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THERAPEUTIC POTENTIAL OF NANOPARTICLES CONJUGATED WITH DRUG IN RELIEVING COLON RELATED DISORDERS

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Abstract:
Globally, the prevalence of illnesses associated to the colon is increasing, with notable regional and national differences in disease patterns and levels. Drug administration can occur in the colon both locally and systemically. Topical therapy of inflammatory bowel disease is made possible by local delivery. On the other hand, if the medications are able to target the colon directly, the systemic adverse effects can be minimized and the treatment become more successful. Among the many benefits of nanoparticles is their larger volume/surface ratio, which increases the drug's contact area at the same dose and improves delivery efficiency. This may lessen the toxicity and adverse effects of drugs. Additionally, nanoparticles' easily modifiable surface enables the creation of sustained release mechanisms. By utilizing the physicochemical alterations that many colonic disorders cause, such as an increase in the infiltration of immune cells that are amenable to targeting in the colon, new developments have improved colon targeting nanosystems. This page provides an overview of diseases connected to the colon, colon-specific drug delivery strategies, an overview of nanoparticles, and a list of previously developed nanoparticulate drug delivery methods for the treatment of colon problems. ***Keywords:*** *Colon, nanoparticles, formulation, characterization, nanotechnology*

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INTRODUCTION:

Over the past 20 years, scientists have welcomed the challenge of delivering medications particularly to the colonic region of the G.I.T. (Parul*et al.*, 2011). Delivering the medication to the intended organ is the aim of targeted drug delivery (Sreelatha and Brahma, 2012). Colon targeted medication delivery is utilized to transfer compounds like proteins and peptides that are broken down in the stomach by the digestive enzymes. Additionally, it is used to distribute steroids and treat a number of illnesses such diarrhea, Crohn's disease, ulcerative colitis, intestinal cancer, and disorders sensitive to circadian rhythms like angina and asthma. Drugs delivered specifically to the colon minimize systemic side effects. Because of the colon's lengthy retention period, a colon-targeted drug delivery system improves the absorption of medications that are difficult to absorb (Sonasaniya*et al*., 2013).

Colon targeted Drug Delivery system

The oral route of administration has garnered the greatest interest for the Colon Targeted Drug Delivery System (CTDDS), however it can also be designed along the lines of a sustained or controlled drug delivery system. This is due to the fact that oral dosage forms are more flexible than parenteral ones, and oral drug administration is generally safer than parenteral drug administration in terms of potential damage at the site of administration and high patient acceptance. For the delivery of protein and peptides, colon-specific drug delivery methods are becoming more and more important for the reasons listed below:

a) The quick advancement of genetic engineering and biotechnology has made protein and peptide medications affordable.

b) Pancreatic enzymes in the small intestine or the stomach's acidic environment degrade and inactivate proteins and peptide medications (Gupta, 2012).

Factors affected in the design of colon specific drug delivery system

Anatomy and Physiology of colon

The stomach, small intestine, and large intestine make up the GI tract. The colon, rectum, and anal canal are the three main sections of the large intestine, which runs from the ileocecal junction to the anus (Singh, 2007). There are five main segments that make up the length of the colon, which is around five feet (150 cm). Mesentery refers to the peritoneal folds that are supported by the ascending and descending colon. The ascending colon, hepatic flexure, caecum, and right part of the transverse colon make up the right colon.The descending colon, sigmoid colon, splenic flexure, and left part of the transverse colon are all located in the left colon. The last anatomical section before the anus is the rectum.

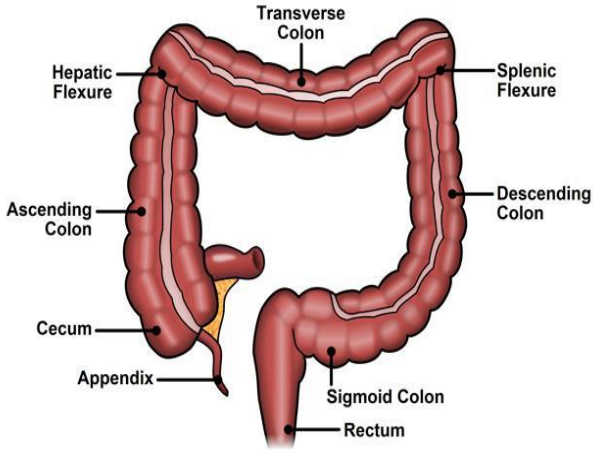

Figure: Anatomy of the colon

pH in the colon

There are differences in the pH of the GI tract across and within subjects. The pH of the gastrointestinal fluid is influenced by food consumption, illness status, and diet. One way to deliver drugs specifically to the colon is by taking advantage of the pH variations that occur along the gastrointestinal tract. The terminal ileum has the greatest pH (7.5±0.5), according to radio telemetry. When the colon enters, the pH falls to 6.4±0.6. The pH values for the left colon are 7.0±0.7 and the mid colon are 6.6±0.8. The presence of short chain fatty acids from bacterial fermentation of polysaccharides causes a drop in pH upon passage into the colon. For instance, the colonic bacteria degrade lactose to produce a lot of lactic acid, which lowers pH to roughly 5.0 (Chourasia and Jain, 2003).

Colonic Microflora and Enzymes

The whole length of the human gastrointestinal tract is home to a vast variety of both aerobic and anaerobic bacteria. Different sections of the GI system employ intestinal enzymes to initiate the release of drugs. These enzymes are often obtained by gut microflora that are abundant in the colon. These enzymes are employed in the degradation of coatings or matrices and in the disruption of the bonds that bind an active agent (i.e., the release of a drug from a prodrug).There are around 400 different kinds of bacteria known to exist, with 20–30% belonging to the genus Bacteroids. The human colon contains approximately 1000 CFU/ml of bacteria. Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, and Peptostreptococcus, Ruminococcus, and Clostridium are the most significant anaerobic bacteria (Threveen *et al*., 2011).

Drug absorption in the colon

Medication is passively absorbed through the transcellular or paracellular pathways. Most lipophilic medications are absorbed through transcellular absorption, which includes the drug passing through cells; most hydrophilic pharmaceuticals, on the other hand, are absorbed through paracellular absorption, which involves the drug being transported through the tight junction between cells.The tight connections between epithelial cells in the colon are the cause of many medicines' poor paracellular absorption.

While medication absorption might theoretically happen anywhere in the gastrointestinal tract, most drug absorption happens in the duodenum and proximal jejunum. For the following reasons, most peptide and protein medications have restricted oral absorption:

• Degradation in the stomach's acidic environment.
• Degradation by enzymes in the large and small intestine.
• Quick transit in the small intestine.
• Low permeability of the mucosa.
• Prolonged first-pass metabolism by the liver and the absorbing membrane (Karanjit and Kwonho, 2009).

Advantages of colon specific drug delivery System (CDDS) over conventional drug delivery

Glucocorticoids and other anti-inflammatory medications are currently used to treat chronic colitis, specifically ulcerative colitis and Crohn's disease (Philip et al., 2008). Systemic side effects include adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption when glucocorticoids, specifically dexamethasone and methyl prednisolone, are administered orally or intravenously (Kulkarni, 1999).According to McLeod *et al.* (1994), targeted drug delivery to the colon may thereby minimize both the necessary dosage and the systemic adverse effects brought on by excessive dosages.

Colonic diseases: Crohn's disease, colon cancer, lymphoma of the colon, ulcerative colitis, diversional colitis, ischemic colitis, and diverticular inflammatory bowel disease.

Limitations and challenges in Colon Targeted Drug Delivery

1. Medication delivery to the colon is a highly intricate process. The colon is particularly challenging to access because of its position in the distal portion of the alimentary canal. Further complicating the dependability and delivery efficiency is the large variety of pH values and various enzymes found throughout the gastrointestinal tract, which the dosage form must pass through before reaching the target site.
2. The drug's stability is another issue that needs to be taken into account while developing the delivery system. The medication may adhere to mucus, feces, intestinal secretions, or leftovers from food in an unspecific manner.
3. By breaking down the medication metabolically, the local microbiota may potentially have an impact on colonic function. Reduced surface area and the relative "tightness" of the colon's tight junctions can also limit the amount of drugs that can pass through the mucosa and enter the bloodstream.
4. Developing a suitable dissolution testing procedure to assess the intended system in vitro is a problem in the creation of colon-specific drug delivery systems. This is because there are many different reasons for using a colon-specific drug delivery system.
5. Drugs delivered through this site must also be in solution before entering the colon, or they must dissolve in the luminal fluids of the colon. However, since the colon has a much lower fluid content and greater viscosity than the upper GI tract, this can be a limiting factor for poorly soluble drugs (Ratna*et al.*, 2010).

Nanotechnology

The disciplines of physics, chemistry, biology, materials science, health sciences, and engineering are all used in nanotechnology. It has broad applicability in practically every area of human endeavor and science. Particulate dispersions or solid particles with a size range of 10–1000 nm are referred to as nanoparticles. A nanoparticle matrix is used to dissolve, entrap, encapsulate, or bind the medication. One can obtain nanoparticles, nanospheres, or nanocapsules depending on the preparation technique used. Nanospheres are matrix systems where the drug is uniformly and physically spread, whereas nanocapsules are systems where the medication is contained within a cavity surrounded by a special polymer membrane (Aarti*et al.*, 2014).

Nanoparticles

Particles that fall within the size range of 1 to 100 nm are referred to as nanoparticles. Because both atoms and molecules function differently at this scale, the formulations have unique purposes that set them apart from others. invisible to the naked eye.Utilizing biocompatible and biodegradable polymers, nanoparticles are created. These polymers have the ability to alter the drug's actual activity by increasing adhesiveness, delaying the drug's release, or both. Because of their smaller size, nanoparticles are different from bulk material. An increase in the surface area per mass of the material allows for a

greater amount of it to come into touch with the surroundings. Sub-nanoscale colloidal drug delivery vehicles are called nanoparticles. Larger particles of the same substance have different properties than nanoparticles. Pharmaceutical nanoparticles are drug carriers that are smaller than a micron and can either be biodegradable or not (Konwarand Ahmed, 2013).

Advantages of Nanoparticles

The following are some benefits of employing nanoparticles as a medication delivery mechanism (Langer, 2000):

a) After parenteral delivery, it is simple to modify the size and surface properties of nanoparticles to accomplish both passive and active drug targeting.

b) They regulate and maintain the drug's release throughout transportation and at the location of localization, changing the drug's distribution throughout the body and its subsequent clearance to improve therapeutic efficacy and lessen negative effects.

Limitations of Nanoparticles

a) Particle-particle aggregation caused by small size and vast surface area can make handling nanoparticles in liquid and dry forms challenging.

b) Moreover, restricted drug loading and burst release are easily produced by tiny particle size and vast surface area. The resolution of these pragmatic issues is necessary prior to the clinical application or commercialization of nanoparticles (Bhadia*et al.*, 2002).

Preparation of nanoparticles

The properties of the medication and polymer determine which preparation technique is best for creating nanoparticles. As a result, the mode of operation is essential to achieving the desired features. Different techniques are used to create nanoparticles. The choice of method is dependent on the well-defined morphology and structures of the nanoparticles, which include chemical, biological, physical, and physiological variables(Krishna*et al.*, 2011).

1. Solvent Evaporation Method

This procedure involves dissolving the polymer in an organic solvent, such as ethyl acetate, dichloromethane, or chloroform, which is also used to dissolve the hydrophobic medication. To create an oil in water (o/w) emulsion, the polymer and drug solution mixture is subsequently emulsified in an aqueous solution containing a surfactant or emulsifying agent. Either by lowering pressure or by constantly stirring, the organic solvent is removed after a stable emulsion has formed. It was discovered that the kind and concentration of stabilizer, homogenizer speed, and polymer concentration all affected particle size. Often, ultrasonication or high-speed homogenization are used to achieve tiny particle sizes (Li*et al*., 2001).

2. Nanoprecipitation

Using this method, polymers are added to solvents such as acetone, ethanol, or methanol, whether or not a surfactant is present. Next, the poly-lactic acid diffused with this solvent phase. Because PLA has an intermediate polarity, dissolving it in a water-miscible solvent causes nanospheres to develop. Submicron-sized (less than 210 nm) nanoparticles are produced via nanoprecipitation after polymer injection into the aqueous phase. Use biodegradable polymers to lessen the harmful effects of nanoparticles. The "ouzo effect" refers to the scattering of nanoparticles caused by the absence of surfactant in the solution phase. The minimal energy input of nanoprecipitation is an advantage (Nishikanth*et al.*, 2018).

3. Emulsification diffusion

Another name for it is the solvent diffusion method. The modified version of the solvent evaporation process is called emulsification diffusion. Due to spontaneous diffusion, turbulence is produced in a mixture of water immiscible and water miscible solvents. Consequently, nanoscale particles developed. The pace at which a solvent diffuses on a dispersed phase determines the generation of products. Aqueous solution's oil-polymer ratio and stabilizer presence promote solvent diffusion to the exterior phase. The emulsification diffusion process has the following benefits: high capsulation efficacy, high batch-to-batch consistency, ease of scaling up, simplicity, and lack of homogenization requirement. Emulsification diffusion was used to create nanoparticles such as doxorubicin-loaded PLA, DNA-loaded PLA, and coumarin-loaded PLA (Manikandan*et al.*, 2015).

4. Salting out

It is a variation on the diffusion technique for emulsion solvents. The drug and polymer mixture in the solvent is emulsified into an aqueous gel. Salting agents include non-electrolytes (sucrose) and electrolytes (magnesium chloride, calcium chloride, and magnesium acetate). This method's ability to effectively encapsulate medications will change if salting out agents is employed. After the process is finished, the salting out agent is removed via filtration.

5. Supercritical Fluid Technology (SCF)

SCF can be used to produce nanoparticles in large quantities. This method has none of the disadvantages of previous methods. SCF is a substitute technique for creating biodegradable nanoparticles and microparticles. Eco-friendly is SCF fluid. Since carbon dioxide doesn't cause

inflammation or toxicity, it is one of the most commonly utilized SCF.

Characterization of nanoparticles

Zeta potential: A typical method for characterizing a nanoparticle's surface charge property is to use its zeta potential. It is impacted by the makeup of the particle as well as the medium in which it is distributed, and it represents the electrical potential of particles. It has been demonstrated that nanoparticles with a zeta potential greater than (±) 30 mV are stable in suspension because the surface charge keeps the particles from aggregating (Couvreur*et al*., 2002).

Particle Shape: Prior to evaluation, the nanosuspension is characterized by SEM and lyophilized to produce solid particles. Using a sputter coater, platinum alloy is applied to the solid particles (Champeau, 2006).

Drug Entrapment Efficiency: Using ultracentrifugation, the nanoparticles were extracted from the aqueous medium after 30 minutes at 50C and 10,000 rpm. After that, the solution with the supernatant was decanted and mixed with phosphate buffer saline (pH 7.4). In order to fully eliminate the drug molecules that were not entrapped, the process was done again. The difference between the total amount of drug used to generate the nanoparticles and the amount of drug present in the aqueous medium was used to calculate the amount of drug entrapped in the nanoparticles. Medication entrapment efficiency (%) = quantity released from the lysed nanoparticle multiplied by 100 The initial dosage of the medication used to create the nanoparticles (Delvecchio, 2006)

Drug release: Drug loading is the quantity of bound drug per mass of polymer and is expressed as a percentage of the polymer. Analytical procedures such gel filtration, centrifugal ultrafiltration, UV spectroscopy, HPLC, and ultracentrifugation are employed (Susan, 2014).

Microscopic techniques: SEM and TEM are two methods primarily utilized to study the morphology of nanoparticles. These methods were employed by numerous researchers to demonstrate that the produced nanoparticles were roughly uniform in size and shape (Xi*et al*., 2016).

Transmission electron microscopy (TEM): A stream of electrons is sent through an incredibly thin specimen during transmission electron microscopy, interacting with the specimen along the way. The interaction of the electrons passing through the specimen creates an image, which is then focused and enlarged to be seen on a fluorescent screen, a layer of photographic film, or to be picked up by a sensor like a CCD camera.

Scanning electron microscope: To ascertain the morphologies, sizes, and shapes of the generated nanoparticles. As needed, SEM provides high resolution images of a sample's surface. The scanning electron microscope operates on the same principles as an optical microscope, except instead of measuring photons, it examines electrons that are scattered from the sample. An electric potential can accelerate electrons, allowing for a shorter wavelength than that of photons.

Applications of Nanoparticles

1. General applications of organic nanoparticles Micelles

- Lowers enzymatic degradation;
- drug inactivation in the treatment of malignant tumors;
- Boosts drug stability;
- Lowers critical micellar concentration.

2. General Applications of Inorganic Nanoparticles

As anti-Infective Agents: It has been suggested that metallic nanoparticles are an HIV preventive treatment. Silver functions as a virucidal agent directly on the virus by attaching to the glycoprotein gp120, as demonstrated by a few investigations. Consequently, this binding hinders the virion binding that is dependent on CD4, thereby reducing the infectivity of HIV-1 (Sun*et al*., 2008).

In Tumour Therapy: According to studies, heparin-binding proteins like VEGF165 and bFGF as well as VEGF-induced angiogenesis in vivo were suppressed by naked gold nanoparticles. According to more research in this field, heparin-binding proteins are absorbed and then denatured onto the surface of AuNPs(Ali*et al*., 2020).

In Rheumatoid Arthritis: Researchers at the University of Wollongong in Australia have developed a novel type of anti-arthritic medication that has fewer side effects and can be administered using gold nanoparticles. An autoimmune condition called rheumatoid arthritis develops when a patient's immune system malfunctions and assaults their joints (Tsai*et al*., 2007).

In Photo Thermal Therapy: Gold nanoparticles effectively and rapidly transform photon energy into heat, which allows them to absorb large amounts of light. An invasive treatment called photothermal

therapy (PTT) uses the conversion of photon energy into heat to kill cancer. Due to the fact that gold is a superior X-ray absorber, radiotherapy tumors treated with the metal absorb more radiation. Consequently, more beam energy is deposited, raising the local dosage that only targets cancer cells. When treating cancer, gold nanoparticles have proven more effective (Minho*et al*., 2019).

Future opportunities and challenges

Drug delivery systems have already used nanoformulations with higher success. Numerous uses, including AIDS treatment, radiation therapy, protein, antibiotics, virostatics, and vaccines, as well as vehicles for blood-brain barrier transfer, have seen great success using nanoparticles (Ibrahim*et al*., 2019).

Table 1: Previously formulated Nanoparticle aided drug delivery to treat colon related disease

Name	Excipients	Method	Reference
Capecitabine	Potato starch, chitosan, 0.1M NaOH,	Mild alkali hydrolysis and ultrasonication techniques	Bhattacharya *et al*., (2024)
Doxorubicin	Chitosan, methacrylamide, Phosphate-buffered saline	Reversible addition-fragmentation chain transfer (RAFT)	Manhas*et al*., (2024)
lenalidomide	Chitosan, aqueous solution	Desolvation method and ionotropic gelation method	Jafari*et al*., (2024)
Capsaicin	Carboxymethyl dextran, N-diclyclohexyl-carbodiimide and 4-Dimethyl aminopyridine	Gelation process	Rajput *et al*., (2024)
Streptomycin	Lecithin/poloxamer	Double emulsion method	Moez*et al*., (2023)
Cefazolin	2-hydroxyterephthalic acid, and 2-amino-4,4′-dicarboxylic acid.	Broth microdilution method	Dastneshan*et al*., (2023)
Trimethoprim and sulfamethoxazole	Chitosan,	Co-precipitation method	Alishir*et al*., (2023)
Diclofenac	Chitosan	Microemulsion method, co-precipitation	Radu*et al*., (2023)
Clarithromycin	Phosphoric acid, Polyethylene glycol 400 and cholesterol	Solvent casting method	Zaid*et al*., (2023)
Cyclosporine	Chitosan, Lactobionic acid, N-hydroxysuccinimide	Simple ultrasonication method	Xiong*et al*., (2023)
Amoxicillin	Chitosan, Sodium tripolyphosphat, Dimethyl sulfoxide	Microbroth dilution method, ionic gelation method	Fayed *et al*., (2023)
Doxorubicin	Hydroxypropyl methyl cellulose phthalate, Cellulose, phthalic acid	Nanoprecipitation method	Alshaman*et al*., (2022)
Bromelain	Balanced Salt Solution, L-α-phosphatidylcholine	Double emulsion solvent evaporation method	Ebrahimian*et al*., (2022)
Tilmicosin	Indomethacin, verapamil, and EDTA-2Na, polyvinyl alcohol	Ultrasonic emulsification method	Zhou *et al*., (2020)

Dextran sulfate	sodium tripolyphosphate, mannitol solution	Gelation technique	Madkhali*et al*., (2021)
Ampicillin	Amoxyclav, Nitrofurantoin, Nalidixic acid	RSM Coupled GA Method	Sharma *et al*., (2019)
Rifampicin	Poly methyl methacrylate, Poly vinyl alcohol	Emulsion solvent evaporation technique	Sheaikh*et al*.,(2018)
Ciprofloxacin	Triethylamine, didecyldimethylammonium bromide	Quasi-emulsion solvent diffusion and solvent injection	Pignatello*et al*., (2018)
Ciprofloxacin	Cyclohexane, ammonium bromide, calcium chloride, sodium carbonate	Micro emulsion method	MalekiDizaj*et al*., (2017)
Ciprofloxacin	Chitosan, Sodium hydroxide, Methyl alcohol, ethyl alcohol ,acetic acid	Ionotropic gelation with slight modification	Ibrahim *et al*., (2015)
Streptomycin	Sodium alginate, lactide:glycolide (50:50)	Solvent diffusion method	Asadi, (2014)
Ampicillintrihydrate	Chitosan and 0.40 %w/v sodium tripolyphosphate	Ionic gelation method	Saha*et al*., (2010)
Glycopeptide	Chitosan ,tripolyphosphate	Ionic gelation method	Safari *et al*., (2021)

CONCLUSION:

For a variety of medication delivery systems, nanoparticles offer a promising drug carrier option. Newer applications of nanotechnology, a revolutionary technology that permeates all fields, are being investigated globally. With nanoparticles, drug solubility and bioavailability issues can be resolved. This technique can be used for any drug that is poorly soluble. Any medication can be converted into drug nanoparticles, which will boost the saturation solubility, rate of dissolution, and overall surface adhesiveness. More and more people are beginning to see the benefits of using nanoparticulate drug delivery systems for biological medications. Furthermore, nanoparticles provide focused and regulated release, which makes them an effective treatment option. For these reasons, nanoparticulate drug delivery systems appear to be a realistic and promising strategy for the biopharmaceutical sector.

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