azo group, also known as azo linkage, employing sub synthetic polymers. The medicine is protected against degradation in the upper GIT by polymer cross-linking with an azo aromatic group when coated, and by the release of these azo bonds in the colon, where the azo bonds were broken. An example of an azo polymer-based drug delivery method is segmented polyurethane-coated budesonide pellets[6,7,8].

C. Polysaccharide-Based Approach:

Naturally occurring polysaccharides are commonly used for drug targeting due to their ease of availability, abundance, and low cost. They're extremely stable, nontoxic, gel-forming, biodegradable, and hydrophilic. Natural polymers such as chitosan, pectin, chondroitin sulphate, and alginates are derived from plants, microorganisms, animals, and algae, and are employed in innovative medicinal dosage forms[6,7,8].

3.2. Novel Approach:

3.2.1. Pressure - Controlled Drug-Delivery System:

As a result of peristalsis, the colon experiences higher pressures than the small intestine. Pressure-controlled colon-delivery capsules are made with ethyl cellulose, which is insoluble in water. In such systems, drug release happens as a function of pressure in the colon lumen and the disintegration of water-insoluble polymer capsules. The thickness of the ethylcellulose membrane is the most essential factor in the disintegration of the formulation. The size and density of the capsules have a role in this system. Because of water reabsorption from the colon, the luminal content viscosity is higher in the colon than in the small intestine. In the context of drug delivery systems for the colon. [9]

3.2.2 Novel Colon Targeted Delivery System:

Problems with pH and time-dependent drug delivery systems are reduced with this technology. pH-sensitive polymers and polysaccharides are broken down by bacteria in the intestine. A three-layer coated core tablet with polymer coatings is used in this technology. The external coating is made of the polymer Eudragit-L. When the pill passes through the pyloric and duodenal valves, the coating dissolves, disclosing the next coating, which is made of Eudragit E. The lactulose contained in the internal core is released by this layer. The unrestrained lactuse dissolves the Eudragit E layer, which is converted into short-chain fatty acids, lowering the surrounding pH. The dissolution of Eudragit E results in the drug's disclosure. Other polysaccharides, such as manitol and maltose, are employed in the core tablet in addition to the medication. [10]

3.3. Osmotically Controlled 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. [11]

3.4. Pulsatile Colon Targeted Drug Delivery:

3.4.1. Pulsincap System:

In this system, the formulation is loaded into capsules. The plug in the capsule is in charge of controlling the drug's release. Swellable hydrogels are utilised to seal the drug's contents. The capsule swells as it comes into contact with the dissolution fluid, and the plug is forced off after the lag time, causing the medicine to be released. The polymers utilised in hydrogel plugs are hydroxyl propyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polymethyl methacrylate. [12]

3.4.2. Port System:

The capsule body is encased in a semi-permeable membrane in this arrangement. The capsule body contains an insoluble plug containing osmotically active chemicals and medication formulation. When the semi-permeable membrane comes into touch with the dissolution fluid, it permits fluid to flow into the capsule, resulting in an increase in pressure in the capsule body and, as a result of the plug expelling, drug release. The medicine is released at regular intervals, with a time delay between each period. [13]

3.5. Azo Hydrogels:

The colon specificity is created in the hydrogel using pH-sensitive monomers and azo cross-linking agents. During their journey through the GIT, these hydrogels inflate as the pH rises. The release of pharmaceuticals encapsulated in the hydrogel is caused by the swelling of the hydrogel, which slices the cross-links in the hydrogel's network. These hydrogels are made by cross-linking N-tart-butyl acrylamide, N-substituted (meth) acrylamides, and acrylic acid with 4, 4-di methacryloylamino azobenzene as cross-linking agents. Polymer-polymer reaction with corresponding copolymer comprising side chains terminating in NH2groups and cross-linking polymeric precursors employing the same polymeric precursor. [14]

3.6. Multi-particulate System:

Multi-particulate systems provide a number of advantages, including reduced local irritation and systemic toxicity as well as enhanced bioavailability. Pellets, microparticle preparation, granules, and nanoparticle creation are some of the multi-particulate processes. Because multi-particulate systems enable the medicine to reach the colon quickly and be kept in the colon for a long time, they are preferred over single-unit dose forms like tablets. These systems easily pass through the GIT due to their small/fine size. Multi-particulate systems scatter more equally in the GIT than single particles, resulting in greater drug absorption[15,16].

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

4.1. Anatomy and Physiology of Colon:

The large intestine runs from the ileum's distal end to the anus. The length of the human large intestine is approximately 1.5 m 6 (Table 1). The colon is made up of the upper five feet of the large intestine and is mostly found in the belly. The colon is a cylindrical tube lined with mucosa, a moist, soft pink lining; the lumen, or passageway, is roughly 2-3 inches in diameter 7. The cecum is the first segment of the colon, leading to the right colon (immediately under the liver), the transverse colon, the descending colon, the sigmoid colon, the rectum, and the anal canal.There are significant differences in the physiology of the proximal and distal colons that affect medication absorption at each location. The luminal content of the colon changes physically as well, from liquid in the cecum to semisolid in the distal colon. [17,18]

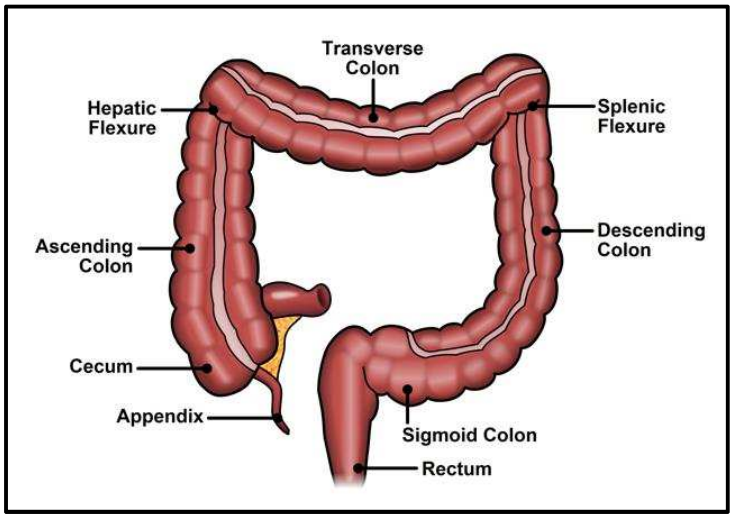

Fig.1: Anatomy of Colon.

4.2. PH in the Colon:

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. Historically, the pH differential between the stomach and small intestine has been used to transfer drugs to the small intestine using pH sensitive enteric coatings. The presence of short chain fatty acids resulting from bacterial fermentation of polysaccharides causes a pH drop at the colon's entry. [19,20]

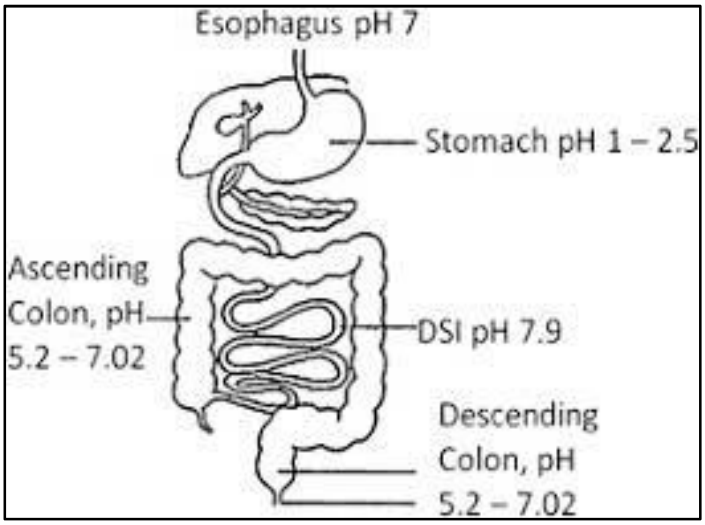

Fig.2: PH in the Colon

4.3 Transit of material in the colon:

The rate of gastric emptying of dosage forms varies greatly depending on whether the individual is fed or fasted, as well as the size and density of the dosage form. The rate of stomach emptying and the small intestine transit time influence when an oral dose form reaches the colon. The passage of materials through the colon is slow and erratic, influenced by a variety of factors including food, dietary fibre content, motion, stress, disease, and medicines. Dosage forms such as capsules and tablets pass through the colon in about 20-30 hours in healthy young and adult males, though it can take anything from a few hours to more than two days. The effects of diseases that influence colonic transit on drug delivery are significant: diarrhoea increases colonic transit while constipation decreases it. In most illness conditions, however, transit time appears to be rather consistent. [21]

4.4. Colonic Micro Flora and their enzymes:

Drug release in various areas of the GIT is triggered by intestinal enzymes. These enzymes are usually produced by gut microflora that is abundant in the colon. These enzymes are employed to break bindings between an inert carrier and an active substance (i.e., the release of a drug from a pro drug) as well as to breakdown coatings/matrices. Over 400 different bacterial species have been discovered, with 20-30% of them belonging to the genus Bactericides. The bacteria concentration in the human colon is 1011- 1012 CFU/ml in the upper portion of the GIT. Bactericides, Bifidobacterium, Eubacterium, Peptostreptococcus, peptococcus, Ruminococcus, and Clostridiums are the most common anaerobic bacteria. [22,23]

NEED FOR COLON TARGETED DRUG DELIVERY

- Direct treatment at the disease site, lower dosing,and less systemic side effects may be ensured by targeted drug delivery to the colon.
- Oral administration of peptide and protein drugs may be done by site-specific or targeted drug delivery systems.[24,25]
- To prolong the drug delivery colon-specific formulation could also be used.
- The colon is a site where topical treatment, local or systemic drug delivery could be achieved i.e. Treatment of bowel disease, ulcerative colitis or crohan's disease. Inflammatory conditions are usually treated using glucocorticoids and sulphasalazine.
- By targeting drugs to colon a number of other serious diseases of the colon may also be treated more effectively e.g. colorectal cancer.
- Formulations that are highly affected by hepatic metabolism, polar or susceptible to chemical and enzymatic degradation in the upper GI tract, are also suitable for colonic delivery.[25]
- Advantages of colon drug delivery systems.
- Lower cost of expensive drugs due to less reduced dose frequency.
- Reduced incidence of side effects and drug interactions due to site targeting.
- Prolonged day or night time activity.
- Enhances the absorption of poorly absorbed drugs because of longer retention time.
- Better patient compliance.
- Bypass early first-pass metabolism.
- Decreases gastric irritation.
- Peptides, oral vaccines, insulin, growth hormones, can be given through this route due to less peptidase activity.
- Oral delivery of drugs to the colon is valuable in the treatment of diseases of the colon (ulcerative colitis, Charon's disease, carcinomas and infections).

- The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.
- The colon is attracting interest as a site where poorly absorbed drug molecules may have improved bioavailability.
- Disadvantages of colon drug delivery systems12. Multiple manufacturing steps. Incomplete release rate.[26]
- The resident micro flora could also affect colonic performance via metabolic degradation of the drug.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.
- Bioavailability of drugs may be low due to the potentially binding of the drug in a nonspecific way to dietary residues, mucus or fecal matter.[27]

TARGETED DRUG DELIVERY

Traditional pro drug design is generally a non-specific chemical method to disguise undesirable pharmacological qualities such low bioavailability, limited site specificity, and chemical instability. Targeted pro drug design, on the other hand, is a novel technique for delivering drugs in a targeted and efficient manner. Pro medicines that target a specific enzyme or membrane transporter, or both, have the potential to be a drug delivery mechanism for can cerchem treatment. Designing a strategy to target specific enzyme or carrier substrate specificity in order to overcome a variety of undesirable pharmacological qualities necessitates extensive knowledge of a specific enzyme or carrier system, including its molecular and functional characteristics. [28]

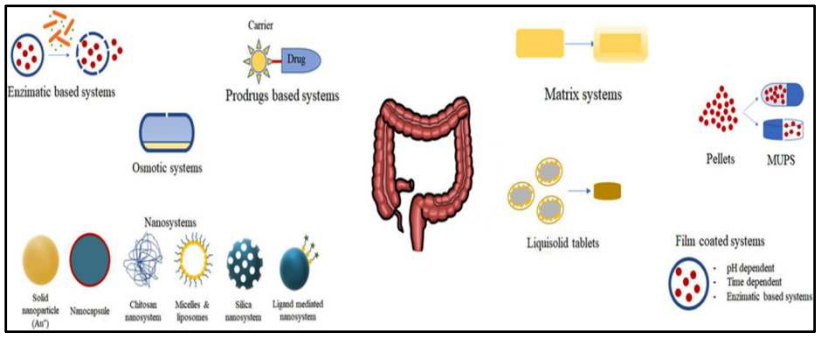

Fig.3: Targeted prodrug Design

6.1Targeting specific enzymes:

Glycoside derivatives are hydrophilic and are poorly absorbed from the small intestine; however, once they reach the colon, they can be successfully freed by bacterial glycosidase to release the free medication, which aids absorption by the colonic mucosa. Dexamethasone glucoside, a glycosidic prodrug, looked to be a superior candidate, with around 60% of the prodrug reaching the caecum as free steroids, while the parent drug was absorbed in the small intestine[28].

6.2 Targeting specific membrane transporters:

When free steroids were given orally, they were virtually completely absorbed in the small intestine, with only 1% of the dose reaching the colon. As a coating material for coating the drug cores and as prodrugs, azo compounds have been used for colontargeting in the form of hydrogels. Sulphasalazine, a rheumatoid arthritis medication, was later discovered to have potential in the treatment of IBD. Anazo is bonded between 5- amino salicylic acid and sulphapyridine in this molecule. [28]

6.3 Polysaccharide based systems:

Because polysaccharide matrices are resistant to digestive action of GI enzymes, they are assessed to remain in tact in the physiological environment of the stomach and small intestine. However, when they reach the colon, they are acted upon by bacterial polysaccharide, which causes matrix degradation. Natural polysaccharide family has appeal in the field of drug delivery because it is made up 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 1,4 D-galactouronic acid and 1,2 D-Rhamnose, with D-galactose and D-arabinose on one side and D-arabinose on the other. The use of a new colonic medication delivery system is being researched. In-vitro tests revealed that high methoxy pectin, when used as a compression coat, was capable of coating tablets in a gastrointestinally stimulating environment while also being susceptible to enzymatic attack. In-vivo gamma scintigraphic studies confirmed the in-vitro findings, indicating that pectin coating tablets disintegrate in the colonic region and demonstrate microflora degradation, necessitating the development of less water soluble pectin derivatives. Calcium pectinate, an insoluble salt of pectin, was used for colon targeted drug delivery of Indomethacin (Rubeinstein et al., 1993). Pectin hpmc compressed core tablets of 5-amino salicylic acid were described by Turkoglu and urugulu for colon administration, [28,29]

TABLETS AND CAPSULES

Even though there are few commercially available solutions, colon focused medication delivery can be performed with film coated tablets or capsules. is a diagram that shows how a pH-sensitive polymer-coated drug delivery device releases drugs into the colon. This technique works with both macromolecules and low-molecular-weight synthesised medicines.Recently, Crowe et al. created the Eudragit L100-coated tablets for the colonic delivery of a new anti-tumor necrosis factor domain antibody (V565) (V565). This tablet displayed the sustained drug release at pH 6 but no drug release during 2-hr incubation in acidic circumstances. The sustained release of V565 in the colon for the topical treatment of IBD was further supported in in vivo investigations in monkeys. Furthermore, drug release characteristics can be altered by altering the ratios of a combination of copolymers. For colon-targeted medication administration, this combination method may be preferable to tablets coated with a single polymer. [29.30]

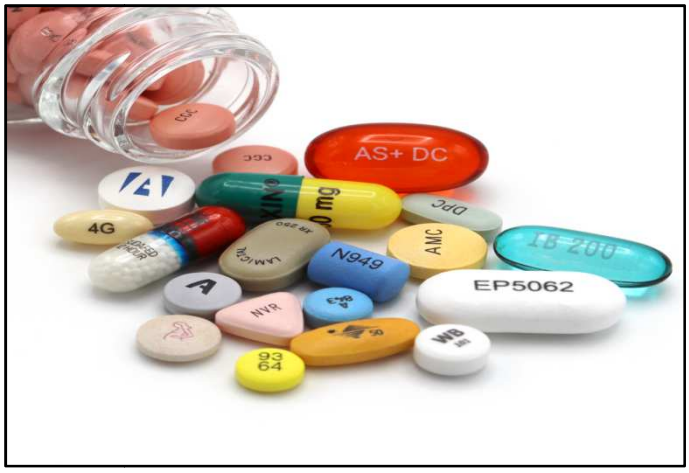

Fig.4: **Tablets and Capsules**

However, because to the variety of pH in the GI tract, tablets coated simply with pH-sensitive enteric polymers still have concerns with premature drug release. Furthermore, differences in GI fluid composition, eating status, and GI transit duration influence site-specific medication release from the pH-dependent system. As a result, ongoing e orts have been made to increase the targeted e ectiveness of multi-unit formulations based on the integration of various mechanism-based systems with pH-dependent coating.Park et al., for example, coated a bisacodyl-loaded multi-unit tablet with various combinations of pH-dependent polymers (Eudragit S and Eudragit L) and time-dependent polymers to create a bisacodyl-loaded multi-unit tablet (Eudragit RS).In the simulated gastric and intestinal fluids, drug release from the optimised tablet was limited, while substantial drug release was seen in the colonic fluid. Foppoli et al. recently published an e ective 5-aminosalicylic acid colonic administration system based on a mix of time-dependent and pH-dependent methods, which was made by coating a tablet core with low-viscosity HPMC and Eudragit® L. Furthermore, they confirmed that there was no premature drug release before reaching the colon in both fed and fasted stages based on a -scintigraphy investigation in humans. [31,32]

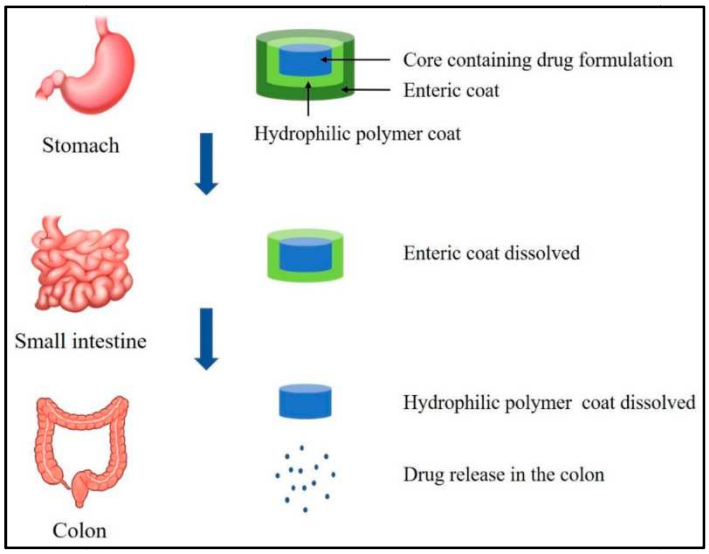

Fig .5: Drug release in the colon from pH-sensitive polymer-based system.

Because Zen is resistant to low pH settings, it could be used as a carrier for controlled-release solid dispersion systems delivering poorly water soluble medicines to the colon[33]. A single-layer film coating of tablets employing biopolymer Zein in conjunction with Kollicoat® MAE 100P recently demonstrated excellent promise for preventing drug release in the upper GI tract for delayed drug release in the colon. The coating component ratio and coating layer thickness have a significant impact on the performance of coated tablets for colonic medication administration. New coating technology has been extensively pursued in recent years 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 speed up disintegration at the target spot. When a super-disintegrant is used in a non-percolating mode, it results in more consistent and pulsatile drug release. ColoPulse tablets have been shown in previous tests to distribute the active material to the ileo-colonic region of Crohn's patients as well as healthy people. Furthermore, the targeted e ectiveness of ColoPulse delivery devices was unaffected by food or the timing of meal consumption. Garb et al. recently used this technology to create ileo-colonic-targeted zero-order sustained-release budesonide tablets for the topical treatment of IBD. The results showed that the designed tablet's medication release began in the simulated ileum. [34,35]

LIPID-BASED FORMULATIONS

Liposomes are a type of drug delivery system made up of two layers of phospholipids. Liposomes are biodegradable, biocompatible, and allow both

hydrophilic and lipophilic medicines to be included. Liposomes' surfaces can be coated with pH-dependent polymers to prevent liposome disintegration in acidic circumstances, as well as ligands to improve site-specificity. Zhao et al., for example, coated the surface of anionic liposomes with glycol chitosan and pH-dependent Eudragit® S100 to create colon-targeted liposomal formulations for sorafenib. [36,37]

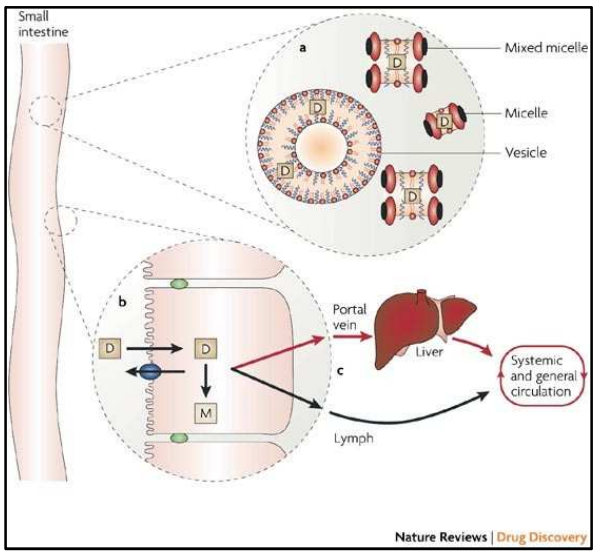

Fig.6: Lipid-Based Formulations

These liposomes exhibited great stability at acidic and neutral pHs with negligible drug leakage, increasing sorafenib systemic exposure in rats. In terms of drug protection, trapping efficiency, and increasing the amount of drug released at specific places, solid lipid nanoparticles are a superior solution. Solid lipid nanoparticles' lipid matrix degrades slowly, allowing for prolonged drug release.

Nano/Microparticles Made of Polymers pH-dependent polymeric nanoparticles have been shown to be effective as colonic medication delivery devices in numerous investigationsMetallic et al. used a pH-sensitive hydrolyzed polyacrylamide-grafted-xanthan gum (PAAm-g-XG) to deliver curcumin nanoparticles to the colon. In acidic circumstances (pH 1.2 and 4.5), the amount of drug released from PAAm-g-XG-modified nanoparticles was small, whereas at pH 7.2, drug release was faster and higher. In IBD rat models, the nanoparticles were effective in reducing colonic inflammation and weight loss. [38,39]

Furthermore, the drug release rate can be controlled using a mixed combination of two pH-sensitive polymers. Sahu and Pandey created HBsAg-loaded nanoparticles for e ective colonic immunisation utilising a combination of Eudragit® L100 and Eudragit® S100, confirming the e ective dispersion of nanoparticles at the colon as well as an increased immune response. Naeem et al. developed budesonide-loaded pH-/time-dependent nanoparticles for the e ective therapy of colitis to increase site-specificity to the colon.

Using an oil-in-water emulsion solvent evaporation process, these nanoparticles were made with Eudragit® FS30D and Eudragit® RS100. Eudragit® FS30D is a pH-dependent polymer that dissolves at pH 7.0 or above, whereas Eudragit® RS100 is a time-dependent, controlled-release polymer with low permeability.Premature drug release in the upper GI tract was reduced by combining these two polymers, resulting in sustained drug release throughout the colon. Furthermore, these pH/time-dependent nanoparticles transported medicines to inflamed colonic regions more anciently in colitis mouse models. [40,41].

ANTIBODIES

Harel et al made anti-transferrin receptor antibody-conjugated liposomes and found that the conjugated liposomes had better cellular internalisation than the unconjugated liposomes. Furthermore, anti-transferrin receptor antibody-conjugated liposomes distributed preferentially to inflamed mucosa rather than normal mucosa, resulting in much larger accumulation at the site of inflammation (more than 4-fold higher) than normal mucosa. For IBD therapy, Xiao et al. produced nanoparticles containing single-chain CD98 antibodies on their surface (scCD98-functionalized).In animals with colitis, CD98 is a heterodimer neutral amino acid transporter that is overexpressed in intestinal macrophages and colonic epithelial cells. CD98-overexpressed cells had a high affinity for scCD98-functionalized nanoparticles. scCD98-functionalized nanoparticles containing CD98 siRNA (siCD98) lowered CD98 expression levels and colitis severity in animals with colitis. [42,43]

PEPTIDES

Peptide is gaining a lot of attention as a possible drug delivery ligand. Biocompatibility, cost-effectiveness, chemical variety, and stimulus responsiveness are all advantages of peptides[44]. Furthermore, because to the wide binding surfaces with receptors, peptide ligands have substantially better binding affinity and specificity than small molecule ligands. Peptide ligands are additionally useful due to their simplicity of synthesis employing automated solid-phase peptide synthesis machines and their accessibility for high-throughput screening[45].Furthermore, metabolic instability caused by proteases can be avoided by altering peptide sequences, allowing peptide ligands to be used in tailored drug delivery systems. Peptide-conjugated drug delivery systems, in particular, are being investigated as a feasible strategy for tumor-targeted drug delivery. [46]

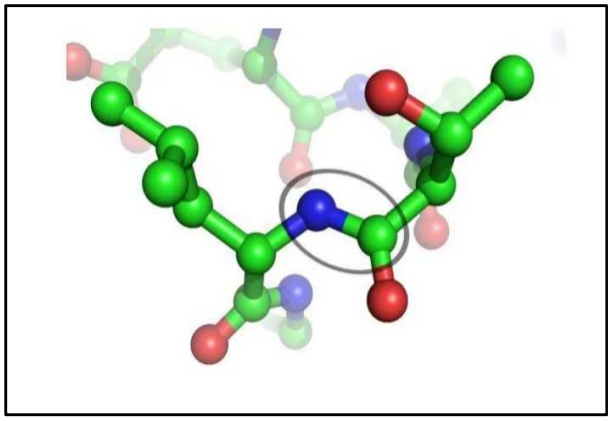

Fig.7: Peptide

Renet al., for example, looked at using a manufactured 12-residue peptide (TWYKIAFQRNRK, TK peptide) to carry anticancer drugs to the colon. Integrin _6_1, a subtype of integrins that is increased in human colon cancer cells, has a high affinity for TK. As a targeting ligand, the TK peptide was coupled to doxorubicin-loaded PEG-PLA micelles.The TK-conjugated micelles had much higher cytotoxicity and entered the tumour spheroids more effectively, suggesting that the TK peptide could be a promising targeting ligand for colon-targeted therapy. Guo et al. developed colon-specific nanoparticles that were co-modified with amphipathic chitosan derivatives (ACS) and cell penetration peptide (CPP) to increase insulin oral bioavailability. CPPs were protected from degradation in the upper GI tract thanks to an ACS modification, and colon-specific drug delivery was obtained. [47,48]

ELECTRONIC DEVICE-ASSISTED FORMULATION DESIGN

In vivo assessment of medication absorption across the GI tract is critical for the development of colon-specific drug delivery systems. As a result, a quick and simple method to precisely and reliably assess drug release qualities within the GI tract to establish whether the tested formulation is valid for modified drug release is urgently needed.In this way, the employment of electronics introduces a novel method to data integration from many sources. IntelliCap® is the first intelligent electronic drug delivery and monitoring device in the world, combining controlled drug delivery, patient monitoring, and real-time wireless communication. Because this electronic capsule includes real-time wireless data recording, caregivers will be able to track the capsule's passage through the GI tract. For a formulation design, sdelivery makes in vivo data available. As a result, IntelliCap® technology provides a quick and easy way to deliver regulated drug delivery to particular locations in the GI tract. Maurer et al. confirmed the ileo-colonic drug release of ColoPulse tablets in people using the Intellicap® system, indicating that the ColoPulse system is a potential colonic drug delivery technology. [49,50]

CONCLUSION

Drug administration and absorption have become increasingly essential in the GIT's colonic area. Drug targeting to the sick colon has the advantages of decreasing systemic adverse effects, lowering medicine doses, only supplying the drug when it is needed, and keeping the drug in its intact form as close to the target site as feasible.

All colon medication delivery methods allow for the treatment of local disorders connected with the colon as well as systemic absorption of pharmaceuticals that are poorly absorbed. The large range of pH levels and different enzymes found throughout the gastrointestinal tract, through which the dosage form must pass before reaching the target location, complicates formulation reliability, delivery efficiency, and colon targeting.

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