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Review Article

A Novel Approach on Nanosphere Based Colon Targeted Drug Delivery System

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Abstract:
Oral route is the most feasible and desired one, CDDS may also employ alternative methods. When administering medications directly to the colon, rectal administration is the fastest method. Rectal administration makes it challenging to reach the proximal portion of the colon. Rectal administration may potentially cause patients discomfort and result in poor compliance. Particles with a diameter between 10 and 200 nm are known as nanospheres. Nanospheres can be crystalline or amorphous in form, and they can shield a medicine from enzymatic and chemical deterioration. When treating colonic illness, targeted drugdelivery to the colon ensures direct therapy at the afflicted area with a lower dose and less systemic adverse effects and provides an appropriate environment for proteins and peptides that are susceptible to gastric fluid and digestive enzymes. It also minimizes the first pass metabolism advantage of the standard dose form and prevents gastrointestinal discomfort brought on by the ingestion of NSAIDs.
Keywords: Nanospheres, CDDS, Nanoparticles, NSAID, gastrointestinal discomfort

Introduction

For the local treatment of a number of bowel disorders such ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, the local therapy of colonic pathologies, and the systemic distribution of protein and peptide medicines, targeted drug delivery into the colon is extremely desirable. The colon specific drug delivery system (CDDS) should be able to protect the drug while it is being delivered to the colon, meaning that neither drug release nor absorption should take place in the stomach or small intestine, nor should the bioactive agent be degraded in either of the dissolution sites [1].
In order to protect peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and eventually release the drug into the ileum or colon, which results in greater systemic bioavailability, CDDS protects peptide drugs from the diversity and intensity of digestive enzymes, which is why CDDS is believed to be a suitable absorption site for peptides and protein drugs. [2].

At the very least, the colon has a significant residence duration of up to 5 days and is quite receptive to absorption enhancers. Although the oral route is the most practical and desired one, CDDS may also employ alternative methods. When administering medications directly to the colon, rectal administration is the fastest method. Rectal administration makes it challenging to reach the proximal portion of the colon. Rectal administration may potentially cause patients discomfort and result in subpar compliance [3].

Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azo-reduction and enzymatic cleavage i.e. glycosides [4-7].

These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration.The stomach and intestine make up the majority of the GIT. The small and large intestines make up the intestine. About 5 meters long, the GIT is. Upper and lower gastrointestinal tracts are used to separate the various GIT components. The oesophagus, stomach, and duodenum are all parts of the upper GIT. Both the small and large intestines are part of the lower GIT [8].

The digestive system ends with the colon. Prior to elimination from the body, it draws water and salt from solid wastes. It is also the location where flora-aided (mostly bacterial) fermentation of unabsorbed material takes place. The colon does not significantly contribute to food and nutritional absorption, in contrast to the small intestine. The colon receives around 1.5 liters, or 45 ounces, of water.The length of the adult human male colon is 65 inches or 166 cm (range of 80 to 313 cm), on average, for females it is 155 cm (range of 80 to 214 cm). The Colon is a part of the large intestine. It is between cecum and the rectum [9]. The colon takes water from the feces that goes through it. The colon in mammals can be divided into four sections:

1. The ascending colon
2. The transverse colon
3. The descending colon
4. The sigmoid colon

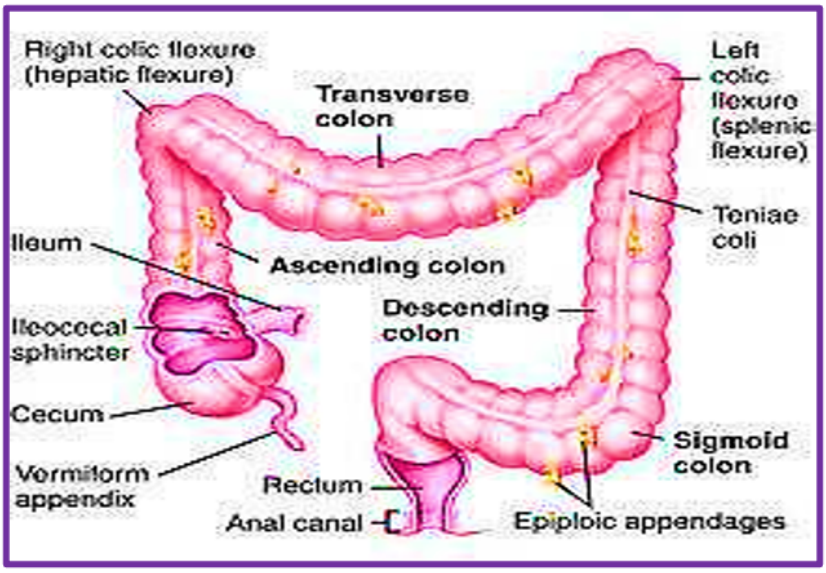

Figure 1: Anatomy of Colon

2. Strategies for Targeting Drugs to the Colon

The approaches for colon specific drug delivery system are prodrug or coated or Nanoparticle preparation. The commonly used approaches are;

- pH dependent
- Time dependent
- Pressure dependent
- Bacteria dependent

2.1 pH Dependent Delivery:

Drug transport to the colon has been facilitated by changes in pH along the gastrointestinal system. This can be accomplished by using coatings that remain intact at lower stomach pH levels but disintegrate at neutral colon pH levels. The stomach has a pH of 1.2, the proximal small intestine has a pH of 6.6, and the distal small intestine has a pH of roughly 7.5. Drugs have been delivered to the small intestine using pH sensitive enteric coating in the past using this pH fluctuation in the stomach and small intestine [10].

These polymer coatings are resistant to the stomach's acidic environment, but they ionize and disintegrate over a certain alkaline pH threshold seen in the small intestine. Therefore, using enteric polymers with a relatively high threshold pH for dissolution and subsequent drug release allows for the application of the same principle to the delivery of medications to the terminal of the ileum or colon. Methacrylic acid and methylmathacrylate, which dissolve at pH 6 (Eudragit L) and pH 7 (Eudragit S), are the most popular polymers used for this purpose have been investigated. [11] This approach depends on the way that the gastrointestinal pH is rise continuously from small digestive tract to colon12. Be that as it may, the pH of the distal is 6. This conveyance framework consequently has a tendency to deliver the medication load preceding arriving at the colon. To defeat the issue of premature drug release, a copolymer of methacrylic corrosive, methyl methacrylate and ethyl acrylate (Eudragit FS) which disintegrate at slower rate and at higher edge pH 7 to 7.5 was accounted for.

2.2. Time Dependent Delivery:

While the average transit time via the stomach is 2 hours, it can vary, the transit time through the small intestine is generally consistent at 3 hours. The average trip time is between 20 and 30 hours. Drug release is permitted by time-dependent drug delivery systems after a predetermined interval. The lag time for the targeted medication release into the colon should be comparable to how long it takes for the system to reach the colon. On the basis of the generally consistent transit time in the small intestine (3 hours), the lag time of 5 hours is often regarded as sufficient; Pulsi cap was the first formulation created using this methodology. For colon-targeted medication administration, Sinha V. R. and Kumaria R. showed the application of shellac, Eudragit L100, and ethyl cellulose at varied thicknesses Shellac and a medication produced encouraging results. Chrono pharmacotherapy with nifedipine and coating in polyethylene oxide-polyethylene glycol mixes that release the medication in the colon was also done utilizing a time-dependent strategy [12].

2.3 Combination of Time and pH dependent:

Colon dosages based only on pH and time would not be constant due to changes in pH and stomach transit time. Therefore, employing Eudragit FS30D and Eudragit RL-RS32, formulations have been designed based on a combination of the pH uniqueness of various polymers and transit duration in the small intestine. This method for chronopharmacology has led to the development of pulsatile devices in the form of capsules [9,13] for improved night time therapy.

2.4. Pressure Dependent Drug Delivery:

The luminal pressure in the colon is higher as a result of the process of forming stools, and this pressure is generated by the muscular contraction of the gut. This pressure varies throughout the gastrointestinal system. The medicine is disseminated in a suppository foundation that has been coated with a hydrophobic polymer for pressure-controlled

delivery. After swallowing, body heat causes the suppository base to melt, increasing the system's volume. The balloon will burst in the colon due to the more severe pressure of the colon's contractions and its greater viscous contents rather than the luminal pressure of the small intestine caused by muscle contraction. [11,13]. When food is also provided, the pressure-based system may work differently since the fed state contraction that occurs in the stomach has the potential to sufficiently influence capsule disintegration. The water-insoluble polymer membrane like ethyl cellulose was used for the inner coat of the empty pressure-controlled colon delivery capsules, and the enteric polymer membrane hydroxyl propyl methyl cellulose phthalate was used for the outer coat.

2.5. Bacteria Dependent Drug Delivery:

Drugs that are encased in an azo-aromatic cross-linked polymer that is susceptible to cleavage by the colonic microflora's azoreductase can be delivered locally and specifically to the colon. It was stated that this method of coating a medicine with biodegradable material targeted the colon and was utilized with significant amounts of the drug. Instead of the host's activity, the rate of medication release is influenced by the bacterial enzyme activity in the colon. There are 400 distinct anaerobic species present, with the overall bacterial population in the colon being 10–11 per gram as opposed to 104 per gram in the upper section of the gastrointestinal tract [10-14].

Azo bond-based polymers for universal carrier systems have been discovered, however their toxicity and safety of these synthetic polymers need to be considered. Natural materials, fundamentally those that are polysaccharide-based, offer a workable alternative to safety problem, material includes chitosan, amylose, dextran, guar gum, insulin and pectin.In vivo, biodegradable polymers break down either with or without the aid of enzymes to provide non-toxic, friendly byproducts. Despite the diversity of the human population, the microflora makeup largely remains consistent. Because amylase is broken down by the enzyme amylase in the colon, amylose, one of the polysaccharides made from starch, has the potential to carry drugs into the colon. After oral treatment, just 12% of the medication was released in the small intestine. The diazoreductase bacteria in the colon break the azo bond when SAS enters the colon following oral treatment, releasing 5-amino salicylic acid and sulfapyuridine into the colon lumen [15]. Osalazine was created to transport 5-amino salicylic acid straight to the colon. It is composed of 5-amino salicylic acid coupled by an azo bond.

3. Polymers for Colon Targeted Drug Delivery Dependent:

3.1 Biodegradable Polymers:

Biodegradation is a natural process by which organic chemicals in the environment are converted to simpler compounds, mineralized and redistributed through elemental cycles such as carbon, nitrogen and sulphur cycles.

Factor Affecting Biodegradation of Polymers:

- Chemical structure.
- Chemical composition.
- Distribution of repeat units in multimers.
- Presents of ionic groups.
- Molecular weight.
- Molecular-weight distribution.
- Morphology (amorphous/semicrystalline, microstructures, residual stresses).
- Presence of low-molecular-weight compounds.
- Physicochemical factors (ion exchange, ionic strength, and pH).
- Mechanism of hydrolysis (enzymes versus water) [16-19].

Table 1: List of biodegradable polymers used in colon drug delivery [20]

Natural polymers	Synthetic polymers
Pectin	Eudragit L 100
Chitosan	Eudragit S 100
Guar gum	Eudragit L 30 D
Chondroitin sulfate	Eudragit RS 30 D
Dextran	Eudragit L 100-55
Cyclodextrin	Polyvinyl acetate phthalate 50
Xanthan gum	Ethylcellulose
Amylose	Hydroxypropyl ethylcellulose phthalate 55
Shellac	Hydroxypropyl ethylcellulose phthalate 50
Alginates	Cellulose acetate phthalate

3.2 Natural Polymers in Colon Targeting:

For the creation of solid oral dosage forms for colonic medication administration, natural polysaccharides are frequently employed. In general, biodegradable polymers have a hydrophilic nature and exhibit modest swelling in an acidic pH. Various bacteria found in the colon secretes various enzymes which might cause hydrolytic breakage of glycosidic linkages e.g. Amylase, pectinase, C-Dglucosidase, D-Dxylosidase, C-Dgalactosidase, and C-Dglucosidase. These polymers are affordable and come in a range of structural options. Several polysaccharides that are often employed in dosage forms include pectin, starch, guar gum, amylase, and karaya gum [21]. In the stomach and small intestine, linear polysaccharides are unaltered, but the bacteria in the human colon break them down, making them potentially helpful in colon-targeted medication delivery systems.

4. Nano-sphere:

The two primary families of nanoparticles are nanospheres, which have a uniform structure throughout the whole particle, and nanocapsules, which have a conventional core-shell structure. Particles with a diameter between 10 and 200 nm are known as nanospheres. Nanospheres can be crystalline or amorphous in form, and they can shield a medicine from enzymatic and chemical deterioration. It has been demonstrated that the reticulo endothelial system can easily opsonize and remove these particles' hydrophobic surfaces. Vesicles are the name for the little drugstore home capsule, and Nanospheres are the name for the solid skeletal structure. [17, 21]. Biodegradable Nanospheres include albumin Nanospheres, modified starch Nanospheres, gelatin Nanospheres, polypropylene dextran Nanospheres and polylactic acid Nanospheres. In addition there are two more types of Nanospheres, immune Albumin Nanospheres, modified Starch Nanospheres, Gelatin Nanospheres, Polypropylene Dextran Nanospheres, and Polylactic Acid Nanospheres are all biodegradable Nanospheres. Magnetic Nanospheres and immunological Nanospheres are two more forms of Nanospheres. Combining both of these kinds of nanospheres can create immuno-magnetic nanospheres, which might greatly enhance targeting. Nanospheres may be used in a variety of ways to target tumors [22], including for long-term circulation and medication administration in the brain. There are multiple ways to make nanospheres, but the solvent displacement approach is the best. Because nanospheres may be swallowed or injected, can be customized for desired release profiles, can be utilized for site-specific drug delivery, and in certain situations, can be used to provide medicine, the administration of drug via such systems is useful.and in some cases can even provide organ-targeted release.

According to biodegradability, it can be divided into biodegradable nanospheres and nonbiodegradable nanospheres. Biodegradable

nanospheres include albumin nanospheres, modified starch nanospheres, gelatine nanospheres, polypropylene dextran nanospheres and polylactic acid nanospheres, etc. According to the current literature reports on nonbiodegradable nanospheres, polylactic acid is the only polymer approved to be used by people and used as a controlled-release agent In addition; reports on immune nanospheres and magnetic nanospheres are also common in recent years. Immune nanospheres possess the immune competence as a result of the antibody and antigen was coated or adsorbed on the polymer nanospheres. Magnetic nanospheres possess a unique magnetic feature, namely their reaction to a magnetic force [21, 23]. These are generally coated with protective shells as magnetic polymer nanoparticles. Immuno magnetic nanospheres can be prepared by combining two kinds of nanospheres, which could significantly improve its targeting.

4.1 Method of Preparation of Nanospheres:

There are various types of method by which Nanospheres are prepared.

- Polymerization (Emulsification polymerization)
- Solvent Evaporation.
- Solvent displacement technique.
- Phase inversion temperature methods [19, 23-24].

Polymerization (Emulsification polymerization):

For emulsification polymerization, polymeric substances like polymethylmethacrylate and polyethylcyanoacrylate are emulsified. Interfacial polymerization of polyalkylcyanoacrylate is another type of polymerization. In the polymerization process, monomers are polymerized in an aqueous solution to create nanospheres. Basically, this method involves dissolving the medicine in the polymerization liquid [25] or adding it to the Nanospheres after polymerization is finished. Nanospheres are then cleaned to remove stabilizers.

Solvent Evaporation:

The macromolecules are dissolved in the phase to be dispersed (often an organic solvent) in this process, which is utilized in the formulation of nanospheres. In this procedure, the organic (and volatile) solvent is eliminated from the formulation, causing polymer precipitation inside the organic phase template. The solvent can be eliminated by diffusion or evaporation. The key distinction from the prior method appears to be the addition of natural macromolecules, such as chitosan, polysaccharides, alginate, gelatin, etc., which increases the biocompatibility of the polymers with possible therapeutic goals.

Solvent Displacement Technique:

A polymer is dissolved in an organic, water-miscible solvent in the solvent displacement process. Adding it to the aqueous phase next, whether or not a surfactant is present. The formation of nanospheres is facilitated by the quick diffusion of organic solvent from the oil phase to the aqueous phase. [23, 27].

Phase inversion temperature method:

Desolubilization of the polymer takes place in this procedure with the aid of nano-emulsion droplets to create nanospheres. The primary benefit of PIT techniques, specifically their use of organic solvents, is lost. [28].

- **Conclusion:**

The Colon is most distal segment of gastrointestinal tract; orally administered formulation must hold back drug release in the upper gastrointestinal regions. CSDDS, Colon has the low fluid environment and nature of luminal contents are viscous which may hinder the dissolution and drug release from the formulation. Moreover stability of the release drug via metabolic degradation is affected by the resident colonic microflora. The stability of the drug also gets decrease by non-specifically binding of drug to secretions of intestine, mucous or general fecal matter which may reduce the concentration of free drug. By this study we can conclude that Nanospheres have

great potential and they have the ability to convert poorly soluble, poorly absorbed drugs into the better deliverable drugs. Nanospheres are site specific and also protect the drug from various body fluids (enzyme action) which can degrade the drug during targeting.

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Ethical approval:

This review article does not include any animal or human studies done by any of the authors.

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