Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Issue 3, 2013

Review Article

NOVEL APPROACHES FOR COLON SPECIFIC DRUG DELIVERY SYSTEM-A REVIEW

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Received: 27 Apr 2013, Revised and Accepted: 12 Jun 2013

ABSTRACT

Day by day there are new developments in field of colon specific drug delivery system. Lot of research is undergoing in colon specific drug delivery as this drug delivery route is not only useful for targeting the drugs required in the treatment of diseases associated with colon, but also as a potential site for the local and systemic delivery of peptide and proteins and other therapeutic drugs. Precise colon drug delivery requires the triggering mechanism in the delivery system that can respond only to the physiological conditions specific to the colon. The primary conventional approaches used to obtain colon-specific delivery were based on prodrugs, pH and time dependent systems or microflora activated systems and achieved limited success. However, recently continuous efforts have been taken on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs. The focus of this review is to provide detailed insight into the conventional as well as recent approaches used to target the therapeutic agents specifically to the colon.

Keywords: Colon specific drug delivery, Conventional and recent approaches

INTRODUCTION

Oral controlled - release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug - release pattern that are not achieved with traditional immediate (or) sustained - release products[1]. Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative 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 duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability[2]. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers. Oral route is the most convenient and preferred route but other routes for CDDS may be used[3].Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult[4]. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal. Drug preparation for intra rectal administration is supplied as solutions, foam, and suppositories[5]. The intra rectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis[6]. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects[7-9]. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. 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.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. [10]

Criteria for Selection Of Drug for CDDS

Drug Candidate

Drugs which showed poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea and colon cancer was ideal candidates for local colon delivery [11].

Criteria for selection of drugs for CDDS are summarized in **Table** 1.

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Antisense Oligonucleotide
Drugs poorly absorption from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbides, Theophylline	Cyclosporine, Desmopressin
Drugs for colon Cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine, 5-Flourouracil, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and Corticosteroids	Bleomycin, Nicotine	Protirelin,sermorel in, Saloatonin
Drugs for targeting	Antiarthritic and antiasthmatic Drugs	Prednisolone, hydrocortisone, 5-Aminosalicylic acid	Somatropin, Urotoilitin

Drug Carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used.

Factors which influence the carrier selection are:

1. Chemical nature

2. Stability

3. Partition coefficient of the drug

4. Type of absorption enhancer chosen

Moreover, the choice of drug carrier depends on the functional groups of the drug molecule[12]. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydrogels or coating agents) influences the release properties and efficacy of the systems.

Need of Colon Specific Drug Delivery

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects

2. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery

3. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).

4. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.

5. Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.[13]

APPROACHES USED FOR SITE SPECIFIC DRUG DELIVERY TO COLON

Methods for Targeting Drugs to the Colon:

To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinaltract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs.

The various strategies for targeting orally administered drugs to the delivery system.There are four practical mechanisms by which a delivery system can be targeted to the colon by oral administrations:

Use of a pH dependent delivery system

Use of time dependent delivery system.

Use of a pressure controlled delivery system

Use of a bacterially triggered delivery system.

Conjugates:

Azo bond conjugates

Glycoside conjugates

Aminoacid conjugates

pH-dependent Delivery

pH sensitivity enteric coatings have been used routinely to deliver drugs to the small intestine these polymers coatings are insensitive to acidic conditions of the stomach yet dissolve at the higher PH environment of small intestine. This pH differential principle has also been attempted for colonic delivery purposes, although the polymers used for colonic targeting tend to have a threshold of pH for those used in conventional enteric coating applications. Most commonly co-polymers of meth acrylic acid and methyl methacrylate that dissolve at a slower rate and at a higher threshold pH (7-7.5), has been developed recently.

The inter and intra-subject variability in gastro-intestinal pH and possibly certain other intrinsic variable such as electrolyte concentration and transit time will therefore impact on the in vivo behavior of pH-responsive system, ranging from early drug release in the small intestine to no release at all, with the formulation passing through the guts intact. [14] The latter intestine, is considerably lower than normal, as is the case in patients with ulcer colitis in spite of their limitation, pH-sensitive delivery system are available for mesalazine and budesonide for treatment of ulcerative colitis and crohn's disease, respectably

Time-dependent Delivery

Time dependent delivery has also been proposed as a means of targeting the colon. Time-dependent system releases their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon. This time is difficult to predict in advance, although a lag time is reported to be relatively constant at three to four hours

Pressure-dependent delivery

Gastro intestinal pressure has also been utilized to trigger drug release in the distal gut. This pressure, which is generated via muscular contraction of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the GIT, with the colon considered to have a higher luminal pressure due to the process that occur during stool formation. Systems have developed therefore to resist the pressure of the upper GIT but rupture in response to the raised pressure of the colon. Capsule shell fabricated from the water insoluble polymer ethyl cellulose has been used for this purpose. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall. [15]

Bacteria-dependent delivery

The resident GIT bacteria provide a further means of effecting drug release in the colon. These bacteria predominantly colonize the distal region of GIT where the bacterial count in the colon is 1011 per gram, as compare to 104 per gram in upper small intestine. Moreover, 400 different species are present. Colonic bacteria are predominantly anaerobic in nature and produce enzymes that are capable of metabolizing endogenous and exogenous substrate, such as carbohydrate and proteins that escape digestion in the upper GIT. Therefore, materials those are recalcitrant to the condition of the stomach and small intestine. Yet susceptible to degradation by bacterial enzymes within the colon, can be utilized as carriers for drug delivery to the colon. This principle has been exploited commercially to deliver 5-aminosalicylic acid to the colon by way of a prodrug carrier. The prodrug sulphasalazine consist of two separate moieties, sulphapyridine and 5-aminosalicylic acid, linked by an azo bond. The prodrug passes through the upper gut intact, but, once in the colon, the azo bond cleaved by the host bacteria, liberating the carrier molecule sulphapyridine and pharmacologically active agent 5-aminosalicylic acid. This concept has to development novel azo-bond based polymer for the purpose of obtaining universal carrier systems. However, issue with regard to safety and toxicity of these synthetic polymers has yet to be addressed. To overcome such concerns, natural materials, essentially those that are polysaccharide based, offer a viable alternative to the problem. Materials include amylase, chitosan, chondroitin sulphate, dextran, guar gum, inulin and pectin. These materials are not, however without limitations. They are hydrophilic in nature, which renders them to soluble or prone to swelling in an aqueous environment and hence unsuitable as drug carriers. To fully realize the potential of these polysaccharides for colonic delivery, some form of structure modification and/ or formulation strategy is required.The colonic region of GIT has becomes an important sites

for drug delivery and absorption. Targeted drug delivery would offer considerable therapeutic benefits to patients, in terms of both local and systemic treatment .systems that rely on gastrointestinal pH, transit time or pressure for release are degraded by bacterial enzyme of colonic origin. Moreover, the cost and ease of manufacture of the delivery system are further consideration that will impact on its likely commercialization and, hence availability to patients. A bacteria-sensitive natural film coating that can be applied to a range of solid oral dosage forms using conventional processing technology would therefore appears to be the delivery system of choice. [16-19]

Azo bond conjugates

The intestinal microflora is characterized by a complex and relatively stable community of microorganism, many with physiological functions,which play vital roles in health and disease. In addition to protection of the patient against colonization of the intestinal tract by potentially pathogenic bacteria, the indigenous microflora are responsible for a wide variety of metabolic processes, including the reduction of nitro and azo groups in environmental and therapeutic compounds.[20]

Glycoside conjugates

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system.Drug glycosides are hydrophilic and thus, poorly absorbed from the small intestine. Once such a glycoside reaches the colon it can be cleaved by bacterial glycosidases, releasing the free drug to be absorbed by the colonic mucosa. [21]

Amino-acid conjugates

Due to the hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids),they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids . Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA.[22-23]

NEWLY DEVELOPED APPROACHES FOR CDDS

Novel colon targeted delivery system (CODES TM)

CODESTM was a unique CDDS technology which is a combined approach involving pH dependent and microbially triggered CDDS and was designed to avoid the inherent problems associated with pH or time dependent systems. It was developed by utilizing a unique mechanism involving lactulose, acting as a trigger for site specific drug release in the colon.The system consists of a traditional tablet core containing lactulose, which is coated with acid soluble material Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The final conclusion of this technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria will enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and thus cause subsequent drug release.[24-26]

Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT was used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 units, each encapsulated within a hard gelatin capsule (**Figure 3**). Each bilayer unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane thus it is called as a push-pull unit. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the pushpull units dissolves. Each push-pull unit was prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered because of its drug impermeable enteric coating. As the unit enters the small intestine, the coating dissolves because of higher pH environment (pH >7) water enters the unit causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice in a rate controlled manner [55-58]. Various *in-vitro*/*in-vivo* evaluation techniques have been developed and proposed to test the performance and stability of CDDS.[27]

Combination of Different Approaches of CDDS

An oral colonic drug delivery system of 5-aminosalicylic acid was developed using combination of pH dependent, time-based and enzyme degradable approaches. The pellets were coated with three functional layers i.e. the outer EudragitL30D-55 layer for protection against GI fluids, the intermediate layer of ethyl cellulose to inhibit the drug release during passage through the small intestine and the inner layer of pectin for swelling and enzyme degradation. *In-vitro* release studies indicated that the coated pellets completely protected the drug release in 0.1M HCl while the drug release was delayed for 3 to 4 h in pH 6.8 phosphate buffer. Pulsatile device was formulated to achieve time or site specific release of theophylline based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body filled with Eudragit microcapsules of theophylline and sealed with a hydrogel plug and finally the enteric device was enteric coated. In this approach, pH sensitive and time dependent delivery systems were combined. In this the thickness of enteric coat is a measure of protection from stomach and intestine pH. Different hydrogel polymers were used as plugs to maintain a suitable lag period. The hydrophilic polymer content is a measure of delayed release of theophylline from microcapsules [28].

Hydrogel based CDDS

Hydrogels are usually formed by the covalent crosslinking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble .Heterogenous polymer mixture may also be used to form hydrogels without the need for covalent crosslinking . Glutaraldehyde cross-linked dextran capsules were prepared for colon specific delivery. Along with magnesium chloride and PEG 400 in water the capsule caps and bodies were prepared on nylon molding pins. Then the dextran capsules were filled with model drug (Hydrocortisone) and drug release was studied. The drug release pattern was suitable for colon targeting[29] . The hydrogels formed by cross-linked polyvinyl alcohol were suitable for colon specific drug delivery systems. In this method polyvinyl alcohol of different molecular weights was cross-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel-forming polymers. The hydrophilic drugs like diclofencac sodium,propranolol hydrochloride and vitamin B6 hydrochloride were used as model drugs. A new microparticulate system containing budesonide.

Other Novel Drug Delivery Systems

A new microparticulate system containing budesonide was prepared by microencapsulation for colon specific delivery[30].A novel colon specific drug delivery system containing flubiprofen microsponges was also designed..Microsponges containing flubiprofen and Eudragit RS 100 were prepared by quassi-emulsion solvent diffusion method and/or flurbiprofen was entrapped in to a commercial microsponge-5640 system using entrapment method.Using these flubiprofen microsponges the colon specific tablets were prepared using triggering mechanism.The particulate form (microsponges)has bee used to provide more uniform distribution of the drug in the colon and help the drug to spread on the colon surface in an appropriate way.

EVALUATION OF COLON TARGETED DRUG DELIVERY

***In Vitro* Evaluation**

No 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 and physical stress and these

factors make it difficult to design a slandered in vitro model.[31] *In vitro* model used for CDDS are

***In vitro* dissolution test**

Dissolution of control

Release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces. 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. Dissolution tests of a colon- specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. [32]Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. In vitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine. Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time)

***In vitro* enzymatic test**

For this there are 2 tests

1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (*Streptococcus faccium* or *B.ovatus*) amount of drug released at different time intervals determined.

2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents[33]. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

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. Eg. 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[34-39]. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host.

Clinical Evaluation

Absorption of drugs from the colon is monitored by colonoscopy and intubation[40-43]Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

High frequency capsule

Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator.Release of drug & radiotracer triggered by an impulse, the release is monitored in different parts of GIT by radiological localization[44].It checks the absorption properties of drug in colon.

Gammascintigraphy

By means of gammascintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gammascintigraphic studies can also provide information about regional permeability in the colon[45]Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy).

Future Prospects

Recent reports indicate interest in colon as a site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines.

However, drug release is not the end point of oral delivery. The bioavailability of protein drugs delivered at the colon site needs to address. The use of drug absorption enhancers into the drug delivery systems is likely to enhance therapeutic efficacy. Studies on drug absorption by the intestinal system have focused on drug transporters that mediate drug influx and efflux and agents which can enhance drug absorption. The colon segment is designed by nature mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

CONCLUSION

From past two decades, considerable amount of research work has been carried out in the area of colon targeting. By considering the advantages of CDDS like providing friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site-specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc., different approaches are designed to develop colonic drug delivery system. The present description is highly illustrative to describe them.

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