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Review Article: Pharmaceutical Approaches to Colon Targeted Drug Delivery Systems.

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ABSTRACT

The colonic region of gastro intestinal tract becomes an increasingly important site for drug delivery and absorption. The targeted drug delivery would offer considerable therapeutic benefits to patients, in terms of both local and systemic treatment. Colonic delivery is more likely to be achieved to systems that utilize natural materials that are degraded by bacterial enzymes of colonic origin.

Keywords: colon-specific delivery; polymers; biodegradable polymers; in vitro-in vivo studies; drug delivery system.

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INTRODUCTION

Traditionally solid oral dosage forms have been designed to release their drug load in upper regions of GIT. Where conditions are generally more suited to drug dissolution and absorption. Recently greater emphasis has been placed on controlling the rate and site of drug release from oral formulations for the purpose of patient compliance and treatment efficiency[1-4].

The colonic region of GIT is one that would benefit from the development and modified release technologies. Although colon is considered by many to be an innocence organ that may simple functions in the form of water and electrolytes absorption and the formation storage and explosion of fecal material. Colon is valuable to a number of disorders including ulcerative colitis, corn's disease, irritable bower syndrome and carcinomas. Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site and lower systemic side effects. In addition to local therapy, the colon can also be utilized as a portal for entry of drug into the systemic circulation, such as peptides and proteins, may be better absorbed from environment of colon. In addition to systemic absorption from colon can also be used as a means of achieving chemotherapy for diseases that are sensitive to circadian rhythms such as asthma, angina[5-7].

For successful colonic drug delivery careful consideration of a large number of factors, including the properties of drug, the type of delivery system and interactions with the healthy or diseased gut for instance, regardless of whether a local or systemic effect is required, the administrated drug must first dissolve in lonely fluid of colon. Aside from drug solubility, the stability of drug in colonic environment is a farther factor that warrants attention. The drug could bind in a non specific manner to dietary residues, GIT secretions or general fecal matter, thereby reducing the concentration of free drug. Materials that are recalcitrant to the conditions of stomach and small intestine can be utilized as carriers for drug delivery to colon. This principle has been exploited commercially to deliver 5-aminosalicylic acid (5-ASA) to colon by way of a prodrug. The prodrug sulphasalazine consists of two separate moieties (sulphapyridine and 5-ASA) linked by as azo-bond. The prodrug passes through the upper gut intact, but once in colon the azo-bond is cleave by the host bacteria, liberating the carrier molecules sulphapyridine and pharmacologically active 5-ASA.There is also evidence to suggest that the activity of the cyctochrome p450 3A class of drug metabolizing enzymes is lower is mucosa of colon than small intensive. Therefore colonic delivery may lead to elevated plasma levels and improved oral bioavailability for drugs that are substrates for this enzymes class. In relation to delivery modified release formulations are usually based on either a single unit tablets or multi unit plat form design[9-14].

Targeted Drug Delivery System

The major goal of any drug delivery system is to supply a therapeutic amount of drug to a target site in a body, so that the desired drug concentration can be achieved swiftly and then maintained. Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non target sites. A targeted drug delivery system is preferred in drugs having instability, low solubility and short half life, large volume of distribution, poor absorption, low specificity and low therapeutic index. Targeted drug delivery may provide maximum therapeutic activity by preventing degradation or inactivation of drug during transit to the target site. Meanwhile, it can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. An ideal targeted delivery system should be nontoxic, biocompatible, and biodegradable and physicochemically stable in vivo and invitro. The preparation of the delivery system must be reasonably simple, reproducible and cost-effective. The targeted drug delivery is dependent on the identification and exploitation of a attribute that is specific to the target organ[15-21].

Colon Targeted Drug Delivery System[22-26]

The colon targeted drug delivery is beneficial for the localized treatment of several colonic diseases mainly inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS) and colonic cancer. To achieve clinically CSDDS (colon specific drug delivery system) relevant bioavailability of poorly absorbed drugs from the upper parts of the gastrointestinal tract because of their polar nature and/or vulnerability to chemical and enzymatic degradation in the small intestine specifically for proteins and peptides. The colonic drug delivery provide more effective therapy of colon associated diseases such as Crohn's disease and ulcerative colitis, and also has potential to deliver macromolecular drugs orally. Colon related pathologies range in seriousness from

constipation and diarrhea to the incapacitating inflammatory bowel diseases through to colon cancer, the third most widespread form of cancer in both women and men.

Colonic Drug Delivery

Rationale

- Topical application of drugs, active at the mucosal level and may reduces adverse effects in the treatment of colonic disease.
- It is important in the treatment of colonic diseases like ulcerative colitis, crohn's disease, cancer and local infections.
- It also provide opportunity to nonsteroidal anti- inflammatory drugs (NSAID).
- Colon is capable of absorbing drugs efficiently.
- Drug absorption enhancer works better in the colon as compare to small intestine.
- Large intestine is potential site for absorption of protein drugs.

Advantages

- Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.
- The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.
- The colon targeted drug delivery can also be used for effective treatment of diseases like asthma, angina and arthritis.

Benefits

- Target drug delivery
- Decrease in dose to be administered
- Decreased side effects
- Improved drug utilization
- It is a promising site for a drug which is unstable or poorly absorbed from upper GI tract

Disadvantages

- There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired site. The pattern of drug release may differ from subject to subject which may cause ineffective therapy.
- The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.
- Poor site specificity.
- Diet and diseases can affect colonic microflora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In diseased conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
- Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.
- Substantial variation in gastric retention time may cause drug release at the undesired site in case of time dependent colonic drug delivery system.

Associated challenges

- The colon is most distal segment of gastrointestinal tract.
- Orally administered formulation must hold back drug release in the upper GI regions.
- 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 released drug is affected by the resident colonic microflora, (via metabolic degradation).
- 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.

Characteristics Of Human Colon[5,36]

The large intestine extends from the ileocaecal junction to the anus which is divided into three main parts colon, rectum and anal canal. The colon constitutes caecum, ascending colon, hepatic flexture, transverse colon, splenic flexture, descending colon and sigmoid colon. The average size of colon is 1.5m long, the transverse colon is the longest and most mobile part and has an average diameter of about 6.5cm. The wall of colon is consisting of four layers namely the serosa, the muscular external, the submucosa and the mucosa. The serosa is the exterior coat of the large intestine. The muscular external is the major muscular coat of the large intestine which composed of an inner circular layer of fibers surrounding the bowel and an outer longitudinal layer. The submucosa is the layer of connective tissue lies immediately beneath the mucosa lining the lumen of the colon. The mucosa has three parts: epithelium, lamina propria and muscular mucosae.

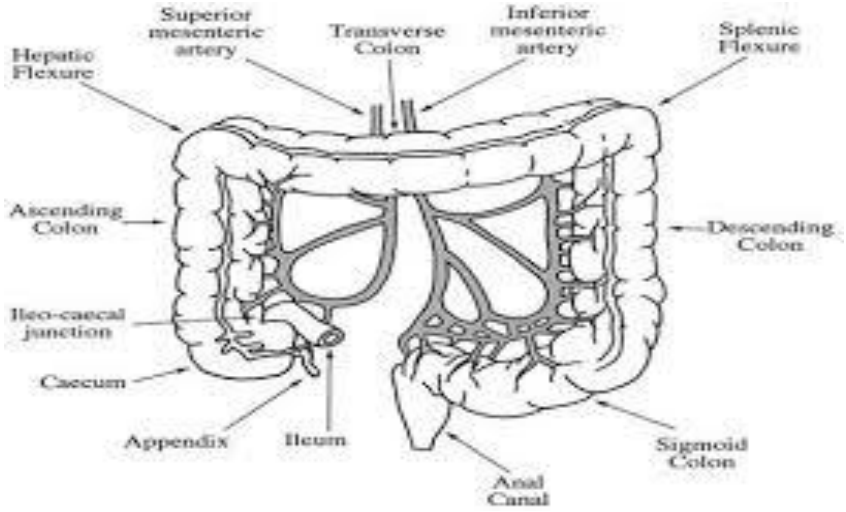

Fig: 1. Ascending, transverse, descending and sigmoid colon.

The main functions of colon

- It creates suitable environment for the growth of colonic microorganisms.
- Fecal contents storage reservoir.
- Eviction of content of the colon at suitable time.
- To secrete K^+ and $HCO3^-$.

Absorption of drug from colon studies in rat have revealed that paracellular absorption is constant through the small intestine, but transcellular absorption appears to be limited to the small intestine, with negligible colonic absorption by this route. The epithelial cell junctions are very tight which may leads to poor paracellular absorption of many drugs in the colon. The drug stays in contact with mucosa in colon for a longer period than in small intestine which compensates the much lower surface areas of colon for absorption.

The colonic contents become more viscous with absorption of water as content travels through the colon. This cause a reduction in dissolution, and sluggish diffusion of dissolved drug through the mucosa. CSDDS Drugs reported to be well absorbed through colon include glibenclamide theophylline, diclofenac, ibuprofen. Drugs shown to be less absorbed are furosemide, piretamide, buftomedil and ciprofloxacin.

Factors Affecting Drug Absorption

The colon specific drug delivery primarily affected by two physiological factors, these are pH level and the transit time. The other factors which need to be considered are as follows:

- Physical characteristic of drug (pka, degree of ionization),
- Colonic residence time as detected by gastrointestinal tract motility,
- Degradation by bacterial enzymes and byproducts,
- Selective and non selective bindings to the mucus,
- Local physiological actions of drug,
- Disease state,
- Use of chemical absorption enhancers.

Inter- and intra-subject variations in gastrointestinal tract pH are reported. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid.

The average pH values in different region of human GI tract.

- Oral cavity 6.2 – 7.4
- Oesophagus 5.0 – 6.0

Stomach

- Fasted condition : 1.5 – 2.0
- Fed condition : 3.0 – 5.0

Small intestine

- Jejunum : 5.0 – 6.5
- Ileum : 6.0 – 7.5

Large intestine

- Right colon : 6.4
- Mid colon and left colon : 6 – 7.6

One of the major determinants of absorption of compound from colon is residence of formulation in some particular segment of the colon. The transit time in the small intestine is reported to be quite consistent than the stomach and colon. The size of the particles influences the colon, small particles exceed through the colonic region more slowly than the larger unit, and on the other hand for larger single unit density and size of has no genuine effect on colonic transit. It has been shown that pellets move faster than the tablets through the ascending colon. So pellets are more favorable than tablets.

COLONIC DISEASE

Inflammatory bowel disease

Inflammatory bowel disease is the communal terms for a group of idiopathic intestinal conditions include ulcerative colitis (UC) and Crohn's disease (CD). IBD is considered to be chronic relapsing disorder allied with uncontrolled inflammation within the gastrointestinal tract which may lead to the development of colorectal cancer later in life. One million people in North America are reported to be affected by IBD which may be due to a deregulated immune response to the host microflora in individuals susceptible genetically. CD and UC can be quite distinct, with different pathogenesis, inflammatory profiles, symptoms and treatment approach.

Crohn's disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract; it is characterized by a granulomatous inflammation affecting any part of the tract, normally form fistulae. The Crohn's disease was first described by the Crohn et al in 1932.

Etiology

The reason for Crohn's disease is not known but clearly involves interplay between genetic and environmental factors. The latter includes smoking and intestinal luminal factors. There is a relative risk of 4 to 6 for Crohn's disease in smokers compared with non-smokers, which is in striking contrast to the reverse association seen in ulcerative colitis. The role of luminal factors is suggested by the tendency of Crohn's disease to heal if the colon is rendered non-functional by an ileostomy and by the effectiveness of an elemental diet for the treatment of active disease. Other mechanisms may contribute to the pathogenesis and include diet, infective agents, ischemia and immune mechanisms.

Pathology

Crohn's disease may occur anywhere in the gastrointestinal tract, although the most common pattern is an ileocolits. The disease is often discontinuous, giving rise to so-called skip lesions. Isolated involvement of the mouth, esophagus, stomach and anus is recognized but such cases are extremely rare.

Drugs commonly used in CD[8,29]

Azatioprine, Prednisolone, Budesonide, Metronidazole, Sulfasalazine, Infliximab, and Mesalazine.

Ulcerative colitis

It is a chronic inflammatory disorder of colon limited to the large intestine as against the case with Crohn's disease where any part of the alimentary tract may be involved. The condition usually manifests in the form of inflammation of the rectum extending further-up to colon. The inflammation may be limited to the left-hand side of the colon or extend to entire colon.

Etiology

The reasons of the disease are not clear. The proposed hypotheses include allergy, infection, immune responses, and abnormality in epithelial cell integrity. The psychosomatic theory is also considered.

Pathology

Macroscopic pathology of ulcerative colitis always involves the rectum but in about 40 percent of patients. Only 20 percent adults will have the whole colon involved, although this proportion rises to about 50 percent in children. Microscopic inflammation of ulcerative colitis is largely confined to mucosa. The capillaries become dilated and congested and there is extravasation of red blood cell.

Drugs commonly used in UC[8,29]

Balsalazine, Azathioprine, Olsalazine sodium, Budesonide, and Mesalazine.

Colonic Cancer

Colonic tumors are growths arising from the inner wall of the large intestine. The large intestine may show benign tumors called polyps, and malignant tumors called cancers. Polyps are not life-threatening as they do not spread to other parts of the body and can be easily removed during colonoscopy. Although if not removed may become cancerous over period of time. Metastasis is the spread of colon cancer to distant organs, the occurrence of metastasis makes complete cure of cancer unlikely. The cancer of the colon and

rectum is third major type of cancer in males and the fourth in females. The adaptation to western diets has shown an increase in incidence of colorectal cancer.

Characteristics of Drug that Favor Colonic Drug Delivery

Colon has less aggressive environment as compare to stomach and small intestine. It has longer retention time and is more responsive to absorption enhancer for the poorly absorbed drugs. Drugs that will benefit from colon targeting include those for the treatment of colonic disease. Drugs that metabolite in upper gastrointestinal tract are also candidate for colon drug delivery system. Drugs like theophyllin, ibuprofen, and low molecular weight peptides and peptide like drugs have been shown to be successfully absorbed from the colonic region. The permeability of colonic epithelium may not be sufficient for achieving a transport rate required for therapeutic activity. This problem may be overcome by using some common colonic drug absorptions enhancers[27-28].

Strategies for Targeting Drugs to Colon[30-33]

The approaches for colon specific drug delivery system are prodrug or coated or matrix preparation.

The commonly used approaches are

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

ph dependent delivery

The change in the pH along the gastrointestinal tract has been used as a mean for colon targeted drug delivery. This can be achieved by means of coating that are intact at lower pH of the stomach but that will dissolved at neutral pH of the colon. The pH in the gastrointestinal tract varies from 1.2 in the stomach, 6.6 in the proximal small intestine and about 7.5 in the distal part of small intestine. This pH variation in the stomach and small intestine has previously been used to deliver drugs to small intestine by way of pH sensitive enteric coating. These polymer coats are recalcitrant to the acidic condition of the stomach but ionize and get dissolved above a certain threshold alkaline pH found in small intestine. Thus it is possible to apply same concept to deliver drugs to the terminal of ileum or colon by use of enteric polymers with a relatively high threshold pH for dissolution and subsequent drug release.

The most commonly used polymer for this purpose is methacrylic acid and methylmathacrylate that dissolve at pH 6 (Eudragit L) and pH 7 (Eudragit S) have been investigated. This approach is based on the fact that the gastrointestinal pH is increase progressively from small intestine to colon. But the pH of the distal is 7.5. This delivery system thus has an inclination to release the drug load prior to reaching the colon. To overcome the problem of premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit FS) which dissolve at slower rate and at higher threshold pH 7 to 7.5 was reported. The gamma scintigraphic study comparing the in vivo performance of these various polymers revealed that Eudragit FS (coated on tablet) was superior as compare to Eudragit L and S polymers in the terms of drug release retardation in the small intestine. That is the intrasubject variability to this polymer is apparent. One must question the impact of gastrointestinal disease on targeting performance.

Time dependent delivery

The average transit time in the stomach is 2hr which may vary; while in the small intestine it is relatively constant around 3hr. Time dependent drug delivery system allow the drug release after a set time delay. For the colon targeted drug release the lag time should similar to the time taken for the system to reach the colon. The lag time of 5hr is usually considered sufficient on the basis of relatively constant transit time in the small intestine. Pulsicap was the first formulation developed based on this approach.

Some researcher demonstrated use of shellac, Eudragit L100 and ethylcellulose at various thicknesses for colon targeted drug delivery of a drug and out of this shellac showed promising result. Eudragit L100 along with channeling agent like sodium chloride has been effectively confirmed for achieving colon target drug delivery based on this approach. Hydroxy propyl methyl cellulose has been used for colon specific drug delivery of pseudoephedrine HCL using this approach. Hydroxy propyl ethyl cellulose, Hydroxy propyl methyl cellulose acetate succinate were also been used for time dependent colon specific drug delivery. HPMC along with pectin has also been shown to produce promising result for colon drug delivery system for sennosides which is used as an herbal purgative. The hydrogel based capsule was reported which swells after definite time and allow drug release after lag time successfully in colon, hence by modifying hydrogel composition and size, lag time could be varied.

Combination of Time and pH dependent

Due to variations in pH and gastric transit time colon drug delivery based only on pH and time would not be consistent. Therefore formulations have been developed based on combination of pH uniqueness of different polymers and transit time in the small intestine using Eudragit FS30D and Eudragit RL-RS32. Pulsatile device in the form of capsule has been developed using this approach for better treatment of nocturnal asthma. Krishnamachari et al, developed controlled release microparticles of budesonide using poly (dl-lactide-co-glycoside) and Eudragit S-100 based on the combinational Crohn's disease treatment. Diclofenac sodium and 5-ASA pellets were coated with ethylcellulose and methacrylic acid copolymers respectively and in vivo studies using dogs shows promising result of colon targeting following oral administration. Akhgari et al, demonstrated combination use of Eudragit S100 and L100 along with Eudragit RS as a single layer coating on pellet for colon targeted drug delivery.

Pressure dependent drug delivery

The muscular contraction of the gut generate pressure for grinding and propulsion of intestinal contents, this pressure is vary all the way through the gastrointestinal tract , luminal pressure in the colon higher due to the process of stool formation. The pressure controlled delivery consists of drug dispersed in a suppository base, coated with the hydrophobic polymer. On swallowing body temperature causes the melting of suppository base and subsequent increases in volume of the system. The balloon doesn't get rupture in the luminal pressure of the small intestine resulting from muscular contraction, but will rupture when in the colon due to more intense pressure of the contractions of the colon and contents of higher viscosity. Co-administered food may affect the performance of system based on pressure, as fed state contraction may be adequately influential to disintegrate the capsule in the stomach. The empty pressure-controlled colon delivery capsules were developed by a dipping method where the inner coat was water-insoluble polymer membrane like ethylcellulose and the outer one was hydroxypropylmethylcellulose phthalate, an enteric polymer membrane.

Bacteria dependent drug delivery

Drug can be administered locally and selectively to the colon if they are enclosed in an azo-aromatic cross-linked polymer subject to cleavage by azoreductase of the colonic microflora. This approach of coating a drug with biodegradable material for the colon targeting was reported for used large amount of the drug. The drug release rate is dependent on of the bacterial enzymes activity in the colon rather than on that of the host. The total bacterial count in colon is reported to be 1011 per gram as compared to 104 per gram in upper part of gastrointestinal tract, 400 different anaerobic species are present. Azo bond based polymer for the obtaining universal carrier systems was reported but the safety and toxicity 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, and pectin. Biodegradable polymers degrade in vivo, either in presence of enzyme or nonenzymatically, to produce products which are non toxic and biocompatible. The microflora composition remains relatively constant across a diverse human population. Amylose one of the polysaccharide obtained from starch shown potential for colonic drug delivery due to degradation by enzyme amylase in colon. Similarly pectin along with ethylcellulose was reported for colon specific drug delivery of 5-flurouracil. The drug sulfasalazin (SAS) used for IBD and rheumatoid arthritis is the earliest example of targeted drug delivery in the colon based on this approach. Only 12% drug was released in the small intestine after oral administration. When SAS reaches the

colon after oral administration the diazoreductase bacteria of colon bacteria cleaves the azo bond releasing 5-amino salicylic acid and sulfapyuridine into colon lumen. Osalazine consist of 5-amino salicylic acid linked by an azo bond was developed to directly deliver 5-amino salicylic acid to the colon. Chitosan, a polysaccharide has been used for colon targeted drug delivery in several dosage forms including, matrices, hydrogel, microspheres and now recently in osmotic pump. Laroyl and crosslinked galactomannan, Cyclodextrins an oligosaccharides, dextran were successfully reported for colonic drug delivery might be influenced by many factors including diet, drugs, and gastrointestinal diseases may influence the metabolic activities, which should be considered while designing of colon targeted drug delivery system based on this approach.

Evaluation of Colon Specific Drug Delivery Systems

A successful colon targeted drug delivery system is one that don't release drug in the stomach and small intestine, but releases the drug in the colonic region. Different in vitro in vivo methods are used to evaluate the colon targeted drug delivery.

***In- vitro* dissolution testing method**[34-35]

Development of appropriate dissolution testing method is one of the major tasks to evaluate the colonic drug delivery system by in vitro. A number of alternative or unconventional approaches have been reported for evaluating the performance of colon targeted delivery system in vitro. Conventional basket method was used for dissolution testing of colon delivery systems in different pH buffers for diverse periods of time to simulate the GI tract pH and transit time of gastrointestinal tract. The dissolution study (paddle method) for colon targeted drug delivery is reported in the 13th edition of pharmacopeia of Japan. The two fluids of pH 1.2 and 6.8 were reported as dissolution media.

The dissolution test can also be performed using continuous-flow apparatus in a pH progression medium at 370c, simulating gastrointestinal conditions. The reciprocating cylinder method (Type 3 USP apparatus) for enteric coated pellet with changing pH used. Flow through apparatus along with sequential dissolution liquid i.e. simulated gastric fluid for 60 min; followed by 3-6 hrs in simulated intestinal fluid has also been utilized. Reciprocating cylinder is suitable and competent as compare to type II apparatus. USP XXIII dissolution apparatus with simulating condition of gastrointestinal tract in media of pH 1.2 with 0.1 N HCl and , pH 6.5 , 6.8 , 7.2 with phosphate buffer for time and pH dependent approach used. An in vitro dissolution test method with enzyme-based fermentation system and compared with conventional technique with human fecal bacteria and shown potential system for in vitro assessment.

Fermentation studies[37-38]

For those formulations in which polymers which are specially degraded by the enzymes and bacteria present in colon the dissolution study is carried out using the rat caecal matter or slurries of human fecal or multi stage culture. Information about coating's digestibility or permeability within the colonic environment is difficult to obtain by general dissolution testing methodology which is possible by batch culture fermentation system. The rat fecal contents were favored because of the easy availability of rats and presence of viable count of bacteriodes and bifidobacteria involved in polysaccharide degradation. Anesthetized rats were used for this purpose and their caecal contents were exteriorized for collecting the contents which was further diluted with phosphate buffered saline. The human fresh fecal slurries have also been commonly reported to explore fermentation of nonstarch polysaccharides. Fecal bacteria represent the large intestine and hence this is used in dissolution medium. As the ascending colon is inaccessible the multistage culture system is used. This scheme consists of glass fermentation vessels arranged in series with working volume of 200 ml, and 280 ml, respectively magnetically stirred and kept at 37oC under atmospheric carbon dioxide; pH adjusted at 5.5, 6.2, 6.8, for 1, 2, 3 vessels respectively represents proximal, transverse and distal colon.

***In- vivo* evaluation of colon-specific drug delivery system**[39-43]

When the system design is conceived and prototype formulation has acceptable in vitro character, the site specificity of drug release and pharmacokinetics information of the drug delivery system to be studied by in vivo studies. Although animal models have obvious advantages in assessing colonic drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems with γ-

scintigraphy imaging. Some research work has reported in vitro in vivo correlation of colon specific delivery system using human volunteers and antipyrine as a model drug, by testing pharmacokinetic data of the drug and gamma scintigraphic analysis. For, CODES^{TM} Gamma scintigraphic studies revealed to achieve target release in the colon despite of the ingestion of food.

Animal model

Rats, mice, pigs and dogs where commonly used animal models was reported for colon targeted drug delivery systems. For simulating the human physiological environment of the colon, appropriate animal model selection is depends on its approach and design of system. For example, guinea pigs have glycosidase and glucuronidase activities in the colon and digestive anatomy and physiology is similar to that of human, so they are appropriate in evaluating prodrugs containing glucoside and glucuronate conjugated for colonic delivery. Other techniques which commonly are used for monitoring the in vivo behavior of colon targeted drug delivery are String technique, Endoscopy, Radiotelemetry, and Gamma scintigraphy.

Advances in Colon Targeted Drug Delivery

The colon specific drug delivery system should be capable of protecting the drug en route to colon (i.e. drug release and absorption should not occur in the stomach and the small intestine and bioactive agent should not be degraded) and to allow drug release only in the colon. The colon is believed to be a suitable site for absorption of peptides and protein drugs for following reasons: (i)Less diversity and intensity of digestive enzymes. (ii)Comparatively proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and eventually releases drugs in the ileum or colon which leads to greater systemic bioavailability. (iii)The colon has along residence time and is highly responsive to absorption enhancers. The concentration of drug reaching the colon will depend on formulation and factors such as chemical nature, stability and partition coefficient of the drug and the type of target sites disease conditions, drug and active agent's topical action, Local action, Systemic action, for that some novel approaches listed here.

Approaches used for site specific drug delivery to Colon[44-45]

Primary approaches

- a - pH sensitive polymer coated drug delivery
- b - Delayed (Time controlled release system) release drug delivery
- c - Microbially triggered drug delivery
    - (i) Prodrug approach for drug delivery
    - (ii) Azo-polymeric approach for drug delivery
    - (iii)Polysaccharide based approach for drug delivery

Newly developed approaches

- a - Pressure controlled drug delivery system (PCDCS)
- b - CODES™ (A Novel colon targeted delivery system)
- c - Osmotic controlled drug delivery to colon (OROS-CT)

In the above approaches following types of drugs to be tried:

- Pharmacological class Non-peptide & Peptide drugs
- Drugs used for local effects in colon against GIT diseases
- Drugs poorly absorbed from upper GIT
- Drugs for colon cancer
- Drugs that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs for targeting
- Anti-inflammatory drugs

- Antihypertensive and Antianginal drugs
- Antineoplastic drugs

CONCLUSION

The colonic region of gastro intestinal tract becomes an increasingly important site for drug delivery and absorption. The targeted drug delivery would offer considerable therapeutic benefits to patients, in terms of both local and systemic treatment. Colonic delivery is more likely to be achieved to systems that utilize natural materials that are degraded by bacterial enzymes of colonic origin[46-51].

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