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Review Article

DESIGN AND EVOLUTION OF COLON SPECIFIC DRUG DELIVERY SYSTEM

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ABSTRACT

Due to greater flexibility in design of dosage form and high patient compatibility, oral administration of different dosage forms is the most commonly used method.But the gastrointestinal tract presents several formidable barriers to drug delivery. In oral colon-specific drug delivery system, colon has a large amount of lymphoma tissue which facilitates direct absorption in to the blood, negligible brush boarder membrane activity, and much less pancreatic enzymatic activity as compared with the small intestine. Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. Different approaches are designed based on pro-drug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure etc. to formulate the different dosage forms like tablets, capsules, multi-particulates, microspheres, liposomes for colon targeting. The efficiency of drug delivery system is evaluated using different in vitro and in vivo release studies. This review updated the research on different approaches for formulation and evaluation of colon-specific drug delivery systems (CDDS).

Key words: Colon specific drug delivery system, Microbial degradation, Osmotic Pressure.

INTRODUCTION

In the past two decades, the pharmaceutical scientists are extensively investigated in the area of colonic region for targeted drug delivery system. Targeted drug delivery to the colon is mainly for the treatment of colonic diseases, for drugs like proteins and peptides, for the treatment of diseases sensitive to circadian rhythms such as Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon. The advent of slow release technologies increase the chances for a drug to be released in the colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations.

In 1942, Svartz discovered that sulfasalazine; the sulfanilamide prodrug of 5- aminosalicylicacid (5-ASA) is effective in the treatment of rheumatoid arthritis and anti-inflammatory disease. The exact mode by which the drug target itself to the colon was elucidated much latter in 1970 i.e., colon specific azoreductase splits sulfasalazine causing the release of the active moiety 5-aminosalicylicacid. After the several other azo-bonds containing compounds designed to locally release 5-aminosalicylicacid were synthesized bensalazine, balsalazide and olsalazine. In1986, Saffron and coworkers described the use of azo containing acrylic polymers to the delivery of protein drugs like insulin to the colon (Girish et al. 2006).

Colon-specific drug delivery system offers the following therapeutic advantages (Girish et al. 2006, Chourasia et al. 2003, Sarasija et al. 2000, Vyas and Roop, 2006):

- Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn's disease etc.)
- By producing the 'friendlier' environment for peptides and proteins when compared to upper gastrointestinal tract
- Minimizing extensive first pass metabolism of steroids.
- Preventing the gastric irritation produced by oral administration of NSAIDS.
- Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.

To achieve successful colon targeting it should overcome the following limitations (Jack et al., 2006).

- The location at the distal portion of the alimentary canal, the colon is difficult to access.
- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.

ANATOMY AND PHYSIOLOGY OF COLON

Irrespective of therapy desired for local (colonic) or systemic delivery of drug, the development and aim of the drug delivery to colon remains same (Vyas and Roop, 2006), that is

- The drug must not absorb from other regions of the gastro intestinal tract (GIT).
- It should only suffer negligible degradation in the small intestine lumen.
- The release of the drug in the colon should be at quantitatively controlled rate and the released drug in the colon should be absorbed from the lumen of the large intestine without any appreciable degradation.

In order to meet these properties, a thorough knowledge of the anatomy and physiology of GIT is required. In GIT, large intestine starts from the ileocecal junction to the anus with a length of about 1.5meters (adults) and is divided into three parts; they are colon, rectum and anal canal. The colon is the upper five feet of large intestine and mainly situated in the abdomen. The colon is a cylindrical tube lined by mucosa. The cecum, colon ascends, colon transversale, colon descendens and recto sigmoid colon made of the colon. Colon is made up of four-layers, serosa, muscularisexterna, sub mucosa, and mucosa. The colon does not have villi, but due to presence of plicaesemilunares (cresentic folds) the intestinal surface of the colon is increased to approximately 1300 cm2. CDDS is primarily dependenton the following physiological factors; they are the pH level, the transit time and the microbialenvironment in the colon, which are governing the release rate of drug from different designs ofCDDS (Vyas and Roop, 2006**,** Vincent et al.2002). Different properties of GIT were given in (Table 1)and different enzymes present in colon, which are responsible for microbial degradation, were reportedby Vincent et al (2002).

COLONIC ABSORPTION OF DRUGS

The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). Different factors affecting colonic absorption were reported by Vincent et al (2002).

- Passes through colonocytes (Trans cellular transport).
- Passes between adjacent colonocytes (Para cellular transport).

Transcellular absorption involves the passage of drugs through cells and thus the route for most
lipophillic drugs takes, where as paracellular absorption involves the transport of drug through thetight junctions between the cells and is the route of most hydrophilic drugs (Vyas and Roop, 2006). Drugs shown to be well absorbed include glibenclamide, diclofencac, theophylline, ibuprofen,metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide,buflomedil, atenolol, cimetidine, hydroclorthiazide, lithium and ciprofloxicin (Sarasija et al. 2000).Different types of absorption enhancers used in CDDS reported by Vincent et al (2002).

DRUGS SUITABLE FOR CDDS

Based on literature review, the following different categories of drugs are suitable for colon drug delivery.

- Drugs used to treat irritable bowel disease (IBD) require local delivery at drug to colon e.g. sulfasalazine, olsalazine, mesalazine, steroids like fludrocortisone, budesonide, prednisolone and dexamethasone.
- Drugs to treat colonic cancer require local delivery e.g. 5-fluorouracil, doxorubicin, and methotrexate.
- Protein and peptide drugs - eliminating drug degradation e.g. growth hormones, calcitonin, insulin,interleukin, interferon and erythropoietin.
- To treat infectious diseases (amoebiasis & helminthiasis) - requires site specific delivery e.g. metronidazole, mebendazole and albendazole.
- To treat rheumatoid arthritis (NSAIDS), nocturnal asthma, angina require delay in absorption dueto circadian rhythms.
- Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport e.g. glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol and oxyprenolol.

DIFFERENT APPROACHES

Prodrug Approach

A prodrug is pharmacologically inactive derivative of a parent drug molecule that requires
spontaneous enzymatic transformation in vivo to release the active drug (Sinha and Rachana, 2001a).In this method the prodrugs (Table 2) are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the carrier.
Different types of conjugates were used to prepare 5-ASA prodrugs, which are succeed inreleasing the 5-ASA in colonic region. They are biodegradable poly (ether-ester) azo polymers (Samynet al.1995), azo-linked polymeric prodrugs (Etienne et al.1996), acrylic type polymericprodrugs (Soodabeh et al.1997) and cyclodextrin prodrugs (Kaneto et al.1997). Glucuronideprodrugswere developed for corticosteriod to deliver the drug to the large intestine of colitic rats (Harold etal.1997). Azo-containing urethane analogues synthesized for colon drug delivery. A urethane-basedanalogue containing an azo aromatic linkage in the backbone was synthesized by reacting touline-2, 6-diisocyanate with a mixture of an aromatic azodiol (Chavan et al. 2001).
Cyclodextrin prodrugs were prepared by conjugating 5-ASA on to the hydroxyl groups of α-,β-, γ-cyclodextrins through an ester linkage and investigated the release in cecum and colon. After oral administration in rats the conjugate passed through stomach and small intestine without degradation orabsorption and in the cecum and/or colon site-specific degradation of conjugate released 5-ASA (Mei et al. 2005). An azoprodrug of 5-ASA with histidine was synthesized for targeted drug delivery to the inflammated gut tissue in inflammatory bowel disease. The synthesized prodrug was found to be equally effective in mitigating the colitis in rats, as that of sulfasalazine without the ulcerogenicity of5-ASA and adverse effective of sulfasalazine (Nagpal et al. 2006).

In a recent study by Yunjin et al. (2006), explained the potential of 5- amino salicyliltaurine as a colon specific prodrug of 5ASA by in vivo evaluation to treat experimental colitis. The prodrug wasprepared by conjugating 5ASA with taurine and tested in 2,4,6, trinitrobenzenesulfonicacid (TNBS)induced colitis rats. Taurine conjugation of 5-ASA greatly reduced absorption of 5-ASA from the intestine. Oral administration of the conjugate not only increased the colonic delivery efficiency of 5-ASA but also decreased the systemic absorption of free 5-ASA as compared to other conjugates prepared with glycine and asparticacid. Taurine conjugate of 5-ASA is slightly more effective than sulfasalazine in alleviating the colonic inflammatory induced by TNBS. N-Nicotinoylglycyl-2-(5-fluorouracil-1-yl)-D, L-glycine was synthesized as a prodrug of 5-fluorouracil colon specific drug delivery (Lee et al. 2007).

pH-Dependent System

The basic principle in this method is the coating of the tablets/pellets etc with various pH sensitive polymers (given in Table 2), which will produce delayed release and also give protection from gastric fluids. Selection of polymers is important thing. The selected polymers to colon targeting should be able to withstand the pH of the stomach and small intestine. Methacrylic acid esters most commonly used polymers for colon targeting because they are soluble at above pH 6. The ideal polymer should be able to withstand the lower pH of the stomach and of the proximal part of the small intestine but able to disintegrate at neutral or shortly alkaline pH of the terminal ileum and preferably at ileocecal junction. Eudragit L and Eudragit S are widely used in the colon targeting because Eudragit L is soluble at pH 6 or above and Eudragit S is soluble at pH 7 or above and the combination of these polymers give the desirable release rates.

A novel colon-specific drug delivery system was developed with methacrylate derivatives of 5-ASA using pH sensitive swelling and drug release properties (Davaran et al. 2001). Composite filmcoated tablets of 5-ASA were prepared for colon specific delivery. In this method 5-ASA core tablets were prepared and coated with dispersion contained Eudragit RS and dessterrifed pectin, polygalacturonic acid, or its potassium and sodium salts. Negligible drug release occurred during first five hours where the coated tablets were in the stomach and small intestine. After that the release of 5-ASA from coated tablets occurred linearly as a function of time due to the action of pectinolytic enzymes (Sriamornsak et al. 2003).

A comparison study of the usual enteric-coated polymers viz. Eudragit, Cellulose acetatephthalate with Shellac and Ethyl cellulose as carriers for colon specific drug delivery was conducted to select a suitable carrier. In this study lactose based indomethacin tablets were prepared and coated with one of the above coating polymers to a varying coating thickness. From the dissolution data at acoat concentration of 3% shellac provided the most appropriate polymer coat for colon-specific drug delivery. Variation in the shellac coat thickness can facilitate drug delivery to terminal ileum, distal or proximal colon (Sinha et al. 2003).

EUDRACOLTM is a novel pH and time controlled multiple unit colon drug delivery systems in which the pellets coated with Eudragit RL /RS and Eudragit FS 30D. Caffeine is used as marker drug for pharmacokinetic studies using the multi particle principle and delayed release in the colon; reduction of dosing frequency may be achieved. Due to its specific coating structure, the Eudracolsystem offers a new dimension for colon drug targeting via the oral route (Brigitte et al 2003). 5-ASApellets were coated with the enteric coating solution containing different ratios at Eudragit L-100 and Eudragit S-100 for colon drug delivery. The release of 5-ASA is depending on the thickness of the layer and the ratio of Eudragit copolymers (Gang et al. 2004). PH-sensitive hydrogels were prepared for colonic delivery of therapeutic peptides, proteins. New pH-sensitive glycopolymers were developed by free radical polymerization of methacrylic acid and 6-hexandiol diacrylate and 6-hexandiolpropoxylatediacrylate (Mahkam M, 2007).

Time-Dependent System

The basic principle involved in the system is the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount (Shweta, et al., 2006). Colon targeting could be achieved by incorporating a lag time into formulation equivalent to the mouth to colon transit time. A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. In this method the solid dosage form coated with different sets of polymers (listed in Table 2) and the thickness of the outer layer determines the time required disperse in aqueous environment.

Colon drug delivery system of diclofencac sodium (DS) was developed using time dependent approach. In this, diclofencac sodium tables were coated with ethylcelluese in ethanol solution cooling diethyl phthalate as a plasticizer and PEG 400 as channeling agent. The lag time of DS release was primarily controlled by thickness of ethycellulose coating layer. By increasing the thickness of the coating layer, longer the lag time of DS release (Gang et al. 2004).

Formulation of fast release enteric coated tablets for colon drug delivery using two different approaches .The first one is using super disintegrate and the second one is based on osmogen. In the first approach core tablets (celicoxib as a model drug) were prepared using different concentrations of super disintegrates like cross-linked PVP. In second approach concentrations tablets were prepared using potassium chloride, sodium chloride as osmogen. Then they are coated with Eudragit L-100:Eudragit S-100 in the ratio of 1:5 to achieve a desired thickness. The tablets with super disintegrates are fast released where the tablets with osmogen are sustain released. The coat weight determines the lag phase that required eliminating the release in stomach and small intestine (Sinha et al. 2006).

Hydroxy Propyl Methyl Cellulose (HPMC) compression coated tablets of 5-fluorouracil were studied for colon drug delivery that based on time-dependent approach. In this, the core tablet was prepared by wet granulation method and then coated with 50% of HPMC/lactose coat powder by compression-coating method. Drug release characteristics were evaluated in distilled water by using a Chinese pharmacopoeia rotatable basket method (Wu B et al. 2007).

Micro flora Activated System

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by release of drug load in colonic region because the bioenvironment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms (Sinha, Rachana, 2003). In this method drugs and/or dosage forms are coated with the biodegradable polymers (Table 2) i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remain intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating.

5-ASA pellets were coated with amylose for colon drug delivery, in which amylose coating solution was prepared along with Ethocel, Eudragit RS/RL 30D and Aquacoat ECD 30 (Snezana et al.1996). Chitosan capsules were developed for colon specific delivery of insulin and its absorption was improved by addition of absorption enhancers (sodium glycocholate, sodium oleate) and protease inhibitors like bacitracin, aprotinin (Hideyuki et al. 1997). Low swelling guar gum prepared by crosslinking with glutaraldehyde that is used as a colon-specific drug carrier (Irit et al. 1998). Chitosansuccinate and chitosan phthalate were synthesized by reacting the chitosan separately with succinicanhydride and phthalic anhydride. These semisynthetic polymers produced stable matrices of diclofencac sodium for colon specific delivery that had more resistance to acidic condition and improved drug release profile under basic conditions (Khaled et al. 1999).

Organic acids like succinic acid, tartaric acid and citric acid were used as excipients in matrix granules to modify the drug release for colon-specific drug delivery (Nykanen et

al. 1999). Amylose-Ethylcelluese film coatings obtained from organic-based solvents were investigated as potentialvehicles for colon drug delivery. In this method amyulose-butanol dispersion and ethycellulose inethyllacttate/ ethnol/propanol with dibutylsebacate as plasticizer were mixed in various proportions and coated on 5-ASA pellets to achieve desired thickness. The drug release regulating parameters are thickness of coating and ratio of amylose to ethylcelluese. The release of drug is irrespective of the solvent used for coating. Formulation containing 1 part amylase and 1 part ethylcelluose of coating thickness, 15% TWG, gives desired release profiles of 5-ASA for colon targeting (Lee et al. 2000).

Phosphated cross-linked guar gum was prepared for colon-specific drug delivery. Guar gum cross-linked with increasing amounts of trisodiumtrimetaphosphate to reduce its swelling properties for use as a vehicle in oral delivery formulations, especially drugs aimed at localizing in the distal portions of the small bowel. Swelling of guar gum in artificial GI fluids was reduced from 100-120-fold to 10-35-fold depending on the amount of cross linker used (Irit et al. 2000).

Colon target drug delivery system for mebendazole was developed using guar gum as a carrier.

In this method mebendazole matrix tablets containing various proportions of guar gum were preparedby wet granulation technique using starch paste as a binder. From the results 20% and 30% guar gum tablets were provided targeting of mebendazole for local action in the colon (Krishnaiah et al. 2001).

The α-cyclodextrin derivate of prednisolone-21-succinate showed anti-inflammatory activity with lowadverse effects when compared to prednisolone alone by intra colonical administration to rats with2,4,6, trinitrobenzenesulfonicacid-induced colitis. The conjugate can alleviate the systemic adverse effect of prednisolone while maintaining the therapeutic activity of prednisolone (Hideki et al. 2001).

A chitosan-dispersed system (CDS) was developed for colon- specific drug delivery, in which the capsule containing acetaminophen was coated with the suspension containing chitosan powder and Eudragit RS, formed a drug release-regulating layer around the capsule. Outer enteric coating layer prevent the dissolving of chitosan under acidic pH. The resultant enteric-coated CDS capsules reached the large intestine with in one to three hours after oral administration and they were degraded at the colon in beagle dogs (Norihito et al. 2002). Masataka et al. (2002), Libo et al. (2003) were studied about the lactulose as a carrier for colon-specific drug delivery by microbial degradation in colon.

Enteric-coated pectin based matrix tablets were prepared for colonic delivery of theophylline.

This approach takes advantage of the combination of pH-sensitive method and microbial-triggered system. In this method theophylline-colon biodegradable pectin matrix tablets were prepared and coated with enteric coating solution (Eudragit S100 in acetone) to overcome the poor compactability of pectin. Emdex, a hydrophilic directly compressible material was used to prepare tablets by direct compression (Paola et al. 2003). The new quaternized chitosan i.e. triethyl chitosan (TEC) is evaluated in pharmaceutical approaches and proved that there is a significant increase in absorption of poorly absorbed compounds in colon specific drug delivery system (Parisa et al. 2004).

Calcium pectinate beads were prepared for colon specific delivery of therapeutic peptides like bovine serum albumin (BSA) by extruding BSA-loaded pectin solution to an agitating calcium chloride solution and gelled spheres were formed instantaneously by an ionotropic gelation reaction.

The drug release was regulated by concentration of pectin, concentration of calcium chloride and total drug loading (Atyabi et al. 2005). The HPMA Copolymer (N-(2-hydroxy propyl) methacrylamide)-9 amino camptothein conjugate containing a spacer was synthesized and characterized for oral colon specific drug delivery. The drug delivery system has potential in the treatment of colon cancer (Song-Qi et al. 2006 and Shinji et al. 2001). Zinc pectinate

beads formed the strongest network matrix in comparison with calcium pectinate and suggested the zinc pectinate beads as efficient carriers for specific drug delivery to colon (Chambin et al. 2006).
Metronidazole tablets were prepared using various polysaccharides like guar gum, xanthan gum, pectin, carrageenan, β-cyclodextrin for colon specific drug delivery to treat ameobiasis (Mundargi et al. 2007).
5-Fluorouracil compression coated tablets were prepared for colonic release of drug using xanthan gum, boswellia gum and HPMC as the coating materials (Sinha et al. 2007).
CDDS of 5-fluorouracil was developed using pectin-ethyl cellulose as a film coat with Fluidized bed coater (Wei et al. 2007).

Combination of Different Approaches of CDDS

An oral colonic drug delivery system of 5-ASA 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 three to four hours in pH 6.8 phosphate buffer (Fude et al. 2007).
Pulsatile device was formulated to achieve time- or site-specific release of theophylline based on chrono pharmaceutical consideration. The basic design consists of an insoluble hard gelation 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 (Mastrholimath et al. 2007).
Pectin based CDDS of 5-fluorouracil was developed using calcium pectinate gel. Calcium pectinate gel beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S-100 and evaluated using USP paddle type dissolution apparatus in different simulated mediums (Jain et al. 2007).
A new microbial-triggered colon targeted osmotic pump (MTCT-OP) was developed for CDDS based on chitosan for a model drug, budesonide. The combination of osmotic technology and microbial-triggered mechanism had a high potential to deliver to drug load in colonic region. In this method the core tablet of budesonide was prepared with chitosan, which is used to produce osmotic pressure, and to form the insitu delivery pores for colon-specific drug release. Cellulose acetate in acetone along with chitosan (as pore forming agent) was coated on tablet as a semipermeable membrane and finally coated with Eudragit L-100-55 in ethanol as an enteric coating layer that could prevent cellulose acetate membrane from forming pore or rupture before reaching colon region. Budesonide release from developed system was inversely proportional to the osmotic pressure to the release medium (Liu et al 2007).

Hydrogel based CDDS

Amydated pectin hydrogel beads prepared for colon specific delivery of indomethacin and sulfamethoxazole (Munjere et al 1997). Glutaraldehyde cross-linked dextran capsules were prepared for colon targeting. 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 specific delivery (Bronsted et al. 1998). 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 corss-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel-

forming polymers. The hydrophilic drugs like diclofencac sodium, propranolol hydrochloride and vitamin B6hydrochloride were used as model drugs (Orient et al. 2001). Methacrylated inulin hydrogels designed for colon targeting the proteins like Bovine serum albumin or Lysozyme (Vanden et al. 2003). Organic redox-initiated polymerization technique was used to fabricate pH responsive hydrogels for colon specific delivery (Emmanuel et al. 2003).

Glutaraldehyde corss-linked guar gum hydrogel discs were prepared as vehicles for colonspecific drug delivery of ibuprofen. Percent drug release increased with glutaraldehyde concentration. Cross-linking decreased the swelling of guar gum. The fabricated hydrogels discs may prove to be beneficial as colon-specific drug delivery vehicles for poorly water-soluble drugs like ibuprofen (Aditet al. 2006).

Novel complex hydrogel beads were prepared using pectin and zein for colon-specific drug delivery. Pectin/Zein complex hydrogel beads showed the capability to protect incorporated drugs from premature release into stomach and small intestine. The inclusion of a small portion of zein (aprotein from corn) in to the pectin efficiently suppressed the swelling behavior of pectin, thus stabilizing the structural property of the pectin networks. Like wise the pectin networks protected the bound zein from protease digestion. These properties made pectin/zein complex beads a promising system for colon specific drug delivery (Linshu et al. 2006). Cross-linked HPMC hydrogels were synthesized and used to develop 5-ASA colon drug delivery system (Davaran et al. 2007).

NOVEL DRUG DELIVERY SYSTEMS FOR CDDS

Now a days the basic CDDS approaches are applied to formulate novel drug delivery systems likeMultiparticulate systems, Microspheres, Liposomes, Microencapsulated particles etc.

Multi particulate systems

Multi particulates (pellets, non-peariles etc.) are used as drug carriers in pH-sensitive, time dependentand microbially control systems for colon targeting. Multi particulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such as more predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules (Laila and Sanjeev, 2006).

A multiparticulate dosage from was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB). Microspheres loaded by an enteric polymer (EudragitS). Here the enteric coating layer prevents the drug release below pH 7. After that CAB microspheres efficiently controlled the release of budesonide, which is depended on the polymer concentration in the preparation (Marta, Jose et al. 1998). Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and (Asu1,7) Eel calcitonin (Hideyuki et al. 2001). A multi particulate chitosan dispersed system (CDS) was prepared for colon drug delivery and it was composed of the drug reservoir and the drug release-regulating layer, which was composed of water insoluble polymer and chitosan powder. The drug reservoir was prepared by drug containing multi particulates like Non peariles in the study. In this study the multi particulate CDS was adopted notonly for colon specific drug delivery but also for sustained drug delivery (Norihito et al. 2003).

A multi particulate system combining pH sensitive property and specific biodegradability was prepared for colon targeted delivery of metronidazole. The multi particulate system was prepared by coating cross-linked chitosan microspheres exporting Eudragit L-100 and S-100 as pH sensitive polymers. The in-vitro drug release studies shows that no release of drug at acidic pH and higher drug release was found in presence of rat caecal contents indicating susceptibility of chitosan matrix to colonic enzymes released from rat caecal contents (Chourasia and Jain 2004). High-Amylose corn starch and Pectin blend

microparticles of diclofencac sodium for colon-targeted delivery were prepared by spray drying technique. The blending of high-amylose cornstarch with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition from ectin based microparticles. The drug released in colonic region by the action of pectinase from microparticles (Kashappa, 2005).

Masataka et al. (2006) investigated the effect of sodium glycocholate as an absorption promoter on orally administrated insulin absorption utilizing a colon-targeted delivery system. A novel insulin colon-targeted delivery system (Insulin- CODES) contains insulin, lactulose as a trigger forcolon-specific release, citricacid as a solubilizer of insulin, meglumine as a pH adjusting agent and sodium glycocholate as an absorption promoter.

Microspheres of anti-cancer drugs

Cross-linked guar gum microspheres containing methotrexate were prepared and characterized for local release of drug in the colon for efficient treatment of colorectal cancer. In this method glutaraldehyde was used as a cross-linking agent and guar gum microspheres were prepared by emulsification method. From the results of in vitro and in vivo studies the methotrexate loaded crosslinked guar gum microspheres delivered most of the drug load (79%) to the colon, where as plain drug suspensions could deliver only 23% of there total dose to the target tissue (Mohini et al. 2006).Colon specific microspheres of 5-fluorouracil were prepared and evaluated for the treatment of colon cancer. In this method core microspheres of alginate were prepared by modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The results showed that this method had great potential in delivery of 5-fluorouracil to the colon region (Ziyaus et al. 2006).

Other novel drug delivery systems

A new microparticulate system containing budesonide was prepared by microencopsulition for colon specific delivery (Marta et al 2001).

In the study by Liu et al. (2003) a novel formulation for bee venom peptide was developed using coated calcium alginate gel beads-entrapped liposome and investigated for colon specific drug delivery in vitro. The release rate of bee venom from formulation was dependent on the concentration of calcium and sodium alginates and the mount of bee venom in the liposome, as well as coating. A human γ-scintigraphy technique was used for in vivo studies and the results showed that this formulation had great potential for colon-specific drug delivery. A novel colon specific drug delivery system containing flubiprofen microsponges was designed. Microsponges containing flubiprofen and Eudragit RS100 were prepared by quasi-emulsion solvent diffusion method and/or flubiprofen 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 been 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 (Mineet al. 2006).

EVALUATION OF CDDS

The drug release in the colonic region from different CDDS is evaluated by different methods of in vitro and in vivo release studies, which show the success rate of different designs of colon drug delivery systems. Depending upon the method of preparation different evaluation methods are proposed. A successful colon specific drug delivery system is one of that remains intact in the physiological environment of stomach and small intestine, but releases the drug in the colon.

In-vitro Evaluation

Different in vitro methods are used to evaluate the colonic drug delivery systems. In in-vitro studies the ability of the coats/carriers to remain intact in the

physiological environment of the stomach & small intestine is assessed by drug release studies in 0.1N HCl for two hours (mean gastric emptying time) and in pH 7.4 phosphate buffer for three hours (mean small intestine transit time)using USP dissolution apparatus. In case of micro flora activated system dosage form, the release rate of drug is tested in vitro by incubating in a buffer medium in the presence of either enzymes (e.g..pectinase, dextranase) or rat/guinea pig / rabbit caecal contents. The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study (Libio et al, 2002).

In-vivo Evaluation

Like other controlled release delivery systems, the successful development of the CDDS is ultimately determined by its ability to achieve release in colonic region thus exerts the intended therapeutic effect. When the system design is concerned & prototype formulation with acceptable invitro characteristics is obtained, in vivo studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetic information of the delivery system. Although animal models have obvious advantages in assessing colon specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems. The preferable animals to evaluate CDDS are rats, guinea pigs and dogs (Libio et al, 2002).

γ-scintgraphic studies were conducted in human volunteers with technetium-99m-DTPA astracers in sodium chloride core tablets compression coated with guar gum showed that the gum coat protect the drug (tracer) from being released in the stomach and small intestine. On entering the ascending colon, the tablets commenced to release the tracer indicating the breakdown of gum coat bythe enzymatic action of colonic bacteria (Krishnaiah et al. 1998a). Technetium-99m-DTPA was usedas a tracer for γ- scintigraphy evaluation of colon specific guar gum directly compressed matrix tabletsin human volunteers (Krishnaiah et al. 1998b). The scintgraphic evaluation conducted for capsule typecolon specific drug delivery system in human healthy volunteers (Ishibashi et al. 1998). In a study by Krishnaiah et al. (2001), showed the effect of metronidazole and tinidazole (antimicrobial agents) on the release of albendazole from guar gum based colon specific matrix tablets. The active antimicrobial agents (7 days) treatment of rat caecal content decreased the release of albendazole due to decreased levels of anaerobic bacteria present in rat. Sangalli et al. (2001) studied the evaluation of chronotopic TMoral system to achieve time and/or site-specific release. In this study in vitro drug release studies were carried out in a USP 24 paddle apparatus. The in vivo testing, performed on healthy volunteers, envisaged the HPLC determination of antipyrine salivary concentration and a γ-scintgraphic investigation to point out the break-up of the units occurred in the colon.

The suitability of different tracers like Tc-DTPA (technisium-99m-diethylene triaminepentaaceticacid)and Tc-sulphur colloid studied for γ- scintigraphy evaluation of CDDS in healthy human volunteers and concluded that DTPA is a suitable targeting for 99m-Tc for evaluation of CDDS containing water soluble drugs by γ- scintigraphy (Krishnaiah et al. 2002). The suitability of locust bean gum and chitosan for bacterially triggered colon specific drug delivery system was studied by invitro and in vivo drug release studies (Chellan et al. 2002).

In vitro evaluation studies were carried out for colon specific tablets containing different binders like xanthan gum, guar gum, chitosan and Eudragit E. From the results formulation with chitosan and Eudragit E would be highly site specific (Sinha et al. 2002). In a study by Jinhe et al. (2002) proved that apparatus III (reciprocating cylindermethod) was more convenient and efficient than apparatus-II (paddle type) by producing various programmable options in sampling times, agitation rates and medium changes and suggested that apparatus-III approach has better potential for in vitro evaluation of CDDS. Summary of general dissolution on conditions for paddle (USP APP-II) and reciprocating cylinder methods (USP PP-III)was reported by Jinhe et al. (2002).

In vitro evaluation studies were conducted for chitosan-containing microparticulate system forcolon drug delivery. In this study fluorescinisothiocyanate-labelled bovine serum albumin (FITCBSA) was used as a model drug. The chitosan hydrogel beads which containing trypolyphosphte as counter ion. The protein release experiments were carried out in vitro under different conditions to simulate the pH and times likely to be encountered drug intestinal transit to the colon. Release of FITC-BSA form the chitosan beads was studied in sealed 25ml conical flasks in a Magniwhirl*constant temperature shaker bath at 370C and 60 SPM. Enzymatic degradations of chitosan by pancreatin and by porcine pancreatic lipase present in simulated intestinal fluid were studied using a viscometric procedure (Hua et al. 2002). The pharmacokinetic evaluation of guar gum based colon targeted tablets of mebendazole against an immediate release tablet was carried out in human volunteers. Six healthy volunteers participated in the study and a crossover design was followed. Inthis study, on oral administration of colon-targeted tablets mebendazole started appearance in the plasma at five hours and reached the peak plasma concentration at 9.4 ± 1.7 hrs (Tmax) whereas the immediate release tablets produced at 3.4 ± 0.9 hrs (Tmax) the results of the study indicated that the guar gum based colon targeted tablets of mebendazole did not release the drug in stomach and small intestine, but delivered the drug to the colon resulting in a slow absorption of the drug and making the drug available for local action in colon (Krishnaiah et al. 2003).

The colon-specific matrix tablets of mesalazine with guar gum were evaluated invtro and invivo studies. In vitro dissolution studies using a flow-through cell apparatus with and without galactomannase enzyme. In-vivo studies conducted in healthy humans using X-ray imaging technique to monitor the tablets throughout the GI system in which barium sulphate as a marker (Fatmanual et al.2004). Tablets consisting of flubiprofen microsponges were developed for colon specific delivery and dissolution test was conducted in USP rotating paddle apparatus at 37±0.50C and 50 RPM. Initial drug release studies were done in 750 ml of 0.1 N HCl for two hours. Then 250 ml of 0.2 M trisodiumphosphate solution was added to the dissolution media and the pH was adjusted to 6.8 with 2N HCl for eight hours. Samples were withdrawn after regulated time intervals and analyzed spectrophotometrically at 248 nm. For the study of enzymatic degradation same method was sed, butat eighth hour pectinexultra SP-L was added to the dissolution media to simulate the enzymatic action to the colonic bacteria (Mine et al. 2006).

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 or protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site specific release to treat colonic cancer, amoebiasis, and helminthiasisetc, 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 release of drug load in colon region is depended on pH of GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule. The preferred CDDS is that should release maximum drug load in colon region. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially activated system and others. Different polymers are used to prepare CDDS by various approaches and are evaluated for their efficiency and safety.

Table 1: Properties of Gastro Intestinal Tract

Region of GIT	Property	Measured value
Total GIT	Surface area	2-10^{6}cm^2
Small intestine • Duodenum • Jejunum • Ileum	Length	20-30 cm 150-250 cm 200-350 cm
Large intestine • Cecum • Ascending colon • Descending colon • Transverse colon • Sigmoid colon • Rectum • Anal canal	Length	6-7 cm 20 cm 45cm 30cm 40cm 12 cm 3 cm
Small intestine Large intestine	Internal Diameter	3-4 cm 6 cm
Stomach Duodenum Jejunum Illeum Colon Rectum	pH	1-3.5 5-7 6-7 7 5.5-7 7
Colon • Ascending • Transeverse • Decending	Redox potential	415 400 380

Table 2: Materials used in Formulation of CDDS

Prodrug conjugates System	pH-Sensitive Polymers	Materials used In Time-Dependent	Microbial degradable polymers
Azo bond conjugates	Eudragit L-100Hydroxy Propyl	Chitosan	Methyl Cellulose
Amino acid (Polypeptide)	Eudragit S-10	Pectins	Hydroxy Ethyl
conjugates	Eudragit L-30 D	Cellulose	Guar Gum
Glycoside conjugates	Eudragit L-100-55	Ethyl Cellulose	Dextrans
Glucuronide conjugates and Sulphate conjugates	Eudragit F S 30 D	Microcrystalline cellulose	Insulin Latulose
Polymeric conjugates Phthalate	Poly Vinyl Acetate Hydroxy Propyl Methyl Cellulose	Amylose	Acetate Succinate
Cyclodextrin Conjugates	Hydroxy Propyl Methyl Cellulose Phthalate 50	Lactose/ Behinic acid	Cyclodextrins
Dextran conjugates	Hydroxy Propyl Methyl Cellulose Phthalate 55	Alginates	Dextran

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