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A systematic review on colon targeted drug delivery system

Hitendra S Chaudhari*, Nishant M Patel, Amitkumar R Dhankani, Rupesh D Savale, Mayuresh P Rajurkar
Department of Pharmaceutics, PSGVPM'S College of Pharmacy, Shahada, Nandurbar, Maharashtra, India

Abstract
In the recent year colonic drug delivery has gained importance for delivery of drug for the treatment of local diseases associated with colon and systemic delivery of therapeutic peptides and proteins. Treatment could be more effective if it is possible for drug to be directly delivered to colon. In past various traditional approaches used for colon targeted delivery like prodrugs, pH dependent system, azo polymeric coating, etc. have achieved limited success. For successful colon targeted drug delivery, the drug needs to be protected from absorption and/or the environment of the upper gastrointestinal tract and then be abruptly released into the colon. Hence continuous efforts have been made on designing colon targeted drug delivery systems with improved site specificity and versatile drug release kinetics to fulfill different therapeutic needs. As the year passes few new systems have been developed for colon targeted drug delivery such as pressure dependent systems, pectin and galactomannan coating, CODES^{TM} technology, etc. which are reported to have better in-vivo site specificity and design rationale than the earlier approaches. An attempt has been made in this review article to discuss in brief about introduction, need, advantages, disadvantages, various approaches and evaluation of colon targeted drug delivery system.

Keywords: colon, approaches, advantages, CODES^{TM} technology, etc

Introduction
The oral route is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach field as intestinal fluid and absorb from these regions of gastrointestinal tract (GIT). Common drawback in conditions when localized delivery of drugs into the colon is required is drugs needs to be protected from the hostile environment of upper GIT. For successful delivery of drugs to the colon via the GIT requires the protection of a drug from being released in stomach and small intestine [1].
The colon specific drug delivery system (CDDS) is capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon [2].

Need of Colon Targeted Drug Delivery System
To assure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's Disease & also a number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar or susceptible to enzymatic & chemical degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides [3].

Advantages of Colon Targeted Drug Delivery System [4, 5, 6]
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Avoid first pass metabolism.
- Extended day-time or night-time activity.
- Improve patient compliance.
- Targeted drug delivery system.
- Utilization of drug is more and lesser amount of dose is required comparatively. Hence lower cost of expensive drugs.
- Side effects can be reduced.

Limitations of Colon Targeted Drug Delivery System [7]
- The resident microflora could also affect colonic performance via metabolic degradation of the drug. Incomplete release of drug
- Multiple manufacturing steps
- Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- No standardized evaluation technique is available for evaluation of CTDDS

Criteria for Selection of Drug for Colon Targeted Drug Delivery System
Drug candidate
Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used in treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery [8].

Drug carrier
The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the

disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule [9]. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems [10].

Approaches for Colon Targeted Drug Delivery System

A variety of approaches have been used to develop an system for the purpose of achieving colonic targeting which are categorized into two parts i.e. Traditional approaches and New approaches.

Traditional approaches

pH Dependent Systems

Coating with pH Sensitive Polymer

There is pH gradient in the gastrointestinal tract with values ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. This pH differential between stomach and small intestine has historically been exploited to deliver drug to small intestine by way of pH sensitive enteric coatings. These polymer coatings are unaffected by the acidic conditions of the stomach but ionize and dissolve above a certain threshold pH found in the small intestine. Thus, it is also possible to apply this concept to deliver drugs to the ileum/ colon by use of enteric polymers with a relatively high threshold pH for dissolution. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S, Eudragit L. The critical factor that influences the performance of these polymers is the pH at which dissolution occurs [11].

pH Sensitive Hydrogels

pH sensitive hydrogels, are three-dimensional networks composed of a polymer backbone, water and crosslinking agents, can swell considerably in aqueous medium without dissolution in response to changes in external pH. The pH sensitive hydrogels shrinks at low pH and swells at higher pH. The drug loaded hydrogels shrinks at low pH of stomach and do not allow the drug release but when systems moves toward higher pH of colon hydrogels starts swelling allowing drug released. Such drug delivery system could allow local treatment of a variety of colonic diseases such as Crohn's disease or ulcerative colitis. CTDDS based on pH sensitive hydrogels have been reported for bovine serum albumin acetaminophen [12, 13].

Covalent Linkage of Drug with Carrier

Formation of prodrugs

Prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body. Covalent linkage is formed between drug and carrier, which upon oral administration reaches colon without being absorbed from upper part of GIT. In the colon drug release is triggered by high activity of certain enzymes in comparison to stomach and small intestine [14].

Glucuronide conjugate

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower gastrointestinal tract secrete glucuronidase that glucouronidate a variety of drugs in the intestine. Since the glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery [15, 16].

Cyclodextrin conjugates

The hydrophilic and ionisable Cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic Cyclodextrins can retard the release rate of water. 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 Cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs. Ibuprofen prodrugs of α-, β-and γ-Cyclodextrins were investigated. Methotrexate prodrugs of α- and γ-Cyclodextrins were also synthesized and result established the primary aim of masking the ulcerogenic potential of free drug, by using 12-fold dose of the normal dose of methotrexate and equivalent doses of the esters [17, 18, 19].

Amino acid conjugation

Due to the hydrophilic nature of polar groups like NH2 and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid [20].

Azo Polymeric Prodrugs/ Azo Polymeric Coating

Some synthetic polymers have been reported to form polymeric prodrug with azo-linkage between the polymer and drug moiety. These have been evaluated for colon targeted drug delivery. Brown *et al.*, 1983 reported a prodrug consisting of a non-absorbable sulphanilamido ethylene polymer linked to 5-ASA was found to be more effective than sulphasalazine in reducing inflammation in guinea pig. [21]

Various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreductase in the large bowel. Coatings of peptide capsules with polymers cross-linked with azo aromatic group have been found to protect drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced and the drug is released [22].

New Approaches

Pressure Dependent Systems

Gastrointestinal pressure has also been utilized to trigger drug release in the distal gut. This pressure, which is generated via muscular contractions of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the gastrointestinal tract, with the colon considered to have a higher luminal pressure due to the processes that occur during stool formation. Systems have therefore been developed to resist the pressures of the upper gastrointestinal tract but rupture in response to the raised

pressure of the colon. It was reported that in healthy subject colonic pressure could be as high as almost 110 mmHg for duration of 14 Sec [23].

Capsule shells fabricated from the water-insoluble polymer ethyl cellulose have been used for this purpose. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall. In-vivo evaluation studies have been conducted in dogs and, to a limited extent, in humans. Although the results appear promising, it has not been proven definitively that rupture occurs in the colon. One must also question the influence of co-administered food on performance, as fed state contractions may be sufficiently powerful to disintegrate the capsule in the stomach. An intestinal pressure controlled colon delivery capsules (PCDCs) which was prepared by coating the inner surface of gelatin capsule with water-insoluble polymer ethyl cellulose. By adjusting the coating thickness of ethyl cellulose membrane to be approximately 40 microns, colon delivery of drug were obtained both in beagle dogs and human volunteers. PCDC containing 5-ASA was prepared and was administered orally to beagle dogs. After administration, 5-ASA appeared into the systemic circulation at 3-5 h that corresponds to the colon arrival time confirmed with sulfasalazine [24, 25].

The relationship between *in vitro* drug release characteristics from colon delivery systems and *in vivo* drug absorption was investigated using three kinds of delayed release systems. 5-ASA, tegafur and carbamazepine were selected as model drugs. Pressure-controlled colon delivery capsules for liquid preparations, time-controlled colon delivery capsules for liquid and solid preparations and Eudragit S coated tablets for solid preparations were used in this study. First *in vitro* dissolution tests for all preparations were performed. Drug release from solid preparations was delayed compared to that from liquid preparations with all three drugs. From the findings of the study it was concluded that drug release from colon delivery systems and drug dissolution in the colonic lumen are very important factors for the systemic availability of drugs from the colon delivery systems [26].

The delivery ability of a PCDC containing caffeine as a test drug was evaluated after oral administration to healthy male human volunteers. The driving force causing PCDC disintegration in the intestinal tract is the physiological luminal pressure, which results from peristalsis. Three kinds of PCDCs having different thickness of a water-insoluble polymer membrane were prepared by coating the inner surface of the gelatin capsules with EC. The mean thicknesses were 40 ± 1 μm for type 1, 44 ± 1 μm for type 2 and 50 ± 1 μm for type 3 PCDC, respectively. Caffeine was dissolved with a suppository base (PEGs 400 and 1000) and the capsules were filled in doses of 15, 45 or 75 mg. After blank saliva samples were obtained, test preparations were orally administered to the volunteers and saliva samples were collected for 1 min intervals hourly from 1 to 10 h in the fasted state study, and from 1 to 20 h and at 25 h in the fed state study. Caffeine concentrations in the saliva samples were analysed by HPLC. The maximum salivary caffeine excretion rate increased as the oral caffeine dose increased [27].

Pectin and Galactomannan Coating

This technology was recently proposed by Lee *et al*., 1999 and Pai *et al*., 2000. It consists of a conventional tablet or capsule coated with two specific polysaccharides, namely pectin and galactomannan. By itself, neither pectin nor galactomannan can be used as a drug carrier for colon-specific delivery due to its high water solubility and swelling characteristics. However, the solubility of the coating produced from the mixture of the two polysaccharides was found to predominantly depend on the pH of coating solution. The coating from a pH>7 aqueous solution of pectin and galactomannan was shown to be strong, elastic and insoluble in simulated gastric and intestinal fluids. Accordingly, such coating could protect drug from being released in the upper GI tract. On the other hand, the coating from the identical solution with pH 7 due to the hydrogen bonding, hydrophobic force, and the formation of an interjunction zone from conformational changes of polysaccharides at the higher pH. Results indicated that the bacterial degradability of films produced by this method was still preserved in the colon. It was also demonstrated that the extent of film resistance to hydration and subsequent solublization, the rate of film degradation by enzymes, and the resultant drug release rate depend on the ratio of pectin to galactomannan. Higher percentage of galactomannan results in decreased bacterial degradation in the colon and prolonged duration of negligible drug release in the upper GI tract. The site specificity of drug release was pharmacoscintigraphically confirmed in human subjects. Compared with the combination of pectin and ethyl cellulose or amylose and ethyl cellulose this technology might have the advantage of faster degradation *in vivo* since both pectin and galactomannan are readily degradable by microflora in the colon [28, 29, 30, 31].

CODES™

CODES™ is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODES™ is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine [32, 33, 34]. Once the tablet arrives in the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid soluble coating and subsequent drug release [35].

The schematics of the conceptual design of CODES™ is shown in Fig. 1 [36].

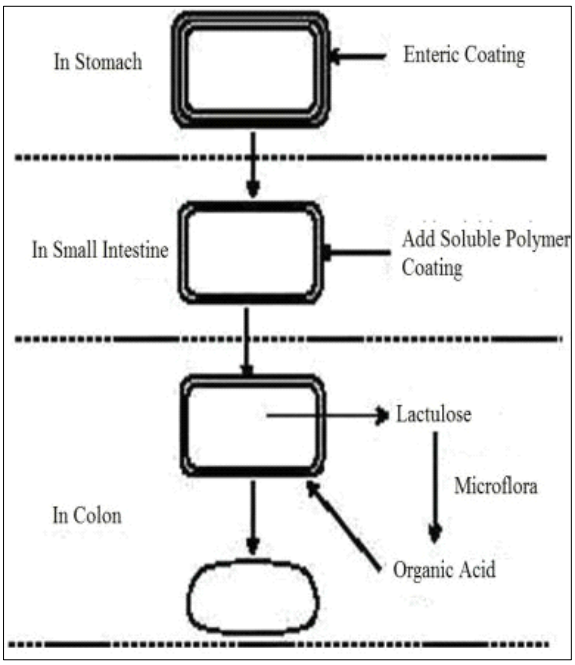

Fig 1: The schematics of the conceptual design of CODES™

Pulsincap

The first formulation introduced based on this principle was Pulsincap® developed by R.R. Scherer International Corporation, Michigan, US. It consists of non-disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell. The length of the plug and its point of insertion into the capsule controlled the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g, polymethacrylates), erodible compressed polymers (e.g, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g, pectin) [3].

The design of Pulsincap system is shown in Fig. 2 [37]

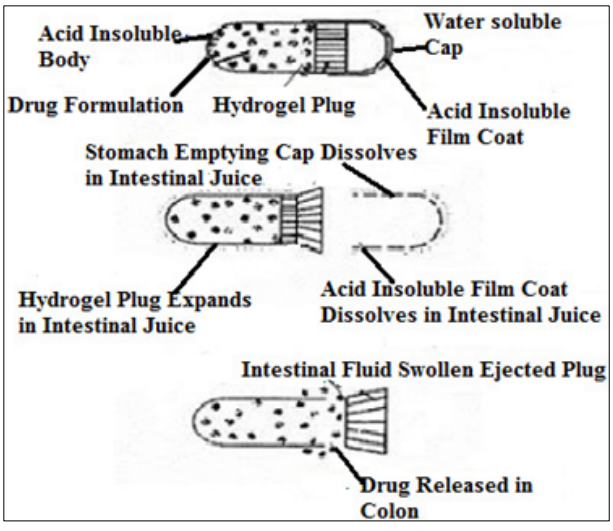

Fig 2: Design of pulsincap system

Evaluation [38, 39, 40]

***In vitro* evaluation**

No standardized evaluation technique is available for evaluation of CDDS because an ideal *in vitro* model should possess the *in vivo* conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and other components of food. Generally these conditions are influenced by the diet and physical stress and these factors make it difficult to design a slandered *in vitro* model. *In vitro* model used for CDDS are:

***In vitro* dissolution test**

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

***In vitro* enzymatic test**

For this there are 2 tests:

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

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

***In vivo* evaluation**

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. 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. 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.

Clinical Evaluation

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gammascintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

High frequency capsule

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

Gammascintigraphy

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

Conclusion

From this review we concluded that, CTDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment and the colonic region of the GIT has become an increasingly important site for drug delivery and absorption. All the approaches traditional as well as new provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbed drugs, but new approaches which are reported to have better in-vivo site specificity and design rationale than the traditional one. The colon targeted drug delivery provides safe, effective and less expensive delivery of drugs with minimum fluctuation at the target site.

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