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A REVIEW ON SMART APPROACHES FOR COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

This review mainly focuses on the novel approaches for selection of the drug delivery system for colon diseases which is helpful in increasing the therapeutic effect of the drug at the desired site. Colon-targeted drug administration not only reduces side effects but also prevents premature drug release in the stomach or small intestine before reaching the colon. There are several approaches for the delivery of the drug in the colon. The novel strategies employed in the formulation of colon targeted drug delivery system (CTDDS) are meant to postpone the drug's release until the colon is reached. This article focuses on the parameters that affect colonic bioavailability, the different approaches used for colon-specific drug delivery, as well as the drawbacks of CTDDS.

Keywords: Colon targeted drug delivery, Smart novel approaches, Challenges, pH sensitive polymers

INTRODUCTION

Colon targeted drug delivery system (CTDDS) is used to deliver drugs that are specifically acting to the colon which may bring local or systemic action to the colon. These types of delivery systems reduce the systemic effects but deliver the effects in the targeted site colon. These systems must be able to protect the drug throughout the GIT until it reaches the colon or to prevent the release of the drug in the stomach and the small intestine. This helps in the delayed and prolonged release of the drug. Colon has a large capacity to absorb water, making the contents highly viscous and leading to inefficient mixing. The development of colon-targeted drug delivery systems requires consideration of factors such as mucus barrier penetration, biodistribution, and safety **[1]**. Though colon targeting can be achieved through oral and rectal routes, oral route is considered the most accepted and convenient route of administration for colon-targeted drug delivery system even though rectal route is the shortest route. Moreover, oral dosage forms have less sterile preparation requirements, offer more manufacturing and design flexibility, improved patient compliance, and are generally safe to administer. Depending on the spreading capacity and retention time of the various rectal dose forms, the extent of drug distribution varies. The dosage form can be retained in the colon for a prolonged period. Because of its almost neutral pH and less variety and intensity of enzyme activity, the colon offers a less hostile environment for the delivery of drugs. Conventional drug delivery systems for colon targeting include prodrugs, pH-dependent, time-dependent, matrix-based, polysaccharides-derived, and bio-adhesive systems. Novel approaches for drug delivery include the use of port systems, pulsincap systems, pressure-controlled systems, osmotic controlled systems, and newly developed techniques using nanotechnology. Polymers such as azo polymeric prodrugs, colon-specific biodegradable delivery systems, and polysaccharide-based delivery systems are commonly used in CTDDS **[2]**.

ADVANTAGES OF CTDDS [3]

CTDDS provides the advantages of both sustained as well as controlled drug delivery systems.

(1) Patient acceptance of the oral drugs is high.

(2) It has high flexibility and reproducibility.

(3) Enhanced bioavailability and unique release patterns

(4) Drug delivery should be at the targeted site or close to the targeted site.

(5) It has high predictability and less subject variation.

(6) No dose dumping.

(7) Improved stability.

(8) Reduced local irritation.

(9) Better patient compliance.

(10) Since the drug is delivered to the targeted site, the adverse effects are less.

(11) We can reduce the conventional dose which may in turn reduce the frequency and systemic side effects.

(12) This system is useful for the enhanced delivery of proteins and peptides such as amylin, insulin, cytokine inhibitors, vasopressin and calcitonin.

(13) Drugs that are broken down by stomach and small intestinal enzymes are best taken by CTDDS.

(14) It shields the drugs from the first pass effect.

(15) It also defence against drug release before time or rupture in the stomach or small intestine before reaching the colon.

(16) Reduced drug interactions

DISADVANTAGES OF CTDDS [4, 5]

(1) Minimal drug concentration.

(2) More than one manufacturing steps.

(3) Incomplete release rate.

(4) Increased plasma levels and consequently, increased bioavailability is the outcome of a longer residence period of three to five days, particularly for medications that function as substrates for this class of enzyme.

TYPES OF COLON TARGETED DDS

The two primary types of colon targeted drug delivery systems are as follows:

(1) Single unit CTDDS and

(2) Multi-particulate CTDDS

Muti-particulate CTDDS are more advantageous than that of the single unit CTDDS as they offer improved absorption and consistent stomach emptying while lowering local irritation and systemic toxicity.

SELECTION CRITERIA OF DRUGS FOR CTDDS

The following are good candidates for CTDDS.

(1) Drugs that are poorly absorbed from the upper GIT (stomach and intestine) such as peptides, antihypertensive drugs etc.

(2) Drugs that undergo significant first pass metabolism like nitroglycerine, corticosteroids etc.

(3) Drugs that are meant to provide local effects such as the drugs that are used for amoebiasis, ulcerative colitis, diarrhea, IBD, colon cancer etc.

(4) Drugs that degrade chemically or enzymatically in stomach and intestine like peptides and proteins.

(5) Drugs that are used to target specifically in colon like prednisolone, amino salicylic acid etc.

(6) Drugs that are inactivated by pancreatic enzymes in the small intestine.

(7) Treatments for conditions like nocturnal asthma, angina, or arthritis, which peak in the early morning, benefit from drug targeting to the colon when a therapeutic delay in drug absorption is needed.

The selection of drug carrier is important for the drug selection process. This mainly depends upon the nature of the disease for which the drug is used as well as the physicochemical characteristics of the drug. Carrier selection is dependent upon the functional group of the carrier molecule, chemical nature, partition coefficient, stability of the drug and the absorption enhancer used which in turn influences the efficacy and release properties of the drug which is illustrated in **Figure 1 [6, 7]**.

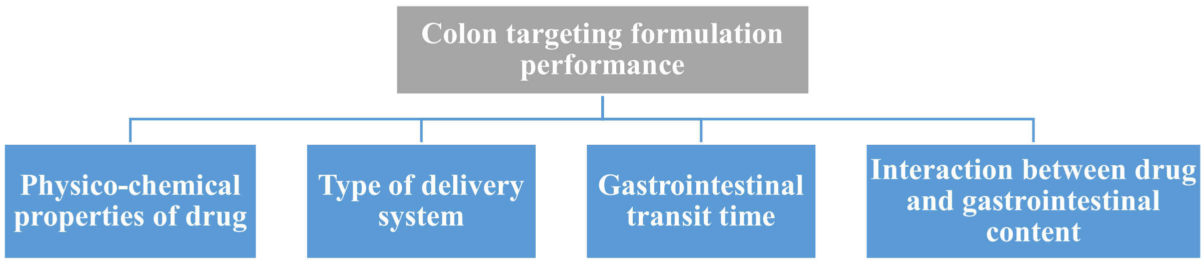

Figure 1: Factors affecting the performance of colon targeted drug delivery system

CHOICE OF POLYMERS FOR CTDDS

Polymers plays a key role in the delivery of drugs in the colon. Drug degradation as well as the targeting of the drugs in the colon can be achieved by selecting the appropriate polymers. Polymers helps to protect the degradation of drugs in acidic pH environment. Hence, the rate of absorption and release is controlled by the polymers that are used for the formulation of the drugs. Natural polymers are preferred, as they are less expensive and are biodegradable than the synthetic polymers **[4, 8]**.

CHALLENGES IN FORMULATING CTDDS

There are two routes for the administration of the drug in the colon. Oral route and the rectal route. The colon is especially hard to reach because of its position at the distal end of the alimentary canal. The rectal route is the shortest one to reach colon. The contents of the intestine are expelled via rectum and most of the patients feel uncomfortable during the rectal administration. Using rectal administration to reach the proximal portion of the colon is challenging. Hence this route is not preferred over oral route. The main challenge in oral drug delivery is the duration in which the drug must pass through various extreme pH conditions without releasing the active pharmaceutical ingredient. Other challenges are diseased condition of the patient, diet intake, fluid volume, acidic pH of the stomach, transit time, basic pH of the intestine, presence of enzymes that acts upon the drug, viscosity of the colon contents, pH of the colon, other indications in the colon that affects the absorption of the drug, bacterial microflora, colonic transient time etc. Sleep and diet intake affect the transient time in the colon. Numerous microorganisms that are present in the colon can affect the metabolism of drug into active or inactive form. The physicochemical property of the drug such as drug solubility is another challenge for preparing the orally administered CTDDS. The success of colon-targeted drug delivery depends on factors such as drug absorption mechanisms in the colon, colonic transient time, colonic fluid volume, colonic luminal viscosity, colonic enzymes, and formulation forms. The drug must also be in solution before entering the colon, or it must disintegrate in the luminal fluids of the colon, but this can be a barrier for drugs that are difficult to dissolve because the fluid content of the colon is higher in viscosity than that of the upper GI tract **[8]**.

SMART NOVEL APPROACHES OF COLONIC DRUG DELIVERY SYSTEM

There are different smart approaches for targeting colon delivery. These innovative approaches shield the drug from the acidic environment in addition to targeting it to the colon.

Transient time-dependent colonic drug delivery system

Time dependent delivery systems are otherwise known as pulsatile release or sigmoidal or delayed drug release system. As gastric emptying time varies from one individual to another, the estimation of lag time is essential to find the drug release. There may be a lag time of 5-6hrs. This is mainly due to the type and the amount of food intake. This system helps in the release of drug after a well-defined lag time. A transient time of 5hrs is required for the drug to reach the colon. This system is mainly used for those drug delivery systems that depend upon the circadian rhythms for curing diseases. The transit time of the larger particles is found to be less than that of the smaller particles. Pulsincap® is one of the commercial drug delivery systems which is based on the transient time in the GIT according to the figure 2. The outer coating of this system is an enteric polymer which holds the active medicament in place until it enters the small intestine and degrades in the small intestine. Underneath the enteric polymer is a hydrogel plug which consists of swellable polymers that swell in presence of water and a semipermeable polymer membrane which helps in the water influx. The hydrogel plug helps in the delivery of drug core in the colon. The central portion consists of drug core and swelling excipients to achieve colon-specific drug release.

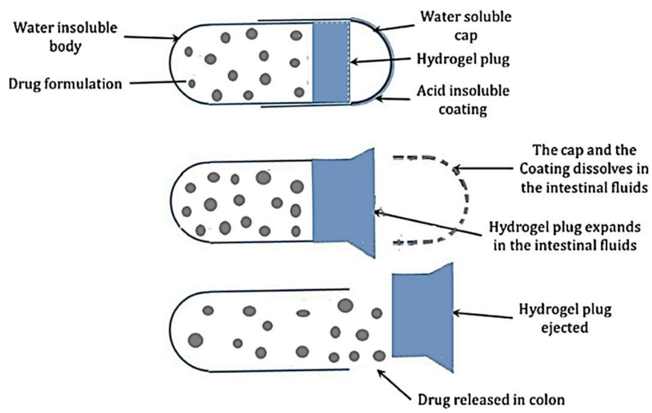

Figure 2: Schematic representation of Pulsincap® colon targeted drug delivery system

A pulsincap drug delivery system of metronidazole that has been modified was formulated by Abraham *et al*. for drug targeting purposes. Results of the in vitro drug release investigations showed that considerable drug release only happened 5 hours after the experiment began. The studies were conducted in buffer of pH 1.2 for two hours, pH 7.4 (simulated intestinal fluid) for three hours, and pH 6.8 (stimulated colonic fluid) for seven hours. Consequently, the modified Pulsincap could effectively target the colon to reduce metronidazole, which would lessen its systemic negative effects. Gazzaniga *et al*. combined a timed-release strategy with pH-sensitive polymers. A formulation comprising a drug-containing core encased in three polymeric layers - two pH-sensitive layers and a hydrophilic layer was formulated. The in vitro evaluation results showed that hydrogel formation and pH protection caused a sustained release of the medication **[9, 11]**.

pH dependent colonic DDS

This approach mainly uses the pH gradient that is present in the GIT. pH of the GIT increases from stomach to colon. These polymers are employed in accordance with the variations in the pH levels in the different locations of the GIT. The drug molecule can be coated with appropriate polymers that break down exclusively in the colon to transport the intact molecule to the colon without absorption at the upper part of the gut. The pH-sensitive polymer coating offers a delayed release and shields the active medicament from gastric fluids which helps in the transit of the drug through the large intestine and targeted delivery of the drug in the colon region. Hence the polymers which are used to target the drug delivery should have the characteristics to withstand the acidic environment in the stomach and the basic environment in the intestine. These sensitive polymers are mainly used for coating the outer layer. The knowledge of the pH sensitive polymers eases the design of the colon targeted drug delivery system. However, the drug core which may be in the form of a granule, tablet, pellet, capsule, microparticle or nanoparticle is coated with lower pH soluble materials, the inner core should disintegrate in the alkaline pH of the colon. In certain cases, the disease condition of the patient or the diet intake affects the intestinal pH. A pH sensitive polymer matrix can be used for encasing the drug. For this pellet of uniform size can be prepared by using extrusion Spheronisation. This helps in the targeted drug delivery in the colon. The choice of combination of polymers, coating thickness of the tablets, pH of the media, electrolyte concentration, intra and inter subject variability, transit time etc influences the pH dependent colonic DDS. Cellulose and the derivatives of acrylic acid are most used pH dependent drug delivery system. Hossein *et al*. developed a capecitabine using nano polymeric micelles and cyclodextrin to allow the treatment of colon cancer. The pH sensitivity of the micelles was demonstrated by the in vitro drug release, which also demonstrated that the drug was released more than 80% within the colon and that it was precisely targeted and controlled **[1, 12]**.

pH and time dependent colonic DDS

The time required for the drug to transit through the stomach varies greatly than that of the intestine. Due to this, it is very difficult to predict the exact time that is required for the drug to reach the colon. To reduce the variation in the gastric residence time, we can opt for a time release system of colon specific delivery. For this, we can use drug core gelatin capsule coated with three layers of polymer. The outer layer disintegrates at acidic pH (>5). The intermediate layer is an enteric coated swellable layer which may delay the release of the drug. The innermost layer is a hydrophobic layer which coats the core tablet, thereby increasing the colon targeted drug delivery system. The thickness of the outer acidic layer regulates the time required to release the active pharmaceutical ingredient. Using the liquisolid (LS) technology, Elkhodairy *et al*. developed a matrix tablet containing indomethacin (IDM) for targeted drug release in the colon. An enzyme-degradable polysaccharide and time-dependent polymethacrylate system was developed for CSDD. Bacterial degradable polysaccharides were introduced as drug-loaded LS systems, whereas Eudragit RL 100 (E-RL 100) was utilized as a polymer that modifies with time. After adding the predicted amount of E-RL 100 and lubricating with talc and magnesium stearate in a 9:1 ratio, liquisolid systems that showed encouraging findings regarding release rate of drug in both pH 1.2 and pH

6.8 were compacted into tablets. According to the release statistics, every formulation was able to maintain drug release for an extended period of time **[13, 14]**.

Chronotropic DDS

Here, a hydrophilic swellable polymer is used to encase the drug core which is demonstrated in the figure 3. This polymer helps in the timely release of the drug into the colon. The thickness and viscosity grade of the polymer helps in the delay of the drug release in the GIT. The thickness of coating may be single or multi layered will affect the solubility of the drug in the system **[15, 17]**.

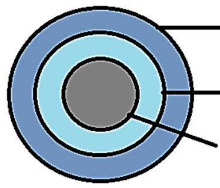

Figure 3: Schematic diagram of Chronotropic drug delivery system

PORT System

In this system, a lipidic plug of the drug formulation and osmotically active agent is enclosed in a gelatin capsule that is coated with a semipermeable membrane. The release of the drug is based on the thickness of the semipermeable coating. When water enters the semipermeable, due to osmotic pressure plug is ejected from the system after a delay **[18]**.

Bacterial enzyme dependent DDS

The microflora of the colon mainly consists of anerobic bacteria which may sustain due to the fermentation of some substrates like polysaccharides, polymers etc. with the help of enzymes such as b-glucuronidase, a-arabinosidase, nitroreductase, azoreducatase, b-xylosidase, deaminase, b-galactosidase, urea hydroxylase etc. Since the presence of biodegradable enzymes are specific to colon, biodegradable polymers are most suitable for the colon targeted drug delivery system. The degree of enzymatic degradation can be impacted by chemical modifications made to the polymers employed in the formulation of CTDDS. Polymer-coated medicines that degrade due to colonic bacteria can be used to target the diseases of the colon. They can protect the drug from the acidic nature of the stomach as well as the basic environment in the small intestine. They undergo breakdown by microorganisms or enzymes in the colon and thereby release the drug in the targeted site. A prodrug-based system is a good example for the bacterial enzyme dependent DDS. The species such as Bifidobacterium, Eubacterum, enterococci, clostridia and Bacteroides influence the hydrolysis and reduction process in the colon. Natural polysaccharides such as chitosan, amylase, pectin, dextran, chondroitin sulphate, guar gum and inulin help to hydrolyse glycosidic bonds in the colon. Roos *et al*. carried out a study in which bovine serum albumin (BSA) hydrogel was formulated by the guar gum with acetyl derivative (AcGGM). It was found that the release of BSA was greatly increased by the addition of β-mannase; after 8 hours, the eznymes enhances the release of BSA by 95%, while only 60% is released in the absence of enzyme **[2, 19]**.

Coating and matrix-based system

In this, the drug molecule is embedded in one or more pH sensitive or biodegradable polymer matrix and another pH independent polymer which is shown in **Figure 4**. These pH sensitive polymer matrices will degrade in basic pH of colon only. The blending of more than one pH sensitive plays a key role in the delivery of the drug in the targeted site. Extrusion technique is a pH sensitive polymer matrix-based system. Polymers such as Eudragit S100, Eudragit L100, HPMC, natural and biodegradable polymers like kondagogu gum and ghatti gum and polysaccharides like chitosan, pectin, alginate cyclodextrins etc. are widely used in the formulation for preparing matrix-based system **[8]**.

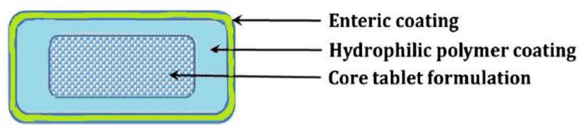

Figure 4: Schematic representation of enteric coated colon targeted delivery system

Multiparticulate system consists of coated pellets in a gelatin capsule, or coated granules compressed in the form tablets. Vemula *et al*. developed flurbiprofen hydroxypropyl methylcellulose matrix tablets with a controlled release mechanism for colon administration. It is evident from the in-vitro trials of the optimized formulation that the drug is delivered in the colon because there was very little drug release during the lag time (5 hours), and then there was regulated release for up to 24 hours **[20]**. In order to effectively transport oxaliplatin (L-OHP) to colon cancers, Folic acid conjugated liposomes were created by Bansal *et al*. and coated with Euragit-S-100 after being encased in alginate beads. Based on in vivo studies, folic acid associated liposomes encased in alginate beads were able to deliver 2.82 ± 0.58 and 21.52 ± 2.76 μg L-OHP/g tissues, respectively, to the colon and tumour after 12 hours, indicating their ability to target both organs. The outcomes unequivocally show that folic acid associated liposome-bearing calcium alginate beads covered with Eudragit can be a promising therapeutic delivery vehicle for colon-specific tumours **[21]**. In order to treat colon cancer effectively, 5-fluorouracil was precisely targeted to the colon with less hazardous side effects, A chitosan-based colon-targeted medication delivery system was developed by Ren *et al*. To test the viability of the composite films as coating materials, they were employed in a bilayer system. Drug release in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) was inhibited by the Eudragit- and chitosan/gelatin-bilayer coating system, according to in vitro drug release studies. On the other hand, In SGF, the active medicament released from a bilayer-coated tablet increased with time, and within 24 hours, the medication was virtually entirely discharged. All things considered, a chitosan/gelatin complex film and a multilayer coating technique were used to accomplish colon-targeted drug delivery **[22]**. Using ethyl cellulose and Eudragit RL 100, either separately or in combination, Abdullah *et al*. produced Mebeverine HCl matrix tablets for colon-targeted drug administration. The process of dissolution involved two hours in 0.1 N HCl and eight hours in pH 6.8 phosphate buffer. Since uncoated forms released over 5% of the medication in 0.1 N HCl, a coat of Eudragit L100 was applied. The findings showed a relatively delayed release profile. Consequently, the matrix was prepared using a single retardant and coated with Eudragit L 100. Additional research was conducted on the matrix comprising 7% Eudragit RL 100 and 6% binder to evaluate the impact of various coats (cellulose acetate phthalate and Eudragit L 100-55) and binders (pectin). Since the final formula remained stable, it can be said that the system that had been designed had the ability to give Mebeverine HCl to the colon in vivo. Yassin *et al*. **[23]** used compression coating in conjunction with granular chitosan coating. The formulation's in vitro assessment revealed that at acidic pH levels, the drug release gradually decreased as coating thickness increased. Furthermore, the in vivo investigations demonstrated that this formulation remained intact until it reached the large intestine. Kadiyam *et al*. **[24]** developed a tramadol HCl matrix-based colonic drug delivery system that was compression-coated with Eudragit® S100 and consisted of almond gum. The findings demonstrated that the release of tramadol HCl may be successfully postponed for 24 hours using compression-coated tablets. The drug was efficiently transported to the colon by the compression-coated tablets, which did not break down in the upper gastrointestinal system, according to in vivo X-ray imaging investigations conducted on rats. Obitte *et al*. **[25]** carried-out studies on metronidazole hydrophobic polymers Eudragit® L-100 and Landolphia owariensis latex (LOL) are used to regulate the drug release with a focus on colon targeting. Drug release increased as pH increased, according to in vitro dissolution experiments. Over a prolonged length of time, LOL and the polymer Eudragit® L 100 showed a cumulative effect in prolonging and subsequently enhancing drug absorption at pH 7.4 **[26]**.

pH and bacterial enzyme dependent colonic DDS

This system is a combined approach that provides the advantages of both pH dependent DDS and bacterial enzyme dependent delivery systems and avoids the limitations of the same. CODES^{TM} is the best example of this which is illustrated in **Figure 5**.

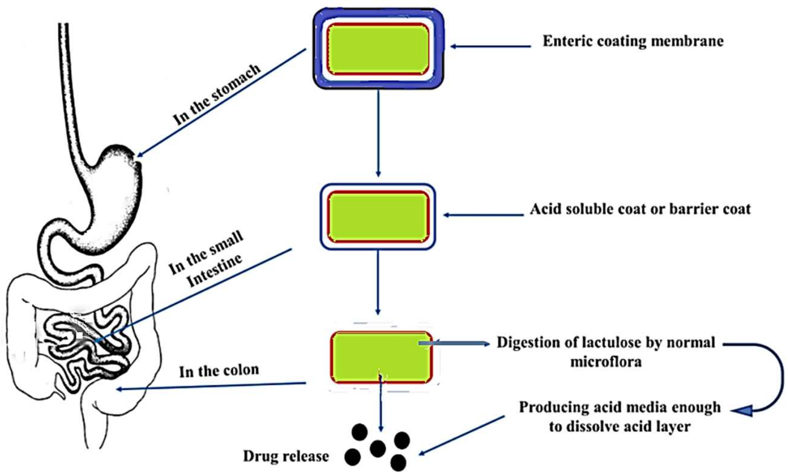

Figure 5: Schematic design of CODES^{TM}

Here the tablet core consists of lactulose, a polysaccharide acts as the trigger for the site-specific drug release which may be mixed with the drug. This is again coated with acid soluble polymer like Eudragit E which protects the drug in the small intestine. This system is subsequently coated with an enteric coated polymer such as Eudragit L which protects the tablet inside the stomach and get disintegrated when it reaches the small intestine. When the tablet reaches the colon, lactulose gets enzymatically degraded by the bacteria into organic acid and lowers the pH resulting in the breakdown of the acidic coating and thereby release of the drug in the colon **[26, 27]**.

Colonic pressure-controlled DDS (PCDC System)

This system is designed based on the increased pressure in the colon. The movement of particles in the upper GI tract is mainly based on peristalsis. But in the larger intestine, mass peristalsis is responsible for the movement of contents from one part to another which in turn increases the pressure inside the lower GI tract. PCDC system is prepared by using a water insoluble polymer capsule. The viscosity of luminal content and pressure inside the colon are high when compared to small intestine due to the reabsorption of water and mass peristalsis. Water insoluble polymer capsule disintegrates because of high pressure that is generated inside the colon and release the drug. Takaya *et al.* created capsules that use luminal pressure to determine the drug's delivery to the colon. The very viscous composition resulting from the reabsorption of water from the colon could be a challenge for site-specific delivery, even if these systems enable the administration of drugs to the colon instead of the small intestine because of increased colonic pressure **[28]**.

Osmotic pressure controlled colonic drug delivery system

An osmotically controlled drug delivery system is used for targeting the drug locally to the colon to achieve systemic drug absorption. OROS-CT is an example of an osmotically controlled system which is shown in **Figure 6**.

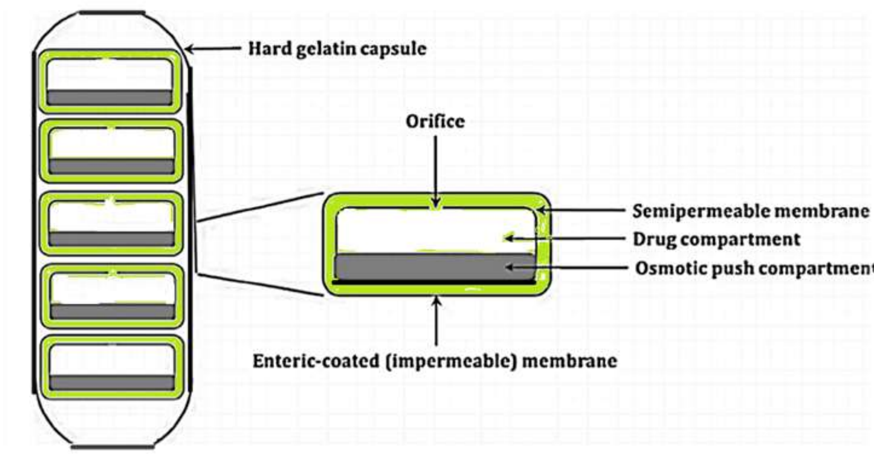

Figure 6: OROS-CT colon targeted drug delivery system

One osmotic unit or more than five push-pull units make up this system, each of 4mm diameter, having a drug layer and osmotic push layer, which is surrounded by a semipermeable membrane. This entire unit is encapsulated in a hard gelatin capsule. When the OROS-CT is administered, the outer gelatin capsule gets dissolved in the stomach. When the unit enters the small intestine, coating starts to dissolve due to the high pH. Water consequently seeps into the device, causing the osmotic compartment to expand. This causes the medicament to be pushed via the aperture located close to the drug compartment at controlled rate. In order to avoid distribution of drug in the small intestine, every unit is engineered with a 3–4 hour lag time and the finally the drug gets released in the colon **[29]**.

Covalent linkage of the drug carrier

When a medicine is taken orally, the moiety in the GIT is left intact due to the covalent bond that forms between the drug and carrier.

a. Prodrug Approach

The covalent linkage of the drug and the carrier chiefly entails the formation of prodrug. Prodrug is an inactive compound of a parent drug molecule which is pharmacologically activated when metabolized**.** The colon should have significantly more hydrolysis than the upper gastrointestinal tract**.** This is mainly used to mask the undesirable aspects of drugs such as chemical instability, limited bioavailability, lack of site specificity etc. Colon targeted prodrug activation can be achieved by leveraging a particular characteristic at the target location, like a changed pH or elevated activity of specific enzymes in comparison to the non-target tissues prodrug-drug conversion. The drug-carrier covalent linkage which has an outer coating of hydrophilic nature helps the drugs to remain intact in the GIT. When the drug enters the colon, a targeted release of drug occurs due to enzyme degradation which may expose the lipophilic core of the drug. Kim *et al*. developed a prodrug of metronidazole, which when introduced into the cecum of rats, was converted to the active drug, metronidazole. This prodrug was found to have significantly decreased systemic absorption and did not metabolize in the small intestine when compared to oral metronidazole **[30]**. Metronidazole and pectin were conjugated by Vaidya *et al*. using the prodrug method. The release of active compound from this formulation was compared with metronidazole-pectin microspheres. The drug release in the upper gastrointestinal tract was notably lower with the pectin-metronidazole (PT-ME) prodrug when compared to the metronidazole prodrug. Studies showed that there is no drug release from the PT-ME prodrug in the acidic environment as 100% of the metronidazole was physically entrapped in pectin microspheres **[31]**.

b. Azo bond conjugates

Azo aromatic polymers are found to be utilized more for colon targeting. The drug carrier, which may be a synthetic or natural polymer, attached to azo bond helps the drugs like peptides to remain intact in the stomach and intestine. Azo polymers can also be used as coating material. As the pH increases in the GIT, the swelling property of the polymer also increases which helps preventing the drug from breaking down by peptidases in the stomach and intestine. Once the drug reaches the colon, the azo reductase enzymes produced by the azo bacteria in the microflora of the colon degrades the azo bonds and helps in the targeted release of the drug in the colon region. Azo bonding is also used to bind a drug to a carrier molecule via covalent bonds which prohibits the breakdown of the drug in the stomach and the intestine.

Certain drugs like steroids attains better absorption in colon due to the azo bonding. Numerous additional factors, such as the type of food consumed, the coadministration of chemotherapeutic drugs, and dietary fermentation precursors, may also influence the bacterial breakdown of polymeric coating. Antibiotic administration has the potential to destroy colonic microbiota entirely or partially, which has a negative impact on the release of bioactive compounds. Another method utilizes the incorporation of hydrolysable molecules in the hydrogel matrix of the active pharmaceutical ingredient. Hita *et al*. formulated metronidazole capsules having unique polymer coating. The results from both in vitro and in vivo experiments demonstrated that the microbiota of colon broke down the layer of azo-aromatic and pH-sensitive polymers which was applied to the metronidazole capsules and locally released metronidazole within the colon. Hita *et al*. coated azo polymers with azo aromatic and pH-sensitive polymers to provide a colonic targeting for metronidazole capsules. Physical characteristics of these polymers were examined, including pH, film-forming abilities, and the impact of colon bacterial flora. Both in vivo performance investigations and in vitro release were conducted on the systems. The results of the tests showed that metronidazole may be effectively targeted to the colon by using azo aromatic polymers, which are cleaved by the colonic bacteria **[32]**.

c. Glycoside Conjugate

Some drugs conjugated with different sugar moieties and form glycosides. These hydrophilic glycosidase moieties break down in the GI tract and release the drug. The glycosidase produced by the intestinal microflora is found to be good candidates for colon targeted drug release. The bacterial glycosidases liberate the drug from the glycosidase derivatives in the colon without considerable absorption in the small intestine **[33]**.

d. Glucoronide Conjugate

Bacteria that is present in the lower portions of the GIT can form a complex with drug as b-glucouronidase as well as split the complex as in deglucoronidation. Deglucuronidation helps in the availability of the active drug and enables the absorption process while glucuronidated drug does not allow the drug to be absorbed **[34]**.

e. Cyclodextrine Conjugate

The bioavailability, stability and safety of the drug can be improved by using cyclodextrine conjugates and is considered as potent drug carriers. These conjugates are made up of an outer hydrophilic layer which can slow down the release rate of water and inner lipophilic layer which helps them to form inclusion complexes with other drug molecules. They degrade in the presence of colonic bacteria and form small saccharides which will readily get absorbed in the colon. Moreover, a and b cyclodextrins are resistant to pancreatic amylases, gastric acid and saliva. Thus, these conjugates are considered as good candidates for the colon targeted drug delivery system **[3, 33]**.

f. Dextran Conjugate

The parts of dextranase are glycoside bonds holding monosaccharides together, which are hydrolyzed by bacteria, moulds, or mammalian cells when dextranase is present. Compared to other regions of the GIT, Bacteroides found in the colon area have higher levels of dextranase activity. In the colon, dextran conjugated drug molecules break down to produce colonic esterase, releasing the free medication **[33]**.

g. Amino acid Conjugate

The carboxyl groups and amine groups reduce the membrane permeability of the amino acid conjugates. They show more enzymatic specificity for hydrolysis by colonic enzymes **[4]**.

h. Polymeric prodrugs

Polymers of natural sources as well as synthetic sources are used as drug carriers for targeting the colon. If the drug molecule is coated with the appropriate polymers that break down exclusively in the colon, it can be transported intact to the colon without absorbing at the proximal portion of the gut. To safeguard the drug core in conditions that mimic in vivo settings, a layer of significant thickness is needed **[9]**.

i. Hydrogels

Hydrogels protects the drug in the acidic pH in the stomach by swelling. As the pH increases, swelling also increases. This helps in the release of the drug at the targeted site. With the ingenious application of cutting-edge gas-shearing technology and the ionic diffusion method, Liu *et al*. created an adhesive colon-targeted hydrogel microsphere that can adhere to the colon region and regulate the microenvironment in the treatment of inflammatory bowel disease. In vivo imaging demonstrates the mucoadhesive properties of the thiolate-hyaluronic acid hydrogel core of the microsphere, which lowers the systematic exposure and lengthens the local drug dwell time, while the degradation experiment reveals the alginate hydrogel shell's anti-acid and colon-targeted properties **[35]**. To improve absorption and extend the duration of action of Tolmetin Sodium, Ramadan *et al*. created rectal mucoadhesive hydrogels. The in-vitro drug release of the optimized formulation exhibited a regulated drug release pattern, reaching 72–92.6% after 8 hours. Relative bioavailability was found to be 357.93% with 2% CMC. Ultimately, there was a strong correlation found between the in-vitro and in-vivo profiles **[36]**.

Bio adhesive Systems

These systems help to increase the contact time of drug with a particular organ. The longer residence time of drug results in high concentration of drug at the targeted site and hence better absorption. To improve the absorption of poorly water-soluble medications in the colon, polymers such as polycarbophil, polyurethane, and polyethylene oxide are employed as bio-adhesive components that cause formulation retention for an extended period in the colon **[8, 37]**.

Polysaccharide based delivery system

Polysaccharide is a biodegradable compound and is a polymer of monosaccharides. It can be obtained naturally from plants or animals from microbes. They are not easily broken down by GIT enzymes. They remain intact in the stomach and intestine and have high affinity for the colonic microbes and are degraded by the enzymes present in the micro flora of the colon. In addition, the polysaccharide linked drugs shows better absorption in colon. For example, non-enteric cellulose esters are insoluble in water and are highly soluble in alkaline pH. They are considered as good candidates for the colon targeting. A comparison of efficacy of several polysaccharides in colon-targeted metronidazole administration was conducted by Mundargi *et al*. The findings demonstrated that the type and concentration of the polysaccharide utilized in the formulation do affect the rate at which metronidazole releases. Gauri *et al*. **[38]** prepared metronidazole matrix tablets using varying quantities of guar gum and xanthan gum. When the tablets were evaluated in vitro in 0.1 N HCl, pH 7.4 phosphate buffer, and pH 6.8 phosphate buffer with 4% w/v rat caecal content, it was observed that the drug released from the matrix tablets varied between 12 and 33% during the first five hours, which corresponded to the time spent in the stomach and small intestine. The matrix tablets were shown to be more vulnerable to colonic enzymes and delayed drug release is observed because of the increased xanthan gum concentration. It has been discovered that employing a mixture of polysaccharides in CTDDS is more successful than using a single polysaccharide in achieving colon specific delivery. Colon-specific distribution can be achieved with the help of polysaccharides like pectin, chitosan, chondroitin sulphate, galactomannan, and amylose, which are safe for the organisms and easily broken down by the colonic enzyme **[39]**.

Multiparticulate Systems

Particle sizes in multiparticulate systems are smaller than in single-unit systems. Since they move more easily through the GI system, they can get to the colon faster. Microspheres which are formulated using biodegradable polymer is one example for the multiparticulate system which can be taken up by macrophages. A metronidazole multiparticulate system comprising crosslinked chitosan microspheres coated with pH-sensitive Eudragit® polymers was the subject of in vitro drug-release research conducted by Chourasia *et al*. Polymers are dissolved in the alkaline pH of the stomach and helps in the release of Metronidazole in the colon **[33]**. To create a multiparticulate system, Vaidya *et al*. coated pH-sensitive polymer Eudragit® S 100 on microspheres of the polysaccharide pectin. The in vitro drug release studies demonstrated that the stomach's acidic pH prevented the release of metronidazole. However, as soon as the colon's pH raised to an alkaline level, metronidazole was continuously released. Furthermore, in vivo evaluation showed that the multiparticulate technology could precisely deliver the drug to the colon **[41]**. Pectin-4-aminothiophenol (Pec-ATP) conjugate was used by Perera *et al*. to develop and assess the microparticles. They found that these particles were significantly more stable in vivo than unmodified pectin microparticles. They suggested that Pec-ATP microparticles proved a better choice for colon-targeted administration **[42]**.

CONCLUSION

Nanotechnology has emerged as a promising approach for colon-targeted drug delivery, allowing for enhanced permeability, better absorption, and targeted drug delivery. The colonic area of the gastrointestinal tract is becoming a more crucial location for the delivery and absorption of drugs. Dual stimuli responsive systems, such as those combining pH and enzyme sensitivity, have shown exceptional drug specificity and selectivity to the colon, reducing systemic drug absorption and side effects. Natural plant derived nanoparticles offer a cost effective and ecofriendly alternative for targeted drug delivery in CTDDS, with improved therapeutic and physicochemical properties. CTDDS is a promising approach for the therapy of colonic disorders, including inflammatory bowel disease and colorectal cancer. The gastrointestinal tract contains a wide variety of pH values and distinct enzymes, which the dosage form must pass through before reaching the target site. This complicates the distribution efficiency and colon targeting of the drug.

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