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Colontargeting drug delivery system

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ABSTRACT

The colonic drug delivery refers to the drug that should released in the colonic environment rather than in the upper gastrointestinal tract. To achieve the site-specificity of the local treatment of the colon such as amoebiasis, colorectal cancer, and inflammatory bowel disease the target-specific drug delivery reacts as an important role. For the target-specific drugdelivery to the colon, the various technique that has be explored include pH-dependent polymer, time-dependent, and bacteria-dependent drug delivery technique. Even the Nanotechnology has been gained a lot interest due to ta specificity and improved of bioavailability and high loading capacity as well. In this review, oral different formulation for colon targeting particular techniquees to enhancement of drug stability in the gastric environment has been included.

Keywords: colon targeting, CDDS, techniques

INTRODUCTION

Oral administered route is the best in the treatingof colonic diseases such as inflammatory bowel disease, colorectal cancer, chronic diarrhoea, colonic dysmotility because targeting region concentration can be achieved[1], with decreased side effects because of unnecessary systemic absorption can be overcome. Compare to the parenteralroute, the oral route is the best convenient for patients because avoidance of pain and possible contamination through injectionand self-administration could not possible in parenteral preparation.[1]

The oral route of drug delivering is conventional drug delivery systems that face many problems before reaching to targeting colon sites as pH of gastrointestinal tract varies site by site. If the drug is not stable in this

different pH range, pancreatic enzymes, bile salt, bicarbonate, and colonic enzymatic activity.[1]

The modified nanoparticle can easy to penetrate mucus layers reach to site and show therapeutic activity. The drug efficacy andretention time can be improved through nanoparticulate formulation, Nanocarriers encapsulated drug can be reached to the inflamed colon by endocytosis process.[1]

Colon-specific drug delivery can be defined as the drug should reach the target site and show therapeutic activity without premature drug release in the stomach acid. Untreated ulcerative colitis leads to colorectal cancer. Day by day ulcerative colorectal cancer active cases increasing and the rate of cancerous colonic polyp selectively low and that is why it took a long time.[2]

The Ulcerative colitis and the Crohn's disease are having major differences as they have common symptoms with different conditions. Crohn's disease refers to the blockage in the intestine and ulceration in the intestine and it is mainly affected to the lower part of the intestine and the first part of the colon. Many symptoms can be seen in Crohn's disease such as abdominal pain, fatigue, cramping, fever, and diarrhoea. The symptoms of ulcerative colitis such as abdominal pain, fever, cramping, loose and bloody stools, fatigue, loss of appetite, and anemia and can increase the formation of holes in the colon, liver disease, bloodclots, and osteoporosis.[2]

Advantage of colon specific drug delivery [3]

Thi system delivers the advantage of more effective therapy at a reduced dosage along with reduced undesirable side effects associated with high dosages.

- Target specificity at the desired location.
- Less enzymatic activity.
- Lesser amount of dose is required to produce therapeuticactivity
- Local and systemic treatment can be possible Suitable for protein and peptides.
- Reduce gastric irritation especially NSAIDs (non-steroidalanti-inflammatory diseases)
- Use to prolong drug therapy.

Disadvantages of colon specific drug delivery[4]

There are some disadvantages of colon targeting drug delivery system are as below,

- Stability problem of drugs and polymer due to different pH,enzymatic activity.
- Gastric empty time can be varying, depending upon foodintake
- Disease condition may be affecting the colonic transit timeand drug release profile.

pH of the colon depends upon disease state and food intakecapacity.

Why colon site specific drug delivery is required[5]

- Ensure direct treatment of the disease site with lower dosing and fewer systemic side effects.
- Allow oral administration of peptide and protein drugs, colon-specific formulation could also be applied to extend the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease such as ulcerative colitis or Crohn's disease. Such inflammatory conditions are normally treated with glucocorticoids and sulphasalazine (site specific).
- Many serious disease of the colon like Colorectal cancer, might be capable of being treated more effectively if drugs were site specific to the colon.

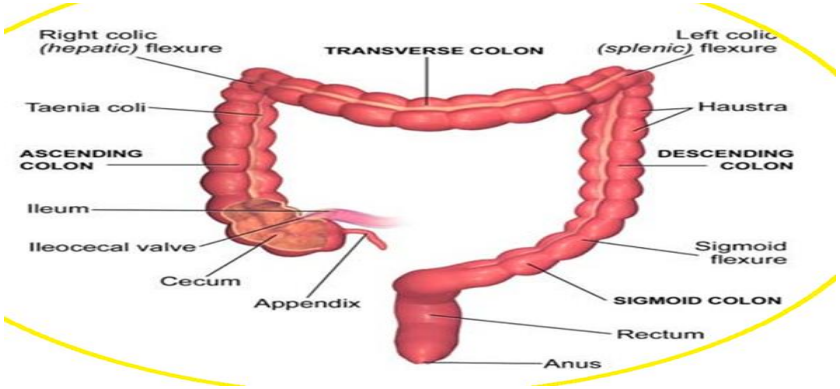

Fig 1: Large Intestine a picture[6]

Factor affecting colon-specific drug delivery

pH of the colon

The pH of the colon may be depend upon inter- intra subject variability which impacts colon-specific drug delivery systems. The gastric environment depended upon many factors like, food intake capacity, disease condition, and regular diets. The drug must need to stable in the variable pH and release at the particular pH region and show proper therapeutic effectiveness. The pH of the colon varies due to long-chain fatty acid obtained from bacterial fermentation of polysaccharides.[6]

The Gastric-intestinal transit

The Gastric empty primarily depends on the fed or fasted, dietary fiber content, stress, mobility, diet, disease, and drugs content. The transit time depends on the size of the particles as smaller particle sizes have more transit time comparison with larger particle sizes.[7]

Colonic microflora and enzymes

The GI tract contains various enzymes released by various microorganisms such as Eubacteria, streptococcus, E. coli, clostridia, lactobacilli, P. Vulgaris, B. subtillis, B. mycoides, A.aerogenes which helps for the metabolism and degrade coating materials as well as breaking bonds between biodegradable and active moiety.[8]

Various techniquees of colon-specific drug delivery systems

The drug should stand stable at different pH regions and degrade inthe colonic microflora when targeting particularly colonic diseases and provide proper therapeutic efficacy and maintaining the therapeutic concentration. The various technique has been developed to achieve colonic targeting area as follows,[9]

- **pH-dependent drug delivery technique**

just because of different pH environments (stomach – 1.5-3.5, small intestine – 5.5-6.8, and colon 6.4-7.5), drugs must have to stablein the upper GIT tract and need to release in the colonic environment.[9]

- **Time-Dependent drug delivery technique**

The time-dependent formulation is consisting of pH-dependent polymers because it is influenced by the gastric transittime and it depends upon the size of the particle and gastric motility. [10]

Basics for selection of drug for CDDS Drug candidate

The Drug which shows very poor or poor absorption from the stomach or bowel, including peptides are most suitable for CDDS. The drugs used in the treatment of inflammatory bowel diseases (IBD), ulcerative colitis, diarrhea and colon cancer are ideal prospects for colonic delivery.[10]

Drug carrier

The selection of carrier for the particular drug candidate dependson the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer selected influences the carrier choice. The choice of drug carrier is always depends on the working groups of the drugmolecules. For example, aniline or Nitro groups on a drug may beused to connect it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the releaseproperties as well as efficacy of the dosage form.[11]

The techniquees employed for site specific drug delivery to Colon (CDDS)

Techniquees used for site-specific drug delivery are:

Primary techniquees for CDDS.[12]

- pH sensitive polymer coated drug delivery to colon
- Delayed (Time controlled release system) release drug delivery tocolon
- Microbially triggered drug delivery to the colon
- Prodrug technique for drug delivery to the colon
- Azo-polymeric technique for drug delivery to the colon
- Polysaccharide based technique for drug delivery to the colon [B]-Newly developed techniquees for CDDS.
- Pressure controlled drug delivery system (PCDCS)
- CODESTM (A Novel colon site specific delivery system)
- Osmotic controlled drug delivery to colon (OROS-CT)
- Pulsatile drug delivery system
- Hydrogels
- Microspheres
- Nanoparticles
- Self-microemulsifying drug delivery system
- Multiparticulate beads

- Liposomes in CDDS
- Bioadhessive systems

Primary techniquees for CDDS

pH sensitive polymer coated drug delivery to colon

In the stomach, pH ranges between 1 and 3 during fasting but increases after consuming the food. The pH is arround 6.5 in the proximal small intestine and of about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the caecum.34

However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is found to be 6.6 as well as in the descending colon is 7.0. Role of pH-dependent polymers are based on these differences in pH levels. The polymers described as pH-dependent on colon specific drug delivery are insoluble at low pH levels. [14]

Delayed (Time controlled release system) release drug delivery to the colon

The Time controlled release system (TCRS) such as prolonged or delayed release dosage forms is also very bright. Due to the potentially large variation of gastric emptying time of dosage forms in man. the colonic arrival time of dosage forms can not accurately predicted, resulting in poor clinical availability.[14]

Enteric-coated time-release press coated (ETP) tablets

The ETP tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function). [14]

Microbially triggered drug delivery to the colon

The microflora of the colon is in the range of 1011-1012 CFU/ml. It is mainly consisting of anaerobic bacterias, such as Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e. g. di, tri and polysaccharides etc. [15]

Prodrug technique for drug delivery to colon

The Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in-vivo to release the active components. For colonic delivery the prodrugs are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, thereby freeing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes.[16]

Azo-polymeric prodrugs

Noval techniquees are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are employed for this function. Subsynthetic polymers have been utilized to form polymeric prodrug with a linkage between the polymer and drug moiety.[16]

Glycoside conjugates

The Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon site specific drug delivery system. Drug glycosides are hydrophilic and thus poorly absorbed from the small bowel. In one case such a glycoside reaches the colon, it can be cleared by bacterial glycosidases, releasing the free drug to be assimilated by the colonic mucosa.[17]

Glucuronide conjugates

The Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs.29 Bacteria of the lower GIT, however, secrete glucuronidase and can deglucuronidate a variety of drugs in the bowel.[17]

Cyclodextrin conjugates

The Cyclodextrins (CyDs) are cyclic oligosaccharides consisted of six to eight glucose units through 1, 4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these particles are relatively lipophilic and the exterior is relatively hydrophilic. They tend to form inclusion complexes with various drug molecules. Nevertheless, they are fermented by colonic micro flora into small saccharides and thus absorbed in the colonic area.[18]

Polysaccharide based delivery systems

The main role of naturally occurring polysaccharides is attracting tons of care for drug targeting to the colon.

These polymers are inexpensive and are available in a verity of a structure with varied properties. They can be modified chemically and biochemically, and are highly stable. They are safe, nontoxic, hydrophilic, gel forming and biodegradable. [19]

Newly developed techniques for CDDS Pressure-controlled drug-delivery systems

Due to peristalsis, higher pressures are taken on in the colon than in the small intestine. Controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following the disintegration of a water-insoluble polymer capsule as a outcome of force per unit area in the lumen of the colon.The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. [20]

Newly developed colon site specific delivery system (CODESTM)

An unique CDDS technology which was contrived to avoid the constitutional problems associated with pH or time dependent schemes. CODESTM is combined technique of pH dependent and microbially triggered CDDS. It has been produced by using an unique mechanism involving lactulose, which works as a trigger for site specific drug release in the colon. The system comprises of a normal tablet core containing lactulose, which is coated over with Eudragit E (the acid soluble material) and further coated with Eudragit L(the enteric coating polymer). [21]

Osmotically controlled drug delivery (ORDS-CT)

Its delivery system OROS-CT from Alza Corporation is much more useful in targeting the drug molecules to the colonic region for their local therapeutic response as well as systemic effect. This system can be either a single osmotic unit or can be comprising of a maximum 5-6 push-pull units, each having the diameter of 4 mm and encapsulated in a hard gelatin capsule. [22]

Pulsatile drug delivery system Pulsincap® system

A Single-unit systems are mostly developed in a capsule form. The interim time is kept in line by a plug, which gets pushed away by swelling or erosion and the drug is expelled as a “Pulse” from the insoluble capsule shell. One such system comprises of a drug reservoir entrapped inside a water insoluble capsule. The drug molecules were sealed by a swellable hydrogel plug present in the capsule body. [23]

The port® system

The Port® System comprises of a gelatin capsule coated with a semipermeable membrane (e. g., Cellulose acetate) containing an insoluble plug (e. g., lipidic) along with an osmotically active agents with the drug formulation. By coming in contact with the aqueous medium, water diffuses through the semi permeable membrane, thus resulting in an increased inner pressure which helps in ejecting the plug after a certain lag time. The interim time is controlled by coating thickness. This system avoids the second time dosing. [23]

Hydrogels

The presence of pH-sensitive monomers and also cross-linking agents in the hydrogel structure produce colon specificity to the expression. As these hydrogel travels through the GIT, their swelling capacity increases as the pH increases, being highest around pH 7.4. The drug entrapped in the hydrogel is put out by the progressive degradation of hydrogen network via the cleavage of the cross-ties.[24]

Microspheres

Cross-linked guar gum microspheres containing methotrexate were developed and characterized for their local release in the colon for efficient treatment of colorectal cancer. In this method gluteraldehyde was used as a cross-linking agent and guar gum microspheres were developed by emulsification method. From the results of in vitro and in vivo studies, the methotrexate loaded cross-linked guar gum microspheres delivered most of the loaded drugs (79%) to the colon, where as the normal drug suspensions could able to deliver only 23% of their total dose to the target tissue. [25]

Nanoparticles

Nanoparticles are expected to become drug carriers for achieving oral peptide delivery. Because of polymeric nanoparticles have the advantages of protecting the protein and peptide drugs from a chemical and enzymatic degradation in the GIT, so increasing their stability and absorption across the intestinal epithelium as well as holding the drug release. A routine of techniques such as polymerization, nanoprecipitation, inverse microemulsion can be utilized to prepare polymeric nanoparticles, however, most of these methods require

theusage of organic solvents, heat and vigorous agitation which may be harmful to the peptide and protein drugs. [26]

Self-microemulsifying drug delivery system

Zhang L et al. Has prepared, characterize, and evaluate a fleet- modified self-microemulsifying drug delivery system (FSMEDDS) with the intension for improveing the solubility of curcumin as well as its delivery to the colon, mediated through endocytosis of FSMEDDS by foliate receptors on colon cancer cells. Ternary phase.[27]

Multiparticulate beads

In the ionotropic gelation method, polysaccharides (alginate, gallant and pectin) are dissolved in water or in weak acidic medium (chitosan). These solutions are then added drop wise under constant stirring to the solutions containing other counter ions. Due to the complexation between oppositely charged species, polysaccharides undergo ionic gelation and precipitate to form spherical particles. The beads are removed by filtration, rinsed with distilled water and dried. [27]

Liposomes in CDDS

Liposomes are the bilayered closed vesicular structures comprises of hydrated phospholipids. Liposomes have the capacity to entrap compounds of different solubilities due to their alternating hydrophilic and hydrophobic structure. How ever the extensive modification or tailoring of basic liposomal structure of hydrated phospholipid bilayer is associated with the physicochemical makeup of the vesicle.[28]

Bioadhesive systems

Some drugs requires high local concentration in the large intestine through oral administration for their optimal therapeutic effects. Bioadhesion is a procedure by which a dosage form remains in contact with a special organ for an augmented period of fourth dimension. This longer residence time of the drug results an increased local concentration. [29]

Valuation parameters of CDDS

For in vitro evaluation, not any standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should posses the in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food. Generally, these conditions are influenced by the diet, physical stress, and these factors make it difficult to design a slandered in-vitro model. In vitro models used for CDDS.[30]

In vitro dissolution test

Dissolution of controlled-release formulations used for colonspecific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces.[46]. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. [32]

In vitro enzymatic tests

Incubate carrier drug system in fermenter containing suitable medium for bacteria (strectococcus faccium and B. Ovatus). The amount of drug released at different time intervals are determined. Drug release study is done in buffer medium containing enzymes (ezypectinase, dextranase), or at or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.[33]

In vivo evaluation

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. [34]

Drug Delivery Index (DDI) and Clinical Evaluation of Colon- Specific Drug Delivery Systems

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and intubation.

Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.[35]

γ–Scintigraphy

With growing complexity in the design of novel drug delivery systems (including colon-specific delivery systems) and associated fabrication process, it is critical to understand the in vivo performance of those delivery systems and demonstrate that the system functions in vivo in accordance with the proposed rationale. In most cases, conventional pharmacokinetic evaluation may not generate sufficient information to elucidate the intended rationale ofsystem design.[36]

Limitations and challenges in colon site specific drug delivery system

- The resident micro flora affects the colonic efficiency by metabolic degradation of the drug. [37]
- As a site for the drug delivery, the colon offers a near neutral pH, a long transit time, reduced digestive enzymatic activity and increased responsiveness to the absorption enhancers; however, targeting of drugs to the colon is really complicated.[38]
- Due to its position in the distal portion of the nutrient canal, the colon is difficult to access[39]
- In summation, the stability of drug must be considered into consideration while designing the delivery organization.[39]
- The drug may potentially bind in a nonspecific way to dietary residues, mucus and intestinal secretions or fecal matter. Opportunities in colon site specific drug delivery[40]
- Drugs targeting to the colonic area is not only associated with the treatment of colonic ailments locally, but also delivering drugs such as proteins and peptides for their systemic effects which are degraded and/or poorly taken up in the stomach and small bowel.[40]
- This is likewise a suitable site for the treating diseases associated with circadian rhythms such as angina, asthma and arthritis.[40]
- The urgent demand for legal transfer of drugs to the colon that reported to be occupied in the colon, such as steroids, which would increase efficiency and shortens the effective dosage.[41]
- The colonic disorders like inflammatory bowel disease, Crohn's disease, irritable bowel syndrome (IBS) as well as colon cancers etc, it is much more needful to achieve a high absorption of the active agent by colon-specific rescue.[42]
- The evolution of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very depressed (due to instability in the GI tract).[43]

CONCLUSION

In this review, oral different formulation for colon targeting particular techniquees to enhancement of drug stability in the gastric environment has been included.

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