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COLON TARGETED DRUG DELIVERY SYSTEMS - RECENT UPDATES

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ABSTRACT

Colon targeting system is used for both local and systemic delivery of drugs. It is also a potential site for systemic delivery of therapeutic proteins and peptides, oligonucleotides and vaccines. It is an alternative system for the orally administrated drugs that pass through GIT which presents several formidable barriers to drug delivery. Treatment could be more effective if it is possible for drug to be directly administered to colon there by dose and systemic side effects can be reduced. To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. Colon targeting is naturally of value for the treatment of diseases of colon such as Crohn's diseases, ulcerative colitis, colorectal cancer and amoebiasis. This review mainly concentrates on primary and novel approaches to target the colon. Primary approaches include pH Dependent, Time-Dependent Delivery, Microbially Triggered Drug Delivery to colon and novel approaches include Pressure Controlled Drug-Delivery Systems, Novel Colon Targeted Delivery System (CODESTM), Osmotic Controlled Drug Delivery (ORDS-CT), Bioadhesive systems and Multiparticulate Systems. These novel approaches are unique in terms of achieving *in vivo* site specificity and feasibility of manufacturing processes.

Key Words:- Colon drug delivery, Drug targeting, approaches, biodegradable polymers.

INTRODUCTION

An ideal targeted drug delivery system is the one which delivers the drugs only to its sites of action and not to the non-targeted organs or tissues. This targeted system is employed for the drugs that are destroyed by the acidic environment of the stomach or metabolized by pancreatic enzymes which are only slightly effective in the colon (Prasanta Choudhur *et al*., 2012). Colon targeting system is used for both local and systemic delivery of drugs, it is also a potential site for systemic delivery of therapeutic proteins, peptides, oligonucleotides and vaccines because this region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine for delivery of proteins and peptides and it is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery (Sarasija *et al.*, 2000) This delivery system is used for the treatment of ulcerative colitis, crohn's disease, colorectal cancer and inflammatory bowel diseases. Colonic delivery mainly accomplished by rectal or oral administration. Rectal administration of colonic delivery is not effective widely; oral administration is the preferred route. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Colon targeting has advantage also for Chronotherapy in asthma, hypertension, cardiac arrhythmias, arthritis or inflammation (Bajpai *et al.*,

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2003). Absorption or degradation of active constituent in the upper part of GIT is the main obstacle and must be circumvented for successful colonic drug delivery. To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered as the optimum site for colon-targeted delivery of drugs.

Colon targeting is need for

- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be 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.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular therapeutic proteins and peptides.

Advantages

- The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.
- Colon targeted drug delivery ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation.
- Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infections).
- Minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption.
- The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery(Sarasija *et al.*, 2000).

Drawbacks and problems associated with colonic delivery

1. Oral administration of dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorption from these regions of the GIT depends upon the physicochemical properties of the drug.
2. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs.
3. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention.
4. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug.

Factors affecting colonic absorption

* Physical properties of drug such as pKa and degree of ionization.
* Colonic residence time as commanded by GIT motility.
* Degradation by bacterial enzymes and metabolic products.
* Local physiological action of drug.
* Selective and non-selective binding to mucus.
* Disease state.
* Transit through GIT.

Anatomy and Physiology of Colon

The colon forms the lower part of the gastrointestinal tract and extends from ileocaecal junction to the anus divided in to three parts colon, rectum and anal–canal. The colon composed of caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon. It is about1.5 m long. The transverse colon is the lowest and the most mobile part with average diameter of about 6.5 cm. However, it varies in diameter from approx. 9.0 cm. in caecum to 2 cm in sigmoid colon(fig:1). Unlike the small intestine, the colon does not have any villi but due the presence of plicae semilunar, which are cresentic folds, the intestinal surface of the colon is increased to 1300 cm^2 **(**Sarasija *et al.*, 2000**;** JitenderMor, 2011).

The activity in the colon can be divided in to segmenting and propulsive movements. A large number of anaerobic and aerobic bacteria are present throughout the entire length of human GIT. The concentration of bacteria in the human colon is 10^{11}-10^{12} CFU/ml (colony forming units/ml).

The ability of selective metabolism of certain carbohydrates and anaerobic environment has been exploited in the development of delivery systems. On the other hand, significant proteolytic activity has implications for delivery of peptides and protein drugs. pH of colon in various regions is given in Tab. 1 and GI transit time is given in Tab.2.

Colon diseases

Inflammatory Bowel Disease

The cause of inflammatory bowel disease is multifactorial and it is due to the inflammatory responses, genetic factors such as multiple genetic factors, candidate genes, chromosome location, etc., infectious agents like Escherichia coli, Measles virus, Cytomegalovirus, etc., dietary factors such as saturated fats, milk products, allergic foods etc. It is a general term that has the following two diseases, **(**Ratna *et al.,* 2010**)**

1. Ulcerative colitis
2. Crohn's disease

Ulcerative colitis, occurs only in the large intestine. Ulcers form in the inner lining of the intestine, or *mucosa*, of the colon or rectum, often resulting in diarrhea, blood, and pus. The inflammation is usually very rigorous in the sigmoid and rectum and usually reduces in the colon.

Crohn's disease, also called regional enteritis, is a chronic inflammation of the intestines which is usually confined to the terminal portion of the small intestine, the ileum. Ulcerative colitis is a common inflammation of the colon, or large intestine. These diseases and other inflammatory bowel disease have been linked with an increased risk of colorectal cancer.

Diagnosis of inflammatory bowel disease

Blood tests.

Endoscopic technique.

The other diagnostic techniques - constellation of positive endoscopic, radiographic, and histological findings with negative stool cultures.

APPROACHES FOR COLON TARGETED DRUG DELIVERY

Primary approaches

pH-dependent Delivery

pH sensitivity enteric coatings have been used routinely to deliver drugs to the small intestine these polymers coatings are insensitive to acidic conditions of the stomach yet dissolve at the higher pH environment of small intestine (Ajmal, et al., 2010). This pH differential principle has also been attempted for colonic delivery purposes. Most commonly co-polymers of methacrylic acid and methyl methacrylate that dissolve at a slower rate and at a higher threshold pH (7-7.5), (Evans et al., 1988) has been developed recently.

The inter and intra-subject variability in gastro-intestinal pH and possibly certain other intrinsic variable such as electrolyte concentration and transit time will therefore impact on the in vivo behaviour of pH-responsive system. Drugs and polymers employed in P^H dependent delivery are outlined in Table 3.

Time dependent delivery

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

Limitations

Gastric emptying time,Gastrointestinal movement, (Fukui *et al.,* 2000), Accelerated transit through different regions of the colon.(Vassallo *et al.,*1992; Vonderohe *et al.,* 1993; Reddy *et al.,*1999)are varies in different subjects based on the type of food intake, physiological status and health condition of patients. Polymers and drugs used in time dependent approach are outlined in Table 4.

Integration of pH sensitive and time release approach

On the other hand, in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time.

E.g.:1. PULSINCAP: (JitenderMor, 2011)

Pulsincap was the first formulation developed based on timerelease principle. It was similar in appearance to hard gelatin capsule. It consists of water insoluble body water soluble enteric coated cap. The contents are placed with in body plugged with hydrogel plug. When it is administered, after predetermined time the enteric coat dissolves and the hydrogel plug starts to swell.

E.g.: 2.ETP TABLET:

Enteric coated time-release press coated (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) (Gazzaniga *et al.,* 1994; Fukui *et al.,* 2000; Hita *et al.,* 1997). The duration of lag phase for timed release is controlled either by the weight or composition of the polymer (HPC) layer (Fig:2).

Microbially triggered drug delivery

The microflora of the colon is in the range of 10^{11} -10^{12} CFU/ml, consisting mainly of anaerobic bacteria, e.g. bacteroides, This vast microflora fulfils its energy

needs by fermenting various substrates for this microflora produce different enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase,etc (Scheline 1973). Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches (Jung et al., 1998). These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength(Peters et al., 1993). They are then unable to hold the drug entity any longer (Huang et al., 1979; Swift,1992; Ratner et al., 1988; Hergenrother et al.,1992; Park et al., 1993).Biodegradable polymers used in colonic delivery are listed in Table 5.

i) Prodrug Approach for Drug Delivery to Colon

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier.

Limitations of the prodrug approach are that it is not a very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers (Sinha *et al.,* 2003).

Azo-bond conjugates

Sulphasalazine was introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazo sulphapyridine (SASP), where sulfapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact (Azad Khan *et al.,* 1982). There it is split at the azo bond by the colonic bacteria with the liberation of sulphapyridine (SP) and 5 -ASA. However sulphapyridine is seems to be responsible for most of the side effects of sulphasalazine and hence various new approaches for the treatment of IBD have emerged (Sarasija *et al.,* 2000; Raffi *et al.,* 1990).

Glycoside conjugates

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

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 b -glucuronidase and can deglucuronidate a variety of drugs in the intestine (Scheline, 1968). Since the deglucuronidation 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.

Cyclodextrin conjugates

In an oral drug delivery system, the hydrophilic and ionizable CyDs can serve as potent drug carriers in the immediate release and delayed release-formulations, respectively, while hydrophobic CyDs can retard the release rate of water-soluble drugs. Since CyDs are able to extend the function of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable tool 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 CyDs can be a versatile means of constructing a new class of colon targeting prodrugs. Many modified CyDs have been prepared for the delivery of bioactive agents to the colon.

Dextran conjugates

Dextran ester prodrug was prepared and *in vitro* release revealed that release of naproxen from prodrug was several folds higher in caecum homogenates than in control medium or homogenates of the small intestine of pig (Larsen *et al.,* 1989; Harboe *et al.,* 1989). Dextran ester prodrugs of metronidazole have been prepared and characterized. McLeod et al., (McLeod *et al.,* 1993; McLeod *et al.,* 1994) synthesized dextran ester prodrugs of dexamethasone and methylprednisolone and proved the efficacy of the prodrugs for delivering drugs to the colon.

Amino acid conjugates

Due to the hydrophilic nature of polar groups like $-NH_2$ 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 (Nakamura *et al.*, 1992). Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA.

ii) Polysaccharide Based Delivery Systems

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharide's are found in abundance, inexpensive and are available in a verity of a structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, non-toxic, hydrophilic and gel forming and in addition, are biodegradable. The polysaccrides can be broken down by the colonic microflora to simple saccharides (Ashord *et al.*, 1993). Therefore, they fall into the category of "generally regarded as safe" (GRAS). Polymers and drugs used in polysaccharide based approach are outlined in Table 6.

Newly Developed Approaches for CDDS

Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water (Takaya *et al.*, 1998). In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for the disintegration of the formulation (Muraoka *et al.*, 1998). The system also appeared to depend on capsule size and density.

Osmotic Controlled Drug Delivery (OROS-CT)

The OROS-CT (Alza Corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule (Swanson *et al.*, 1987)**.** Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane (Fig:3).

Combined approach of pH dependent and microbially triggered CDDS (CODES^{TM})

CODES^{TM} is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems (Watanabe *et al.*, 1998; Takemura *et al.*, 2000). CODES^{TM} 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 drug release pattern is given in Fig 4.

The new prodrug approaches for colonic delivery

ADEPT (antibody-directed enzyme prodrug therapy) (Fig:5) GDEPT (gene-directed enzyme prodrug therapy), which attempt the localization of prodrug activation enzymes into specific cancer cells prior to prodrug administration. (Fig:6) **(**Basit *et al.*, 2004; Stella *et al.*, 1985; Higuchi *et al.*, 1975**)**

Bioadhesive system

It is a process by which a dosage form remains in contact with particular organ or site for an augmented period of time. Therefore longer residence time of drug allows high local concentration or improved absorption in case of poorly absorbable drugs. This strategy can be applied to colonic delivery. Various polymers investigated for colonic bioadhesive system are polycarbophils, polyurethanes, and polyethylene oxide-polypropylene oxide copolymers (Gurny *et al.*, 1989; Lenaerts *et al.*, 1990).

Other systems

Old systemic and topical steroids

Synthetic glucocorticoids such as prednisone, prednisolone, methyl-prednisolone, hydrocortisone, and ACTH are the most commonly used traditional corticosteroids in the treatment of ulcerative colitis. **(**Ratna *et al.*, 2010**)**

Topical system

Topical Preparations (foams, suppositories or enemas) plays major role in ulcerative colitis, either alone or in combination with oral steroids. They should generally not be used once a patient requires high-dose oral or intravenous steroid therapy. **(**Ratna *et al.,* 2010**)**

Redox-sensitive polymers

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzed non-enzymatically by enzymatically generated flavins (the electron mediator) are being developed for colon targeting(Gingell *et al.,* 1975, Roxon *et al.,* 1967). Redox potential is an expression of the total metabolic and bacterial activity in the colon and it is believed to be insensitive to dietary changes. The mean redox potential in proximal small bowel is - 67 ± 90 mv, in the distal small bowel is -196 ± 97 mv and in the colon is -145 ± 72 mv. Thus, microflora-induced changes in the redox potential can be used as a highly selective mechanism for targeting to the colon.

Hydrogels

The hydrogels contain acidic co-monomers and enzymatically degradable azoaromatic cross-links. In the acidic pH of stomach, the gels have a low degree of swelling, which protect the drug against degradation by digestive enzymes. As the gels pass down the GI tract, the degree of swelling increases. On entering the colon, the gels reach a degree of swelling making the cross-links accessible to enzymes (azoreductases) or mediators (electron carriers). Biodegrable hydrogels such as amylose, chondroitin sulphate, chitosan, inulin, guar gum, and pectin have also been successfully used to achieve oral colon-targeted delivery. The release of drug is closely related to the swelling characteristics of the hydrogels, which in turn, is a key function of chemical architecture of the hydrogels. **(**Hamman *et al.,* 2007; Orienti *et al.,* 2001; Kinget *et al.,* 1993; Bronsted *et al.,* 1995; Krishnaiah *et al.,* 2001**)**

Multiparticulate systems

Multiparticulates (pellets, non-peariles etc.) are used as drug carriers in pH-sensitive, time- dependent and microbially control systems for colon targeting. Multiparticulate 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).Most commonly investigated multiparticulate formulations for colon specific drug delivery include pellets, granular matrices, beads, microspheres, and nanoparticles. **(**Prasanta KC *et al.,* 2012**).**

Microspheres

A multiparticulate dosage form 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).

Coated pellets

Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and Eel calcitonin.

Non peariles

A multiparticulate 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 multiparticulates like Non peariles in the study. In this study the multiparticulate CDS was adopted not only for colon specific drug delivery but also for sustained drug delivery (Norihito *et al.,* 2003).

Coated calcium alginate gel beads-entrapped liposome

A new microparticulate system containing budesonide was prepared by microencapsulation for colon specific delivery (Marta *et al.,* 2001). In the study by 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 amount of bee venom in the liposome, as well as coating.

Microsponges

Using these flurbiprofen 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 (Mine *et 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 (Libio *et al.,* 2002).

In vitro enzymatic tests

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.

In vivo Evaluation

In vivo methods offer various animal models, Guinea pigs, dogs, and rats are generally used to evaluate the drug delivery to colon as they have anatomical and physiological similarities with human GIT microflora. 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 (Prasanta KC *et al.,* 2012).

Clinical evaluation tests

Colonoscopy and intubation can be used to monitor the absorption of drugs from the colon. At present Gama scintigraphy and high frequency capsules are the most preferred techniques used to evaluate colon drug delivery system.

Current and future developments

Currently, there are several modified release solid formulation technologies available for colonic delivery. These technologies rely on GI pH, transit times, enterobacteria and luminal pressure for site-specific delivery. Each of these technologies represents a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up/manufacturing. It appears that microbially-controlled systems based on natural polymers have the greatest potential for colonic delivery, particularly in terms of site-specificity and safety. In this regard, formulations that employ a film coating system based on the combination of a polysaccharide and a suitable film forming polymer represents a significant technological advancement **(**Langer *et al.,* 1998; Kost *et al.,* 2001**)**

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Opportunities in colon targeted drug delivery

- This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Moreover, there is an urgent need for delivery of drugs to the colon that reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose.
- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and other colon diseases.
- The bioavailability of protein drugs delivered at the colon site needs to be addressed.

Table 1. pH of colon in various regions

Location	Average pH
Ascending colon	6.4
Transverse colon	6.0-7.4
Descending colon	6.0-7.4

Table 2. Transit time of dosage form in GIT

Organ	Transit time of dosage form in GIT (hrs.)
Stomach	<1 (fasting), > 3 (fed)
Small intestine	3-4
Large intestine	20-30

Table 3. Outline of drugs and polymers employed in P^H dependent delivery:

Technique employed	Polymer (s) used	Drug used
pH dependent delivery	Eudragit L100 and S100	Mesalzine
	DudragitL100 and S100	NS
	Eudragit L 100 andS100	Diclofenac sodium and 5-ASA
	Eudragit S, Eudragit FS, Eudragit P4135F	Prednisolone
	Eudragit L 30 D-55 and Eudragit FS 30D	Paracetamol

Table 4. Outline of polymers and drugs used in time dependent approach

Technique employed	Polymer (s) used	Drug used
Time dependent	Hydroxy propyl methyl cellulose	Pseudo ephedrine HCl
	Hydroxyethyl cellulose, ethyl	Theophylline
	Cellulose, microcrystalline cellulose Lactose/behinic acid	Indomethacin
	Hydroxy propyl methyl cellulose	NS
	Hydroxy propyl methyl cellulose acetate succinate	Diltiazem HCl

Table 5. Microbial degradable polymers used for Colonic drug delivery system

Class	Examples
Disaccharides	Lactose, Maltose.
Oligosaccharides	Cellbiose, Cyclodextrin, Lectulose, Raffinose, Stachyose.
Polysaccharides	Alginates, Amylose, Arabinogalactan, Arabinoxylan, Cellulose, Chitosan, Chondroitin sulfate, Xextran, Galactomnam(Guargum,Locust bean gum), Laminarian, Pectins and Pectates, Starch, Tragacanth, Xanthum gum and Xylan.

Table 6. Outline of polymers and drugs used in polysaccharide based approach:

Technique employed	Polymer(s)used	Drug used
Polysaccharide based	Chitosan	Declofenac sodium
	Pectin	Indomethacin
	Guar gum	Dexamethasone
	Chondroitin sulphate	Indomethacin
	Amylose	5-Acetyl salicylic acid

Fig 1. Anatomy of colon

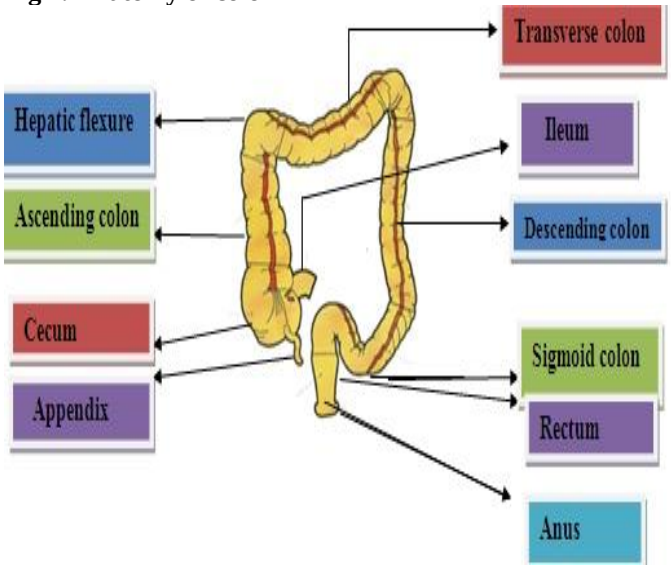


Fig 2. Design of enteric coated time release press coated tablet (ETP tablet)

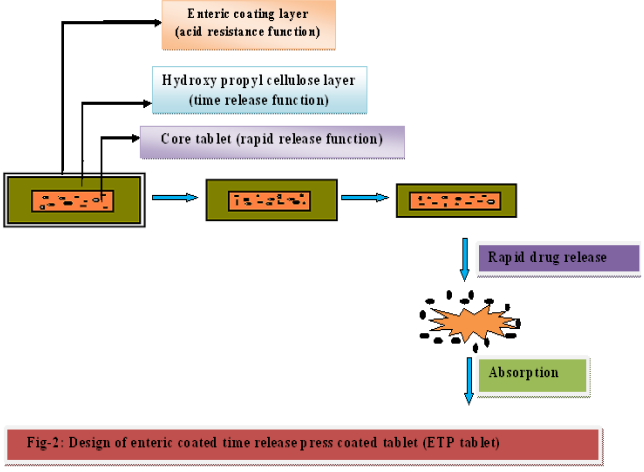


Fig 3. Cross-section of OROS-CT Colon targeting drug delivery system

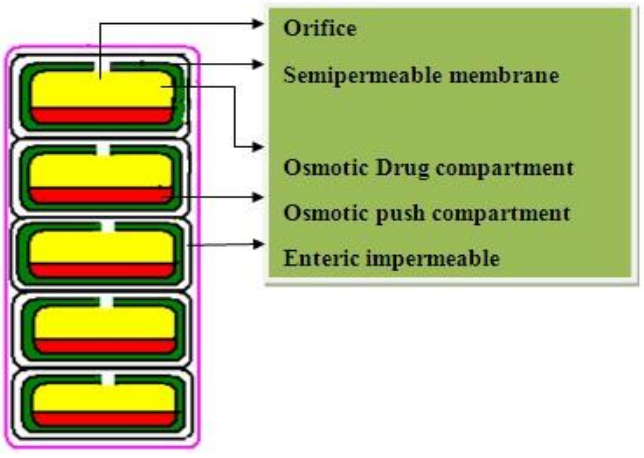


Fig-4: Schematic representation of design of CODES^{TM}

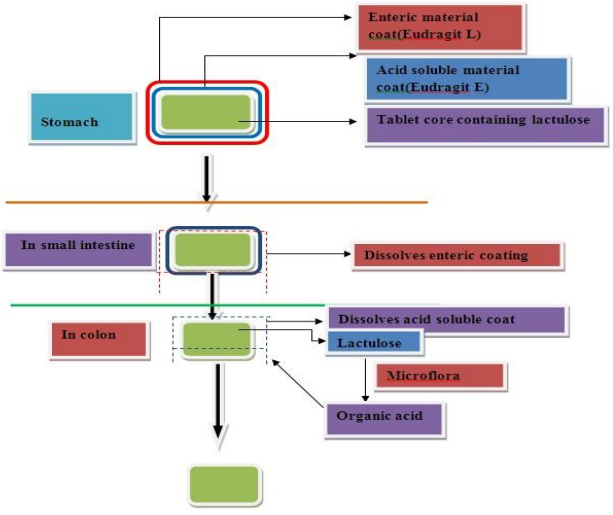


Fig 5. Schematic representation of ADEPT

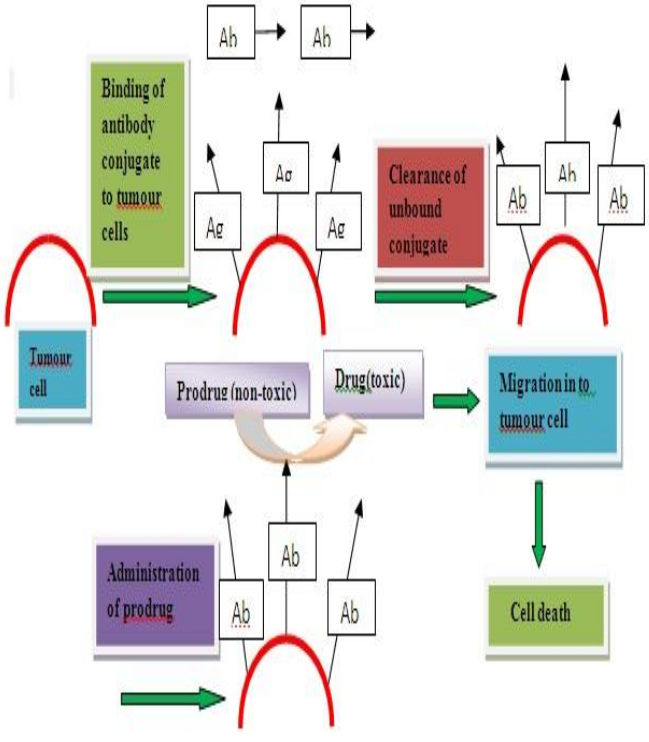
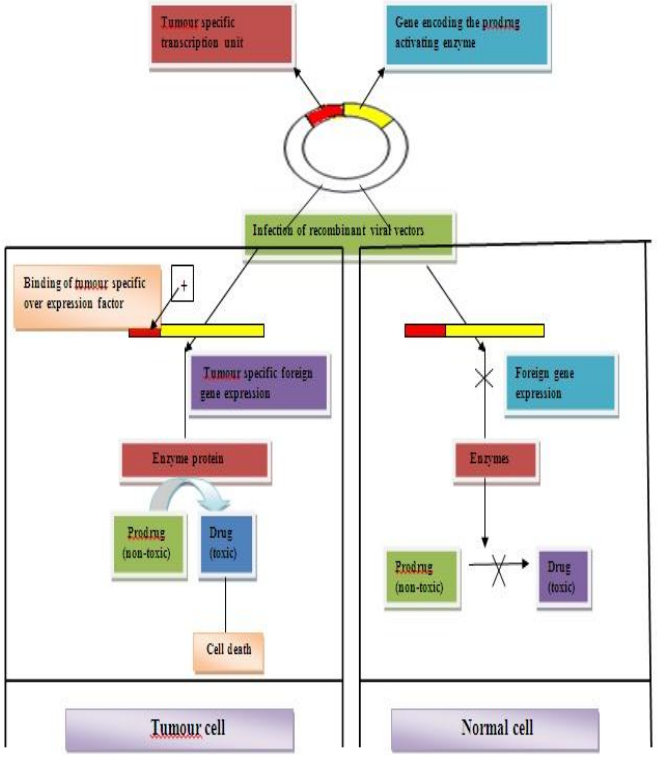


Fig 6. Schematic representation of GDEPT



CONCLUSION

Colon targeting systems become very important and attracting site of scientists towards its development because of its less hostile environment and efficient local and systemic delivery of drugs and it's a potential site for systemic delivery of therapeutic proteins, peptides, oligonucleotides and vaccines. The formulation of colonic controlled release systems lead to decrease in dose, side effects and increased therapeutic efficacy. Colon targeting is naturally of value for the treatment of diseases of colon such as Chron's diseases, ulcerative colitis, colorectal cancer and amebiasis.

There are many primary and novel approaches are employed to specifically target colon.Colon specialty is more likely to be achieved to systems that utilize natural materials that are degraded by bacterial enzymes of colonic origin. Moreover the cost and case of manufacture delivery system are further considerations that will impact on its likely commercialization. Bacteria sensitive natural film coating that can be applied to a range of solid oral dosage forms using conversional processing technology would therefore appear to be delivery system of choice in the very upcoming researches by the pharmaceutical scientists.

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