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Review Article

COLON TARGETED DRUG DELIVERY SYSTEM-AN APPROACH FOR TREATING COLONIC AILMENTS

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ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for instance, allow topical treatment of inflammatory bowel disease. Treatment could be made more efficient if it was possible for drugs to be targeted like a shot to the colon. Systemic side effects could also be reduced. Colon specific systems might also allow oral administration of peptide and protein drugs, which are normally inactivated in the upper portions of the gastrointestinal tract. Primary approaches for CDDS (Colon Specific Drug Delivery), which includes prodrugs, pH and time dependent systems and microbial triggered drug delivery system achieved limited success and accepting limitations. Newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDCS), CODESTM and osmotic controlled drug delivery are unparalleled in terms of achieving *in vivo* site specificity and feasibility of fabrication operation. This review also focuses on evaluations of CDDS in general.

Keywords: Colon specific drug delivery, Prodrugs, CODESTM, PCDCS.

INTRODUCTION

Targeted drug delivery to the colon is extremely desirable for local treatment of inflammatory bowel diseases such as ulcerative colitis, Crohn's disease etc., amoebiasis, colonic cancer, as well as for the systemic delivery of protein and peptide drugs [1]. The colon specific drug delivery system (CDDS) should be capable of protecting the drug enroute to colon (i.e. Drug release and absorption should not take place in the abdomen and the small intestine and bioactive agent should not be degraded) [2]. and to allow drug release only in the colon. The colon is believed to be a suitable site for absorption of peptides and proteinous drugs for following reasons: (i) Less diversity and strength of digestive enzymes. (ii) The proteolytic activity of colon mucosa is comparatively very less than that of small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum. The release of drug molecules in the ileum or colon leads to greater systemic bioavailability. (iii) The colon has a long residence time (up to 5 d) [3]. and is extremely responsive towards absorption enhancers [4]. Oral route is the most convenient and preferred route [5]. but other routes for CDDS may also be employed. Rectal administration offers the shortest route for targeting drugs to the colon. However, arriving at the proximal portion of the colon via rectal administration is difficult. Rectal administration can also be uncomfortable for the patient and the compliance may be less than optimal [6]. Drug preparations for intrarectal administration is supplied as the solution, foam and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine [7]. Corticosteroids such as hydrocortisone and Prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are ingested from the large bowel, it is broadly conceived that their efficacy is due mainly to topical application. The absorption of drug reaching the colon will depend on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been registered to retain mainly in the rectum and sigmoid colon. Enema solutions have a great spreading capacity. Because of the high water absorption capability of the colon, the colonic contents are considerably viscous and their blending is not efficient. Hence availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora (a population of up to 1010 bacteria per gram of colonic contents). The reactions carried out by these gut flora are like azoreduction, enzymatic cleavage etc. These metabolic processes may be responsible for the metabolism of many drugs and may likewise be applied to the colon-targeted delivery of peptide based macromolecules like insulin by oral administration.

The important bacterias present in the colon such as *Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Lactobacillus, Clostridium* secrete a wide range of reductive and hydrolytic enzymes such as β-glucuronidase, β-xylosidase, β-galactosidase, α-arabinosidase, nitroreductase, azoreductase, deaminase and urea hydroxylase. These enzymes are responsible for degradation of di, tri and polysaccharides [8, 9].

Need of colon targeted drug delivery [10].

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

Advantages of CDDS

Chronic Colitis e. g. ulcerative colitis and crohn's disease are currently treated with glucocorticoids and other anti-inflammatory agents. Administration of glucocorticoids e. g. Dexamethasone and methyl prednisolone by the oral and i. v. routes produces systemic side effects including adenosuppression, immunosuppression, Cushinoid symptoms and bone resorption. So the selective delivery of drug for colon could lower the required dose and thus reduce the systemic side effects [11]. The system delivers the advantage of

more effective therapy at a reduced dosage along with reduced undesirable side effects associated with high dosages [12].

Standards for selection of drug for CDDS

Drug candidate

Drugs which shows poor absorption from the stomach or bowel, including peptides are most suitable for CDDS. The drugs used in the treatment of inflammatory bowel diseases (IBD), ulcerative colitis, diarrhea and colon cancer are ideal prospects for colonic delivery [13].

Drug carrier

The selection of the carrier for the particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen influences the carrier choice. Moreover, the choice of drug carrier depends on the working groups of the drug molecules [14]. For example, aniline or Nitro groups on a drug may be used to connect it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties as well as efficacy of the dosage form [15].

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

Approaches used for site-specific drug delivery are:

[A]-Primary approaches for CDDS [13].

a) pH sensitive polymer coated drug delivery to colon

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

c) Microbially triggered drug delivery to the colon

(i) Prodrug approach for drug delivery to the colon

(ii) Azo-polymeric approach for drug delivery to the colon

(iii) Polysaccharide based approach for drug delivery to the colon

[B]-Newly developed approaches for CDDS [11].

- Pressure controlled drug delivery system (PCDCS)
- CODESTM (A Novel colon targeted delivery system)
- Osmotic controlled drug delivery to colon (OROS-CT)
- Pulsatile drug delivery system
- Hydrogels
- Microspheres
- Nanoparticles
- Self-microemulsifying drug delivery system
- Multiparticulate beads
- Liposomes in CDDS
- Bioadhessive systems

[A] Primary approaches for CDDS

pH sensitive polymer coated drug delivery to colon

In the stomach, pH ranges between 1 and 2 during fasting but increases after consuming food [16]. The pH is arround 6.5 in the proximal small intestine and of about 7.5 in the distal small intestine [14]. From the ileum to the colon, pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers [12]. The pH in the transverse colon is found to be 6.6 as well as in the descending colon is 7.0. Role of pH-dependent polymers are based on these differences in pH levels. The polymers described as pH-dependent on colon specific drug delivery are insoluble at low pH levels, but become increasingly soluble as the pH goes up. Although a pH-dependent polymer can protect a formulation in the stomach and proximal small intestine, it may goes to dissolve even in the lower small intestine and the situation-specificity of formulations can be measureable [15]. The decline in pH from the remainder of the small bowel to the colon can also result in problems such as longer lag times at the ileo-cecal junction or rapid transportation system through the ascending colon can also result in poor site-specificity of enteric-coated single-unit formulations [14].

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

Time controlled release system (TCRS) such as prolonged or delayed release dosage forms are also very bright. Yet due to the potentially large variation of gastric emptying time of dosageforms in man [16]., the colonic arrival time of dosage forms can not accurately predicted, resulting in poor clinical availability [17]. Disadvantages of this system are-(i) Gastric emptying time varies markedly between subjects or in a manner depending on the character and quantity of food intake. (ii) Gastrointestinal movement, especially peristalsis or contraction in the stomach would results in a change in gastrointestinal transit time of the drug [13]. (iii) Accelerated transit through different areas of the colon has been noticed in patients with the inflammatory bowel disesases (IBD), [18]. the carcinoid syndrome and diarrhea and the ulcerative colitis [19]. Therefore time dependent systems are not ideal to deliver drugs to colon, especifically for the treatment of colonic diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon [17]. The time-release function (or timer function) should operate more efficiently in the small intestine as compared to the stomach. In the small intestine drug carrier will be given up to the target position and drug release will start at a predetermined time period after gastric emptying. On the other hand, in the stomach, the drug release should be inhibited by a pH sensing function (acid resistant) in the dosage form, which would cut down variation in gastric residence time [13].

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

ETP tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function) [20]. Tablet does not relese the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer dissolves rapidly and the intestinal fluid begins to slowly gnaw at the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time on that point. The duration of lag phase can be controlled either by the weight or adjustment of the polymer (HPC) layer [21].

Microbially triggered drug delivery to the colon

The microflora of the colon is in the range of 1011-1012 CFU/ml [18]. It is mainly consisting of anaerobic bacterias, such as Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e. g. di, tri and polysaccharides etc [20]. For this fermentation, the microflora produces a huge number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase deaminase, and urea dehydroxylase [16]. Because of the compartment of the biodegradable enzymes present in the colon, the usage of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches [15]. These polymer shields the drug from the environments of the stomach and small intestine and are able to rescue the drug to the colon. On turning over the colon, they undergo assimilation by micro-organism or degradation by enzymes or breakdown of the polymer backbone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical force. They are then unable to halt the drug entity any longer [21].

Prodrug approach for drug delivery to colon

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in-vivo to release the active components. For colonic delivery the prodrugs are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, thereby freeing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes [22]. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been organized where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose etc. Limitations of prodrug approach is that it is not very versatile approach as its expression depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities and require a great deal of evaluation before being employed as bearers [23].

Azo-polymeric prodrugs

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are employed for this function. Subsynthetic polymers have been utilized to form polymeric prodrug with a linkage between the polymer and drug moiety [23, 24]. These have been evaluated for CDDS. Various azo polymers have also been evaluated as coating materials over drug cores. They have been set up to be similarly susceptible to cleavage by the azoreducatase in the large intestine. Coating of peptide capsules with polymers cross linked with azoaromatic group has been found to protect drugs from digestion in the stomach and small intestine. In the colon the azo bonds are broken by azoreductase and the drug is going to be released [25].

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 bowel. In one case such a glycoside reaches the colon, it can be cleared by bacterial glycosidases, releasing the free drug to be assimilated by the colonic mucosa. The major glycosidases identified in human expressions are: 1) D-galactosidase, 2) D-glucosidase, 3) L-arabinofuranosidase, 4) D-xylopyranosidase Due to the bulky and hydrophilic nature of these glycosides, they do not get through the biological membrane upon ingestion [26].

Glucuronide conjugates

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower GIT, however, secrete glucuronidase and can deglucuronidate a variety of drugs in the bowel. Since the deglucuronidation process results in the passing of active drug and enables its re-absorption, Glucuronide prodrugs would be required to be superior for colon targeted drug delivery [27, 28].

Cyclodextrin conjugates

Cyclodextrins (CyDs) are cyclic oligosaccharides consisted of six to eight glucose units through 1, 4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these particles are relatively lipophilic and the exterior is relatively hydrophilic. They tend to form inclusion complexes with various drug molecules. Nevertheless, they are fermented by colonic micro flora into small saccharides and thus absorbed in the colonic area [28, 29]. Because of their bio adaptability and multi functional characteristics, kids are capable of alleviating the undesirable attributes of drug particles in various routes of administration through the formation of inclusion complexes. In an oral drug delivery system, the hydrophilic and unusable CyDs can serve as potent drug carriers in the immediate release and delayed release formulations respectively, while hydrophobic kids can check the release rate of water-soluble drugs. Since, kids are able to continue the use of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable creation in the improvement of drug formulation. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with kids can be a versatile means of constructing a novel division of colon targeting prodrugs. The 5-ASA concentration in the rat's stomach and small intestine after the oral administration of CyDs-5-ASA conjugate was much more depressed than that after the oral administration of 5-ASA alone. The lowest concentration was attributable to the enactment of the conjugate through the abdomen and small intestine without significant degradation or absorption, followed by the debasement of the conjugate site-specific in the cecum and colon. The oral administration of CyD-5-ASA resulted in lower plasma and urine concentration of 5-ASA than that of 5-ASA alone [30].

Polysaccharide based delivery systems

The role of naturally occurring polysaccharides is attracting tons of care for drug targeting to the colon. These polymers are inexpensive and are available in a verity of a structure with varied properties [31]. They can be modified chemically and biochemically, and are highly stable. They are safe, nontoxic, hydrophilic, gel forming and biodegradable. These include naturally occurring polysaccharides from plants (guar gum, inulin), animals (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran). These are broken down by the colonic microflora to simple mono saccharides [32]. So these fall into the category of "generally regarded as safe" (GRAS).

Table 1: Showing Polysaccrides studied for colon specific drug delivery with their dosages forms along with their results summary.

Polysaccharides already studided	API used	Developed dosage forms	Types of model used (*In vitro/In vivo*)	Functionalization of the system
Chitosan	5-(6) carboxy fluorescein (CF)	Enteric-coated Chitosan capsules	*In vitro*	Little release of CF in upper GIT conditions and 100% drug release in 33% cecal contents within 4 h of dissolution [33].
Amidated pectin	Paracetamol	Matrix tablets	*In vitro*	These matrices were not suitable for drug delivery to colon [34].
Chondroitin sulphate	Indomethacin	Matrix tablet	*In vitro*	Drug release increases in presence of rat cecal content. Also it was observed that as crosslinking increased, drug release decreased [35].

[B] Newly developed approaches for CDDS

Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are taken on in the colon than in the small intestine. Takaya *et al.* (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following the disintegration of a water-insoluble polymer capsule as a outcome of force per unit area in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation [36]. The system also appeared to depend on capsule size and compactness. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has

therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human [37].

Newly developed colon targeted delivery system (CODESTM)

It is an unique CDDS technology which was contrived to avoid the constitutional problems associated with pH or time dependent schemes. CODESTM is combined approach of pH dependent and microbially triggered CDDS. It has been produced by using an unique mechanism involving lactulose, which works as a trigger for site specific drug release in the colon. The system comprises of a normal tablet core containing lactulose, which is coated over with Eudragit E (the acid soluble material) and further coated with Eudragit L(the enteric coating polymer). The intension behind the technology is that CODES™ remains intact in the stomach due to the enteric protection, but the enteric and barrier coating will dissolve in the small intestine, where the pH is above 6. Because Eudragit® E starts to dissolve at pH-5, the inner Eudragit® E coating is only slightly permeable and swellable in small intestine. Upon entry into the colon, the polysaccharide inside the core tablet will dissolve and diffuse through the coating. The bacteria will enzymatically degrade the polysaccharide into organic acid. This lowers the pH surrounding the system sufficient to effect thedissolution of the acid-soluble coating and subsequent drug release [38].

Osmotically controlled drug delivery (ORDS-CT)

The delivery system OROS-CT from Alza Corporation is much more useful in targeting the drug molecules to the colonic region for their local therapeutic response as well as systemic effect [22]. The above system can be either a single osmotic unit or can be comprising of a maximum 5-6 push-pull units, each having the diameter of 4 mm and encapsulated in a hard gelatin capsule. Each bilayer pull push unit contains a drug layer and an osmotic push layer, both of them are surrounded with a semi permeable membrane. An opening is drilled on the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule having the pull push units gets dissolved. Each pull push unit is prevented from uptaking of water in the acidic aqueous environment/medium of the stomach due to the presence of drug-impermeable enteric coating, hence no drug release had been observed. As the unit travels into the small intestine, the coating gets dissolved in the higher pH environment (pH>7), water starts entering into the unit, which leads to swelling of the osmotic push compartment and concomitantly develops a valuable gel in the drug compartment. Swelling of the osmotic push compartment helps in forcing the drug gel segment out of the orifice at a rate significantly controlled by the pace of water entered through the semi permeable membrane. In order to treat ulcerative colitis, each pull push unit is designed with a 3-4 hour post gastric delay for preventing the delivery of drugs in the small intestine. Drug release begins when the unit arrives at the colon. OROS-CT units can sustain a constant discharge rate for up to 24 h in the colon. Evaluation of colon specific dissolution system. Several *in vitro*/*in vivo* evaluation techniques has been developed and offered to test the operation and stability of CDDS [39].

Pulsatile drug delivery system

Pulsincap® system

Single-unit systems are mostly developed in a capsule form. The interim time is kept in line by a plug, which gets pushed away by swelling or erosion and the drug is expelled as a "Pulse" from the insoluble capsule shell. One such system comprises of a drug reservoir entrapped inside a water insoluble capsule. The drug molecules were sealed by a swellable hydrogel plug present in the capsule body. As soon as the capsule comes in contact with the dissolution fluid, it starts swelling and after a certain lag time, the plug pushes itself outside the capsule and resulting in the release of the drug. Polymers used for the hydrogel plug are different viscosity grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate, polyvinyl acetate and poly ethylene oxide. The length of the plug and its level of introduction into the capsule controls the lag time [28, 40].

The port® system

The Port® System comprises of a gelatin capsule coated with a semipermeable membrane (e. g., Cellulose acetate) containing an insoluble plug (e. g., lipidic) along with an osmotically active agents with the drug formulation. By coming in contact with the aqueous medium, water diffuses through the semi permeable membrane, thus resulting in an increased inner pressure which helps in ejecting the plug after a certain lag time. The interim time is controlled by coating thickness [28]. This system avoids the second time dosing [40]. The coming of the pulsatile drug delivery system is based on the principle of delaying of drug release until the system transmits from mouth to colon. The transit time of the small intestine is about 3-4 h so lag-time of 5 h is usually believed, which is comparatively invariant.

Hydrogels

The presence of pH-sensitive monomers and also cross-linking agents in the hydrogel structure produce colon specificity to the expression. As these hydrogel travels through the GIT, their swelling capacity increases as the pH increases, being highest around pH 7.4. The drug entrapped in the hydrogel is put out by the progressive degradation of hydrogen network via the cleavage of the cross-ties. They can be obtained by cross-linking polymerization of N-substituted (meth) acryl amides, N-tert-butylacrylamide and acrylic acid with 4,4'-di (methacryloylamino) azobenzene, 4,4'-di (N-methacryloyl-6-aminohexanoylamino) or 3,3',5,5'-tetrabromo-4,4, 4',4'-tetrakis (methacryloylamino) azobenzene as the cross linking agents. The hydrogels were also prepared by polymer–polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH2 groups. The degradation rate of hydrogel was associated with the equilibrium degree of swelling and being inversely proportional to the cross linking density [40, 41].

Microspheres

Cross-linked guar gum microspheres containing methotrexate were developed and characterized for their local release in the colon for efficient treatment of colorectal cancer. In this method gluteraldehyde was used as a cross-linking agent and guar gum microspheres were developed by emulsification method. From the results of *in vitro* and *in vivo* studies, the methotrexate loaded cross-linked guar gum microspheres delivered most of the loaded drugs (79%) to the colon, where as the normal drug suspensions could able to deliver only 23% of their total dose to the target tissue. Colon specific microspheres of 5-fluorouracil were developed and valued for the treatment of colon cancer. In this method core microspheres of alginate were prepared by modified emulsification method in liquid paraffin by using calcium chloride as a cross-linking agent. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the gastric as well as small intestine area. The outcomes indicated that this method had great potential in the delivery of 5-fluorouracil to the colon region [26].

Nanoparticles

Nanoparticles are expected to become drug carriers for achieving oral peptide delivery. Because of polymeric nanoparticles have the advantages of protecting the protein and peptide drugs from a chemical and enzymatic degradation in the GIT, so increasing their stability and absorption across the intestinal epithelium as well as holding the drug release. A routine of techniques such as polymerization, nanoprecipitation, inverse microemulsion can be utilized to prepare polymeric nanoparticles, however, most of these methods require the usage of organic solvents, heat and vigorous agitation which may be harmful to the peptide and protein drugs. More recently the ionic gelation technique has been used as the most favorable [40].

Self-microemulsifying drug delivery system

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

diagrams were generated in order to get the most effective self-emulsification region, and the formulation of curcumin-loaded SMEDDS was optimized by a simplex lattice experiment design. And so, three lipophilic foliate derivatives (foliate-polyethylene glycol-distearoylphosphatidylethanolamine, flat-polyethylene glycol-cholesterol hemisuccinate, and foliate-polyethylene glycol-cholesterol) used as a surfactant were incorporated to curcumin-loaded SMEDDS formulations. The optimization of the formulations of FSMEDDS were carried out through an in situ colon perfusion method, applied on rats. Curcumin-loaded FSMEDDS was then filled into colon-targeted capsules and the *in vitro* release was investigated. The optimal formulation of FSMEDDS obtained with the established in situ colon perfusion method in rats was comprised of 57.5% Cremophor(®) EL, 32.5% Transcutol(®) HP, 10% Capryol™ 90, and a small amount of folate-polyethylene glycol-cholesteryl hemisuccinate (the weight ratio of folate materials to Cremophor EL was 1:100). The results obtained from the *in vitro* release study indicated that, the formulation of curcumin could reach the colon efficiently and release the drug succesfully. Cellular uptake studies analyzed by fluorescence microscopy and flow cytometry indicated that the FSMEDDS formulation could efficiently bind to the folate receptors on the surface of positive folate receptor cell lines. In addition, FSMEDDS showed greater cytotoxicity than SMEDDS in the above two cells. FSMEDDS-filled colon-targeted capsules are a possible carrier for colon delivery of curcumin [42].

Multiparticulate beads

In the ionotropic gelation method, polysaccharides (alginate, gallant and pectin) are dissolved in water or in weak acidic medium (chitosan). These solutions are then added drop wise under constant stirring to the solutions containing other counter ions. Due to the complexation between oppositely charged species, polysaccharides undergo ionic gelation and precipitate to form spherical particles. The beads are removed by filtration, rinsed with distilled water and dried. The counter ions used for ionotropic gelation can be divided into two major categories: Low molecular weight counter ions e. g. $CaCl_2$, $BaCl_2$, $MgCl_2$, $CuCl_2$, $ZnCl_2$, $CoCl_2$, pyrophosphate, tripolyphosphate, tetrapolyphosphate, octapolyphosphate, hexametaphosphate and [Fe (CN)6].-4/$[Fe(CN)_6]$.; High molecular weight ions *e. g.* octyl sulphate, lauryl sulphate, hexadecyl sulphate, cetylstearyl sulphate [43].

Liposomes in CDDS

Liposomes are the bilayered closed vesicular structures comprises of hydrated phospholipids. Liposomes have the capacity to entrap compounds of different solubilities due to their alternating hydrophilic and hydrophobic structure. How ever the extensive modification or tailoring of basic liposomal structure of hydrated phospholipid bilayer is associated with the physicochemical makeup of the vesicle. This versatility of liposomes are very much useful in various applications such as in radiology, cosmetology and Vaccinology. Liposomes with a size range from 25 millimeter to several micrometers are usually propagated in an aqueous medium. Several nomenclatures are there for defining liposome subtypes depending upon their method of vesicle preparation or on structural parameters. Liposomes are also can be distinguished according to their size and number of lamellae such as large unilamellar vesicles (LUV), Small unilamellar vesicles (SUV), and large multilamellar vesicles or multivesicular vesicles. SUVs with low particle sizes within nm range are of interest as liposomal nanocarriers for drug and antigen delivery [44].

Bioadhesive systems

Some drugs requires high local concentration in the large intestine through oral administration for their optimal therapeutic effects. Bioadhesion is a procedure by which a dosage form remains in contact with a special organ for an augmented period of fourth dimension. This longer residence time of the drug results an increased local concentration. In case of poorly absorbable drugs it helps in improveing absorption characteristics. This strategy is much more useful in formulating CDDS. Several polymers like polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for Bioadhesive systems. However, Bioadhesion has been believed to be showing a better performance and increasing the mean residence time of colonic drug delivery systems [45].

Table 2: List of marketed preparations available against colonic ailments

Brand name	API	Dosage form	Application	Manufacturing company
Oxitan	Oxaliplatin	100 mg and 50 mg Injection	Colon cancer	Fresenius Kabi, India
Camptosar®	Irinotecan	20 mg/ml Injection	Colon cancer	Pfizer ltd.
Erbitux™	Cetuximab	2 mg/ml Injection	Colon cancer	Bristol-Myers Squibb Company
Avastin™	Bevacizumab	25 mg/ml injection	Colon cancer	Genentech ltd
Xeloda®	Capecitabine	500 mg tablets	Colon cancer	Genentech ltd
Salazopyrin	Sulfasalazine	500 mg tablets	Crohns disease	Pfizer Limited
Azulfidine	Sulfasalazine	500 mg tablets	Ulcerative Colitis	Pfizer Limited
Dipentum	Olsalazine	250 mg Capsules 500 mg tablets	Crohns disease	UCB ltd
Pentasa	Mesalazine	250 mg tablets	Crohns disease	Ferring Pharmaceuticals
Salofalk	Mesalazine	250 mg tablets	Crohns disease	Dr Falk Pharma UK Ltd

Evaluation parameters of CDDS

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

a) *In vitro* dissolution test

Dissolution of controlled-release formulations used for colonspecific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces.[46]. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colonspecific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied.[47]. 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 simulatethe ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4 [48].

b) *In vitro* enzymatic tests

Incubate carrier drug system in fermenter containing suitable medium for bacteria (strectococcus faccium and B. Ovatus). The amount of drug released at different time intervals are determined. Drug release study is done in buffer medium containing enzymes (ezypectinase, dextranase), or at or guinea pig or rabbit cecal

contents. The amount of drug released in a particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

c) *In vivo* evaluation

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human.[49]. 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 bascularizes within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.

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

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

ii) γ–Scintigraphy

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

γ-Scintigraphy is an imaging modality, which enables the *in vivo* performance of drug delivery systems to be visualized under normal physiological conditions in a non-invasive manner. Since first employed to investigate the functionality of tablets and capsules *in vivo* more than two decades ago [50, 51]. γ-scintigraphy has become an established technique and extensively used to monitor the performance of novel drug delivery systems within human GI tract. The underlying principles of γ-scintigraphy and its applications in pharmaceutical research and development are available in the literature [52-54]. Through γ-scintigraphy imaging, the following information regarding the performance of a colon-specific delivery system within human GI tract can be obtained: the location as a function of time, the time and location of both initial and complete system disintegration, the extent of dispersion, the colon arrival time, stomach residence and small intestine transit times.

Limitations and challenges in colon targeted drug delivery

- The resident micro flora affects the colonic efficiency by metabolic degradation of the drug. Relative tightness of the tight junctions in the colon as well as ower surface area can restrict the drug transport across the mucosa and into the systemic circulation.

- As a site for the drug delivery, the colon offers a near neutral pH, a long transit time, reduced digestive enzymatic activity and increased responsiveness to the absorption enhancers; however, targeting of drugs to the colon is really complicated. Due to its position in the distal portion of the nutrient canal, the colon is difficult to access

- In summation, the stability of drug must be considered into consideration while designing the delivery organization. The drug may potentially bind in a nonspecific way to dietary residues, mucus and intestinal secretions or fecal matter [55].

Opportunities in colon targeted drug delivery

- Drugs targeting to the colonic area is not only associated with the treatment of colonic ailments locally, but also delivering drugs such as proteins and peptides for their systemic effects which are degraded and/or poorly taken up in the stomach and small bowel.

- This is likewise a suitable site for the treating diseases associated with circadian rhythms such as angina, asthma and arthritis. The urgent demand for legal transfer of drugs to the colon that reported to be occupied in the colon, such as steroids, which would increase efficiency and shortens the effective dosage.

- The colonic disorders like inflammatory bowel disease, Crohn's disease, irritable bowel syndrome (IBS) as well as colon cancers etc, it is much more needful to achieve a high absorption of the active agent by colon-specific rescue.

- The evolution of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very depressed (due to instability in the GI tract) [41].

CONCLUSION

Now a days colon is becoming the best target site for drug delivery in the GI tract. CDDS is providing much more therapeutic advantages for both systemic as well as local theraphy. For colon targeted drug delivery four primary approaches were proposed for CDDS like prodrugs, pH, time dependent systems and microbially triggered drug delivery system. Of these first three approaches are not ideal for CDDS. New approaches developed for CDDS are more specific. Colon specificity is more probable to be achieved with systems by using materials from natural sources and degraded by colonic bacterial enzymes. It was also concluded that more than one testing method is essential to determine the drug release and justify system objective for conducting *in vitro* evaluation of a colon-specific drug delivery system. Depending upon the sophistication of colon-specific drug delivery systems and the uncertainty of current dissolution methods in establishing possible *in vitro*/*in vivo* correlation, challenges are there for pharmaceutical scientists to train and validate a dissolution method that incorporates the physiological features of the colon and even can be used routinely in an industrial setting for the evaluation of CDDS.

CONFLICT OF INTERESTS

The authors have declared no conflict of interest

REFERENCES

1. Adkin DA, Davis SS, Sparrow RA, Wilding IR. Colonic transit of different sized tablets in healthy subjects. J Controlled Release 1993;23:147-56.
2. Ahrabi SF, Madseh G, Dyrstad K, Sande SA, Graffner C. Development of pectin matrix tablets for colonic delivery of model drug ropivacanie. Eur J Pharm Sci 2000;10:43-52.
3. Ahmed S. Effect of simulated gastrointestinal condition on drug release from pectin/ethyl cellulose as film coating for drug delivery to the colon. Drug Dev Ind Pharm 2005;31:465-70.
4. Aiedeh K, Taha MO. Synthesis of chitosan succinate and chitosan phthalate and their evaluation as suggested matrices in orally administered colon specific drug delivery system. Arch Pharmacol Res 1999;332:103-7.
5. Akala EO, Elekwachi O, Chase V, Johnson H, Marjorie L, Scott K. Organic redox initiated polymerization process for the fabrication of hydrogel for colon specific drug delivery. Drug Dev Ind Pharm 2003;29:375-86.
6. Ashord M, Fell JT, Attwood D, Sharma H, Woodhead P. An evaluation of pectin as a carrier for drug targeting to the colon. J Controlled Release 1993a;26:213-20.
7. Asford M, Fell JT, Attwood D, Sharma H, Woodhead PJ. Studies on pectin formulations for colonic drug delivery. J Controlled Release 1994;30:225-32.
8. Sinha VR, Rachna K. Coating polymers for colon specific drug delivery: A comparative *in vitro* evaluation. Acta Pharm 2003;53:41-7.
9. Cavalcanti OA, Mooter GV, Soares IC, Kinget R. Polysaccharides as excipients for colon-specific coatings, permeability and swelling properties of casted films. Drug Dev Ind Pharm 2002;28:157-64.

10. Mehta TJ. Need of colon specific drug delivery system: review on primary and novel approaches. Int J Res Dev 2011;3:134-53.
11. Hita V, Singh R, Jain SK. Colonic targeting of metronidazole using azo aromatic polymers, development and characterization. Drug Delivery 1997;4:19-22.
12. Basit A, Bloor J. Prespectives on colonic drug delivery. Business briefing: Pharmtech; 2003. p. 185-90.
13. Bussemer T, Bodmeier IRO. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Syst 2003;18:433-58.
14. Chan RP, Pope DJ, Gilbett AP, Sneta PJ, Baron JH, Bennardjones JF. Studies of two novel sulphasalazine analogs I. P. salazide and balsalazide. Dig Dis Sci 1983;28:609-716.
15. Chavan MS, Sant VP, Nagarsenker MS. Azo-containing urethane analogues for colonic drug delivery: synthesis, characterization and *in vitro* evaluation. J Pharm Pharmacol 2001;53:895-900.
16. Jung YJ, Lee JS, Kim HH, Kim YK, Han SK. Synthesis and evaluation of 5-aminosalicylicylglycine as a potential colon specific prodrug of 5-aminosalicylic acid. Arch Pharmacol Res 1998;21:174-8.
17. Vandelli MA, Leo E, Forni F, Bernabei MT. *In vitro* evaluation of a potential colonic delivery system that releases drug after a controllable lag-time. Eur J Pharm Biopharm 1996;43:148-51.
18. Cole E, Scott R, Connor A, Wilding I, Petereit HU, Schminke C, *et al*. Enteric coated HPMC capsules designed to achieve intestinal targeting. Int J Pharm 2002;231:83-95.
19. Cummings JH, Englyst HN. Fermentation in the human large intestine and available substrates. Am J Clin Nutr 1987;45:1243-55.
20. Cui N, Friend DR, Fedora RN. A budesonide prodrug accelerates of colitis in rats. Gut 1994;35:1439-46.
21. Davis SS, Hardy JG, Fara JW. Transit of pharmaceutical dosage forms through the small intestine. Gut 1986;27:886-92.
22. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988;29:1035-41.
23. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, *et al*. Chitosan capsules for colon-specific drug delivery: improvement of insulin absorption from the rat colon. J Pharm Sci 1997;86:1016-21.
24. Friend DR, Chang GW. A colon-specific drug delivery system based on drug glycosides and glycosidase of colonic bacteria. J Med Chem 1984;27:261-6.
25. Friend DR, Chang GW. Drug glycosides: potential prodrugs for colon specific drug delivery. J Med Chem 1985;28:51-7.
26. Choudhury PK, Panigrahi TK, Murthy PN, Tripathy NK, Behera S, Panigrahi R. Novel approaches and developments in colon specific drug delivery systems-a review. Web Center Pharm Sci 2012;3:1-20.
27. Philip AK, Philip B. Colon targeted drug delivery system: a review on primary and novel approaches. Oman Med J 2010;25:70-8.
28. Singh KI. Colon specific drug delivery system: review on novel approaches. Int J Pharm Sci Res 2012;3:637-47.
29. Kishore G. Development and evaluation of colon targeted tablets of praziquantel and its β-cyclodextrin complex to treat schistosomiasis. J Pharm Sci Technol 2010;2:269-75.
30. Zou MJ, Cheng G, Okamoto H, Hao XH, An F, Cui FD, *et al*. Colon-specific drug delivery systems based on Cyclodextrin prodrugs: *In vivo* evaluation of 5-aminosalicylic acid from its cyclodextrin conjugates. World J Gastroenterol 2005;11:7457.
31. Friend DR, Phillip S, Tozer TN. Colon specific drug delivery from a glucosidic prodrug in the guinea pig efficacy study. J Controlled Release 1991;15:47-54.
32. Fukui E, Miyamura N, Kobayashi M. An *in vitro* investigation of the suitability of presscoated tablets with hydroxypropylmethylcellulose acetate succinate (HPMCAS) and hydrophobicn additives in the outer shell for colon targeting. J Controlled Release 2001;70:97-107.
33. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, *et al.* Chitosan capsules for colon-specific drug delivery: improvement of insulin absorption from the rat colon. J Pharm Sci 1997;86:1016-21.
34. Wakerly Z, Fell J, Attwood D, Parkins D. Studies on amidated pectins as potential carriers in colonic drug delivery. J Pharm Pharmacol 1997;49:622-5.
35. Rubinstin A, Nakar D, Sintov A. Chondroitin sulphate: a potential biodegradable carrier for colon-specific drug delivery. Int J Pharm 1992;84:141-50.
36. Fukui E, Miyamura N, Verma K, Kobayashi M. Preparation of enteric coated time released press coated tablets and evaluation of their function by *in vitro* and *in vivo* tests for colon targeting. Int J Pharm 2000;204:7-15.
37. Gazzaniga A, Iamartino P, Maffino G, Sangalli ME. Oral delayed release system for colonic specific drug delivery. Int J Pharm 1994;108:77-83.
38. Hata T, Shimazaki Y, Kagayama A, Tamura S, Ueda S. Development of a novel drug delivery system, time-controlled explosion system (TES). Part 5 Animal pharmacodynamic and human bioavailability studies. Int J Pharm 1994;110:1-7.
39. Hay DJ, Sharma H, Irving MH. Spread of steroid containing foam after intrarectal administration. Br Med J 1979;1:1751-3.
40. Kothawade PD. Conventional and novel approaches for colon specific drug delivery: a review. J Sci Technol 2011;2:33-56.
41. Nanoparticle for colon specific drug delivery system. 3rd International conference on Nanotech and Expo, Las Vegas, USA; 2013.
42. Patel PB, Dhake AS. Multiparticulate approach: an emerging trend in colon specific drug delivery for Chronotherapy. J Pharm Sci 2011;1:59-63.
43. Onuigbo EB, Okore VC, Ngene AA, Esimone CO, Attama AA. Preliminary studies of a stearylamine-based cationic liposome. J Pharm Res 2011;10:25-9.
44. Onuigbo EB, Okore VC, Esimone CO, Ngene A, Attama AA. Preliminary evaluation of the immunoenhancement potential of newcastle disease vaccine formulated as a cationic liposome. Avian Pathol 2012; 41:355-60.
45. Goyal S, Vashist H, Gupta A, Jindal S, Goyal A. Development of alginate gel beads-entrapped liposome for colon specific drug delivery of prednisolone. Pharm Sin 2011;2:31-8.
46. Saffron M, Field JB, Pena J, Jones RH, Ohuda Y. Oral insulin in diabetic dogs. J Endocrinol 1991;131:267-78.
47. Wakerly Z, Fell J, Attwood D, Parkins D. Studies on amidated pectins as potential carriers in colonic drug delivery. J Pharm Pharmacol 1997;49:622-5.
48. Ahrabi SF, Madseh G, Dyrstad K, Sande SA, Graffner C. Development of pectin matrix tablets for colonic delivery of model drug ropivacanie. Eur J Pharm Sci 2000;10:43-52.
49. Rubinstin A, Nakar D, Sintov A. Chondroitin sulphate: a potential biodegradable carrier for colon-specific drug delivery. Int J Pharm 1992;84:141-50.
50. Alpsten M, Ekenved G, Soelvell L. A profile scanning method of studying the release properties of different types of tablets in man. Acta Pharm Suec 1976;13:107–22.
51. Casey DL, Beihn RM, Digenis GA, Shambu MB. Method for minitoring hard gelatin capsule disintegrationtimes in human using external scintigraphy. J Pharm Sci 1976;65:1412–3.
52. Digenis GA, Sandefer E. Gamma scintigraphy and neutron activation techniques in the *in vivo* assessment of orally administered dosage forms. Crit Rev Ther Drug Carrier Syst 1991;7:309–45.
53. Wilding IR, Coupe AJ, Davis SS. The role of γ-scintigraphy in oral drug delivery. Adv Drug Delivery Rev 1991;7:87–117.
54. Newman SP, Wilding IR. Imaging techniques for assessing drug delivery in man. Pharm Sci Tech Today 1999;2:269–88.
55. Patel A. Novel approaches for colon targeted drug delivery system. J Pharm Cosmetol 2011;1:85-97.