



A Generous Review: Novel Approaches for Colon Targeted Drug Delivery System

Gopavaram Sumanth^{1*}, Pooja Prakash Atpadkar¹, Pandupalli Krishna Reddy¹ and Gorthi Nihar²

¹*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER) – Raebareli, Uttar Pradesh, India.*

²*Department of Industrial Pharmacy, JSS Collage of Pharmacy – Mysuru, Karnataka, India.*

Authors' contributions

This work was carried out in collaboration among all authors. Author GS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors PPA and PKR managed the analyses of the study. Author GN managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The colon is where both systemic and local conveyance of medications can occur. Local conveyance permits site treatment of inflammatory bowel disease, Crohn's illness, ulcerative colitis, and so forth in any case, treatment can be created compelling if the medications can be focused on straightforwardly into the colon, in this way diminishing the systemic adverse effects. A medication should be shielded from degradation to accomplish effective colon targeting delivery, release, and absorption in the upper bit of the gastro intestinal tract (GIT) and afterward to be certain controlled delivery in the proximal colon. Pressure controlled colonic conveyance capsules, CODESTM, and the osmotic controlled medication conveyance are the more up to date advances in particular which are having in vivo site explicitness, and attainability of manufacturing process. To beat previous technique's restrictions new frameworks and advancements have been created for colon targeting. This review gives data about CDDS, new advances, limitations.

*Corresponding author: Email: sumanth925@gmail.com;

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1. INTRODUCTION

The object of a targeted drug delivery system is to deliver a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site. It is appropriate and needed for the medications having unsteadiness, low solvency, short half-life, a huge volume of dispersion, helpless retention, low explicitness, and therapeutic index. Targeting may give the most extreme restorative action (by forestalling corruption or inactivation of medication). In the interim, it can likewise limit adverse effects, the harmfulness of powerful medications by decreasing dose [1]. The colon drug delivery system (CDDS) should be equipped for securing the medication enroute to the colon (i.e., Drug delivery and retention ought not happen in the mid-region and the small digestive system and bioactive specialist ought not be corrupted) [2]. Site-explicit conveyance into the colon isn't just required for local therapy of an assortment of colon illnesses, like ulcerative colitis, Chron's sicknesses, amoebiasis, colon malignant growth, but also a systemic release of proteins and peptides. This is a result of less variety and force of stomach related compounds and less proteolytic action of colon mucosa than that saw in the small digestive system. Next to the colon infections, this framework is likewise useful in the treatment of asthma, angina, and rheumatoid joint inflammation for exploiting chronotherapeutic drug conveyance and for conveyance of steroids [3].

2. ADVANTAGES OF COLON TARGETING DRUG DELIVERY SYSTEM [4]

- Colon is an ideal site for the release of agents aimed to treat the local diseases of the colon.
- Local treatment has the benefit of requiring smaller drug doses.
- Decreases dosage frequency. Hence reduce the cost of expensive drugs.
- The colon is a striking site where less absorbed drug molecules may have an enhanced bioavailability.
- Bypasses the first pass metabolism.
- It has a longer retention time and seems highly responsive to agents that increase the absorption of poorly absorbed drugs.
- Possibly leading to a decreased incidence of side effects and drug interactions.
- Improves patient compliance.

- Targeted drug delivery system.
- Colon is an ideal site for the transport of vehicles to fix the nearby infections of the colon.

3. CRITERIA FOR SELECTION OF DRUGS FOR CDDS

3.1 Drug Candidate

Drugs that show less absorption in the stomach or bowel, including peptides are most appropriate for CDDS. The drugs utilized in the action of inflammatory bowel diseases (IBD), ulcerative colitis, diarrhoea, and colon cancer are ideal predictions for colonic delivery [5].

3.2 Drug Carrier

The choice of the carrier for the specific up-and-comer medication relies upon the physiochemical idea of the medication just as the illness for which the framework is to be utilized. The elements, for example, substance nature, steadiness, and partition coefficient of the drug, and the kind of absorption enhancer picked impact the transporter decision. In addition, the decision of the drug carrier relies upon the working groups of the drug molecules [6]. For instance, aniline or Nitro groups on a drug might be utilized to associate it with another benzene group through an azo bond. The transporters, which contain added substances like polymers (might be utilized as networks and hydrogels or covering specialists) may impact the delivery properties just as adequacy of the dosage form [7].

4. COLONIC DISEASES

- Crohn's Diseases
- Ulcerative Colitis
- Diversional Colitis
- Ischemic Colitis
- Diverticular Inflammatory Bowel Disease
- Colon Cancer
- Lymphoma of the Colon

5. NEWLY DEVELOPED APPROACHES FOR CDDS

5.1 Pressure-Controlled Drug-Delivery Systems

Because of peristalsis, higher pressures are experienced in the colon than in the small

intestine. Takaya et al. [8] have created pressure-controlled colon release capsules prepared using ethyl cellulose, which is insoluble in water. In such frameworks, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose layer is the main factor for the disintegration of the formulation. The system also seemed to rely upon capsule size and thickness. On account of reabsorption of water from the colon, the consistency of luminal content is higher in the colon than in the small intestine. It has in this manner been reasoned that drug dissolution in the colon could present an issue concerning colon-specific oral delivery systems. In pressure-controlled ethyl cellulose single-unit capsules, the drug is in a liquid. Lag times of three to five hours according to drug absorption were noted when pressure-controlled capsules were given to humans [9].

5.2 Newly Developed Colon Targeted Delivery System (CODES™)

It is an extraordinary CDDS innovation that was created to evade the established issues related

to pH or time subordinate plans. CODES has joined methodology of pH subordinate and microbially set off CDDS. It has been delivered by utilizing an interesting system including lactulose, which fills in as a trigger for site explicit medication discharge in the colon. The frame work includes a characteristic tablet center joined with lactulose, which is enclosed over with Eudragit E (corrosive solvent material) and further enclosed with Eudragit L (enteric covering polymer). The intention of this innovation is that CODES™ stays unblemished in the stomach, however the enteric and border covering will break up in the small digestive system, where the pH is over 6.) Because Eudragit® E starts to disintegrate at pH-5, the inward Eudragit® E layer is just slightly penetrable and swellable in a small digestive system. Upon entry into the colon, the polysaccharide inside the center tablet will break up and diffuse through the covering. The microorganisms will enzymatically debase the polysaccharide into natural corrosive. This brings down the pH encompassing the framework adequate to impact the disintegration of the corrosive dissolvable covering and resulting drug discharge [10].

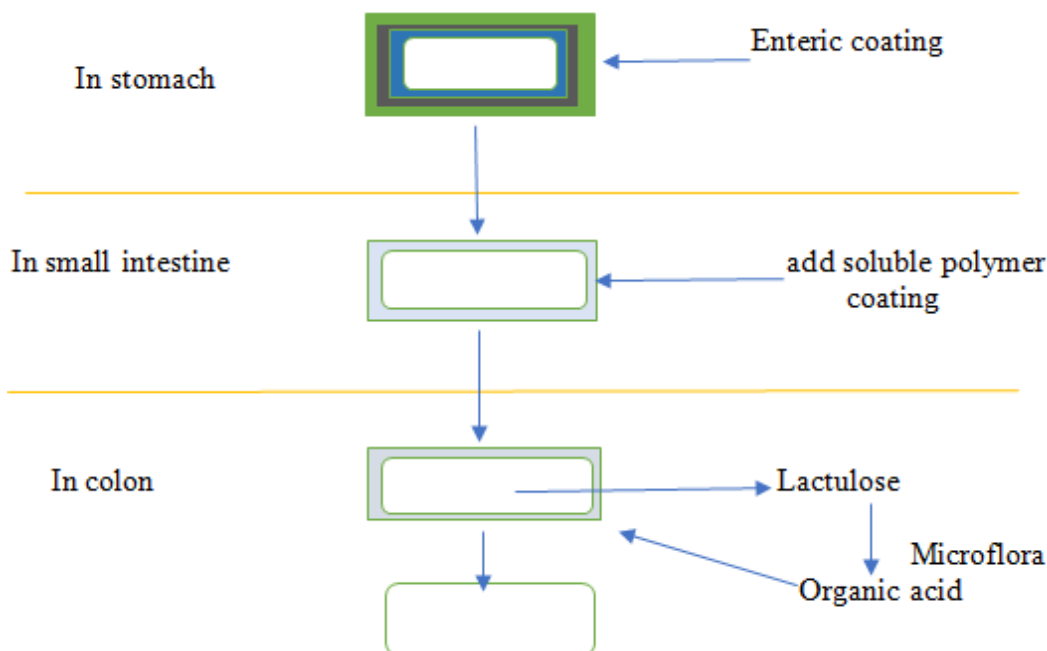


Fig. 1. Schematic design of CODES™

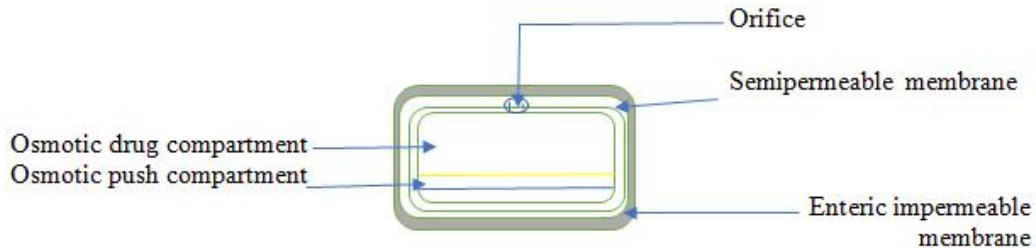


Fig. 2. Schematic design of OROS-CT

5.3 Osmotically Controlled Delivery System (OROS-CT)

This framework comprises of osmotic units. The osmotic units are utilized either independently or upwards of 5-6 push-pull units that are exemplified in a hard gelatin case. The push-pull units are bilayered with external enteric impermeable layer and inward semi penetrable film. The inward or focal piece of the push-pull unit comprises of the medication layer and push layer. The semipermeable membrane which is available close to the medication layer comprises a hole through which the medication substance is removed throughout time. The capsule body enclosing the push-pull units gets dissolved suddenly after administration [11]. During the section of the push get units through the GIT the enteric semi-permeable film forestalls the water ingestion into the unit. The covering gets disintegrated once it arrives at the small digestive system because of higher pH (>7). Water enters the unit through the semipermeable film causing the push layer to expand. The swelling of the push compartment forces the drug into the surrounding climate through the orifice. These osmotically controlled drug delivery frameworks convey the drug at a steady rate for up to 24hr [12].

5.4 Liposomes in CDDS

High molecular weight particles include e. g. octyl sulfate, lauryl sulfate, hexadecyl sulfate, cetyl stearyl sulfate [13]. Liposomes are the bilayered covered vesicular structures involves hydrated phospholipids. Liposomes can entrap compounds of various solubilities because of their substituting hydrophilic and hydrophobic structure. Nonetheless, the broad change or fitting of the fundamental liposomal structure of the hydrated phospholipid bilayer is related with the physicochemical makeup of the vesicle. This

flexibility of liposomes helps in different applications, for example, in radiology, cosmetology and Vaccinology. Liposomes with a size range from 25 millimeters to a few micrometers are generally proliferated in a fluid medium. A few terminologies are there for characterizing liposome subtypes relying on their technique for vesicle preparation or on underlying boundaries. Liposomes can be recognized by their size and number of lamellae, for example, large unilamellar vesicles (LUV), Small unilamellar vesicles (SUVs), and huge multilamellar vesicles or multivesicular vesicles. SUVs with low molecule sizes inside the nm range are of interest as liposomal nanocarriers for drug and antigen delivery [14].

5.5 Bioadhesive Systems

A few drugs require high concentration in the large intestine through oral administration for their ideal therapeutic impacts. Bioadhesion is a system by which a dosage form stays in contact with a unique organ for an expanded time of the fourth dimension. This more extended residence time of the drug results in an enhanced local concentration. If there should arise an occurrence of poorly absorbable medications, it helps in improving absorption qualities. This system is significantly more valuable in the formulation of CDDS. A few polymers like polycarbophil, polyurethanes, and polyethylene oxide polypropylene oxide copolymers have been examined as materials for Bioadhesive frameworks. In any case, Bioadhesion has been accepted to show a superior exhibition and expanding the mean residence time of CDDS [15].

5.6 Nano Drug Delivery System (NDDS)

Nanoparticles are relied upon to become drug transporters for accomplishing oral peptide

conveyance. On account of polymeric nanoparticles have the upsides of shielding the protein and peptide drugs from a compound and enzymatic debasement in the GIT, so expanding their strength and retention across the intestinal epithelium just as holding the drug discharge. An everyday practice of strategies, for example, polymerization, nanoprecipitation, inverse microemulsion can be used to plan polymeric nanoparticles, be that as it may, a large portion of these techniques requires the utilization of natural solvents, heat, and incredible disturbance which might be unsafe to the peptide and protein drugs. All the more as of late the ionic gelation strategy has been utilized as the most ideal [16].

5.6.1 Redox-responsive NDDS

Formulation of drugs that react to changes in redox potential could be a promising system in the treatment of colorectal cancer (CRC) and ulcerative colitis (UC) [17,18]. Overproduction of reactive oxygen species (ROS) by provocative cells in response to oxidative pressure has been related to UC [19,20]. Along these lines, NDDS, which are corrupted by ROS, could deliver tranquilizes explicitly to inflamed colon tissues. In light of this idea, redox nanoparticles (RNPs) having nitroxide radicals as ROS scroungers in their center have been accounted for to suppress UC in mice [21]. As of late, a similar group exhibited that RNPs explicitly accumulated in malignancy tissues and essentially suppressed colitis-related colon disease [18]. Although ROS-responsive nano-conveyance systems speak to a novel way to deal with explicitly target aggravated tissues in UC [22], a few hurdles, for example, premature drug discharge, and unsteadiness in the upper GI tract could limit positive therapeutic results. To constrict these issues, numerous improvements responsive NDDS could be an ideal methodology.

5.6.2 Plant-derived edible nanosystems

Synthetic NDDS have shown great potential in the management of colon-specific diseases. However, their long-term use may carry the risk of possible *in vivo* toxicity. Secondly, large-scale production for clinical applications may be costly and technically challenging [23]. Conversely, the use of NPs derived from natural sources is believed to be safe and cost-effective and can overcome the limitations of synthetic NPs. Direct administration of a natural drug is often limited owing to low solubility, absorption, and bioavailability [24]. Decrease the particle size is

one of the most operative and suitable techniques for solubility improvement of a poorly water-soluble drug [25]. Consequently, the application of nanotechnology is an appropriate method to improve the physicochemical and therapeutic assets of a naturally-derived drug source [26]. Recently, it has been stated that plant-based NPs from ginger, grapes, grapefruits, carrots, and tomatoes may be secluded using eco-friendly techniques [27]. Recently, ginger-derived edible NPs (GDNPs) have been proposed for the prevention and treatment of IBD and CRC. The size of GDNPs was ~230 nm, and the surface charges were negative. These NPs confined high levels of lipids, a few proteins, miRNAs, and huge amounts of bioactive ginger-derived agents. The GDNPs showed no toxicity in animal models. The study showed that GDNPs mitigated colitis, improved intestinal healing, and avoided chronic colitis and associated CRC [28]. Grape exosome-like NPs and broccoli-derived NPs have also shown protective effects against experimental UC in mice [29,30]. In addition, NPs fabricated from plant-derived lipids may be employed to load drugs, as well as surface functionalization for efficient delivery to a specific organ. Zhang et al. [22,33,28,31] collected NPs from ginger and reconvened their lipids into ginger-derived nano vectors (GDNVs) that showed excellent biocompatibility. Doxorubicin (Dox) was loaded in GDNVs with high efficiency, and FA was conjugated for targeted delivery on the surface of nano vectors. Compared with free Dox, the FA-Dox-GDNVs significantly inhibited the growth of Colon-26 tumors in mice [31]. These observations advise that the use of plant-based edible NDDS could be a novel strategy for the safe therapy of colon-specific disease.

5.7 Pulsatile Colon Targeted Drug Deliver [32]

5.7.1 Pulsincap system

These (single-unit) frameworks are generally evolved in a capsule structure. The medication is delivered as a "pulse" from the insoluble case body by growing or disintegration of attachment (control slack time). A swellable hydrogel plug was used to cover the medication substance into the capsule body, and after contact with the disintegration liquid, it swells, and after a slack time, the fitting propels itself outside the case and quickly delivers the medication. The length of the attachment and its place of inclusion into the container controls the slack time.

5.7.2 Port system

This system was created on the principle of delayed drug release. This system contains:

- Gelatin capsule covered with a semipermeable membrane (g., cellulose acetate) casing,
- An osmotically active agent along with the medication formulation
- An insoluble mass (g., lipidic)

6. LIMITATIONS [33,34]

- Colon offers a close to impartial pH, at the site of medication conveyance diminished enzyme movement a long travel time and expanded responsiveness to absorption enhancers.
- Wide scope of pH values and various enzymes present all through the gastrointestinal tract, through which dosage form needs to go prior to arriving at the target site.
- For better drug distribution it should be in solution form before it reaches the colon
- Fluid content in the colon is a lot lower and it is thicker than in the upper part of the GIT.
- The stability of medicament is also a concern and must be taken into consideration while scheming the delivery system.
- The drug may potentially fix in a non-specific manner to dietary residues, intestinal emissions, mucus, or fecal matter.
- The inhabitant microflora could likewise influence colonic performance via metabolic corruption of the drug.
- Lower surface region and relative tightness also disturbs the bioavailability of drugs.

7. CONCLUSION

CDDS produce both local and systemic impacts. The benefit of CDDS is, long transit time near neutral pH, decreased enzymatic activity, and enhanced sensitivity to absorption enhancers. The objective of CDDS is to protect the formulation during its movement over the stomach and small intestine, the primary objective of CDDS is to secure the formulation. Novel approaches are more precise compared to primary approaches such as pressure-controlled, CODES, pulsing cap system, OROS-CT, bioad-

hesion. For colon targeting, both synthetic polymers and polysaccharides are used. The delivery of colon-targeted drugs offers safe, efficient, and more affordable delivery of drugs at the target site with minimal variability.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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