ISSN: 2321-2152

IJMECE

International Journal of modern electronics and communication engineering

E-Mail
editor.ijmece@gmail.com
editor@ijmece.com

www.ijmece.com

ISSN2321-2152www.ijmece .com

Vol 12, Issue.2April 2024

REVIEW ON NOVEL APPROCHES FOR COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT:

Numerous routes of drug administration have been proposed and explored for the effective delivery of the drug to the target site.Colon is a site where both systemic and local drug are used for situated diseases. Local delivery allows the topical treatment of inflammatory bowel disease, Crohn's disease, ulcerative colitis, etc. Various drugs are been used for targeting systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. Colon target aimed mainly because of microbial flora, less enzymatic activity, longer transit time so it is suitable to delivering especially the protein and peptide molecules. Different primary and novel approaches are designed based on time-dependency (lag time), prodrug approaches, microbial degradation, pH-sensitivity to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes for colon targeting. Novel colon targeted delivery system like osmotic controlled drug delivery system, Pulsincap system, time clock system, chronotropic system. The effectiveness of drug delivery system is evaluated using different in vitro and in vivo release studies and using recent evaluation models through x-ray imaging and gamma-scintigrapy studies.

INTRODUCTION:

The per-oral dosage form is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach and intestinal fluid hence absorb from these regions of gastro intestinal tract GIT. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, and colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs. The colon specific drug delivery

system (CDDS) should be capable of protecting the drug 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 1. Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and/or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. A colonic targeted approach found to be effected in minimizing uncertain side effects . Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as (ulcerative colitis, crohn's disease) amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs . The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine and bioactive agent should not be degraded and to allow drug release only in the colon.The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stom- ach fluid or intestinal fluid and absorb from these regions of the GIT depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT prof- fers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infec- tions) whereby high local concentration can be achieved while 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 pro- duces rapid local production of antibodies and this helps in efficient vaccine delivery.The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is recognized as having a

somewhat less hostile environ- ment with less diversity and intensity of activity than the stomach and small intestine.

Objective for Colon Targeted Drug Delivery:

To ensure direct treatment at the disease site, minimize 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. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. 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 and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism.

Advantages of colon specific drug delivery system:

1. Minimizes the side effects in the treatment of colon diseases.

2. Prevents gastric irritation resulting due to the administration of non-steroidal anti inflammatory drug NSAIDs.

3. Minimizes first pass metabolism.

4. Increases patient compliance.

5. Maximum bioavailability at small doses.

6. High retention time thus increasing the bioavailability of poorly absorbable drugs.

7. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid

and digestive enzymes.

8. Decreased frequency of administration, hence decreased cost of therapy.

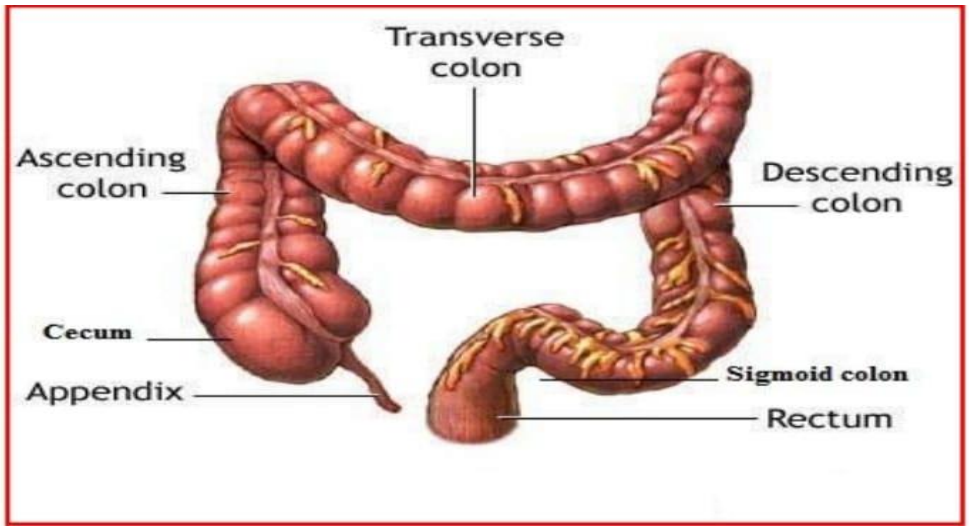
9. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis,

crohn's disease, etc.

Factors to be considered in the design of Colon-Specific Drug Delivery System:

Anatomy and Physiology of the Colon:

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long 9. The colon is upper 1.52 meter of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 5-8 cms in diameter10 (Table 1). The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal11 (Figure 1). The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.



p^H in the Colon:

The p^H of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the p^H of the gastrointestinal fluid. The change in Ph along the gastrointestinal tract has been used as a means for targeted colon drug delivery. There is a pH gradient in the gastrointestinal tract with value ranging from pH 1.2 in the stomach through pH 6.6 in the proximal small intestine to a peak of about pH 7.5 in the distal small intestine (Table 1). The pH

difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

Criteria for selection of drug for Colonic Drug Delivery:

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 delivery17.

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 molecule18. 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 systems19

Factors affecting Colon Absorption:

1. Physical properties of drug such as drug pKa and degree of ionization.

2. Colonic residence time as commanded by GIT motility.

3. Degradation by bacterial enzymes and metabolic products.

4. Local physiological action of drug.

5. Selective and non-selective binding to mucus.

6. Disease state

PRIMARY APPROACHES FOR COLON TARGETED DRUG DELIVERY (CTDD) SYSTEM:

pH Controlled release:

In pH controlled release systems, the different pH of human GIT is exploited by coating the dosage form with pH dependent polymers which remains as such in the upper

GIT and degrade in the large intestine where the pH is high i.e., pH 7-8. This approach can be used in any dosage form such as tablets, capsules, pellets etc. On coating the dosage forms with pH sensitive polymers, the active drug is protected from gastric fluid and also a delayed release is obtained. By gathering the maximum information of polymers and their solubility at different pH, delivery systems are designed to target drug to desired location. Methacrylic acid and methyl methacrylate are the most commonly used polymers for colonic drug delivery. On the in vitro evaluation of Eudragit S and Eudragit FS, it was found that the latter proves to be more appropriate for ileocolonic drug delivery.Combination of different polymers, coating level, pH of media are some factors that affect the dissolution rate of Eudragit. The pH controlled systems are commercially available for some drugs like mesalazine (5 ASA) (Asacol and Salafalk), budesonide (Budenofalk and Entrocort) for the treatment of ulcerative colitis and crohn's disease respectively. Depicting enteric coating polymers along with their threshold pH25-28 as mentioned in (Table 4)

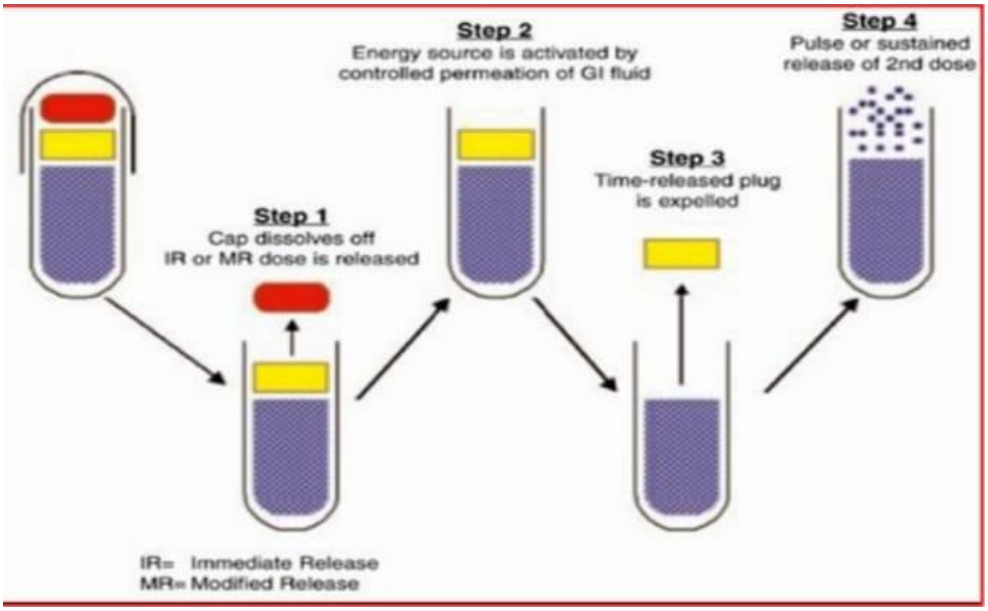
Time Controlled Release System:

The time controlled systems works on the principle of drug release after a predetermined lag time at the desired site of action and time of release29. A considerable lag time of five hours is considered adequate for colon targeting. The coated polymer or mixture of polymers and their thickness influences the time required for dosage form to release drug in colon. As the gastric emptying time of dosage forms differ from person to person, the colon arrival time of dosage form can't be predicted accurately 30. However, these systems are useful in the therapy of diseases based on circadian rhythms 31-34. Here the balance between the thickness of water insoluble membrane and the amount of swellable excipient controls the release time of drug from dosage form. The swellable excipients may be L-HPC, sodium starch glycolate etc .

PORT System:

The Port system (Figure 4) was developed by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of a gelatin capsule coated with a semi permeable membrane. Inside the capsule an insoluble plug (lipidic) consisting of osmotic active agent and the drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug

after a lag time. The lag time is controlled by coating thickness. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans. The system proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children.



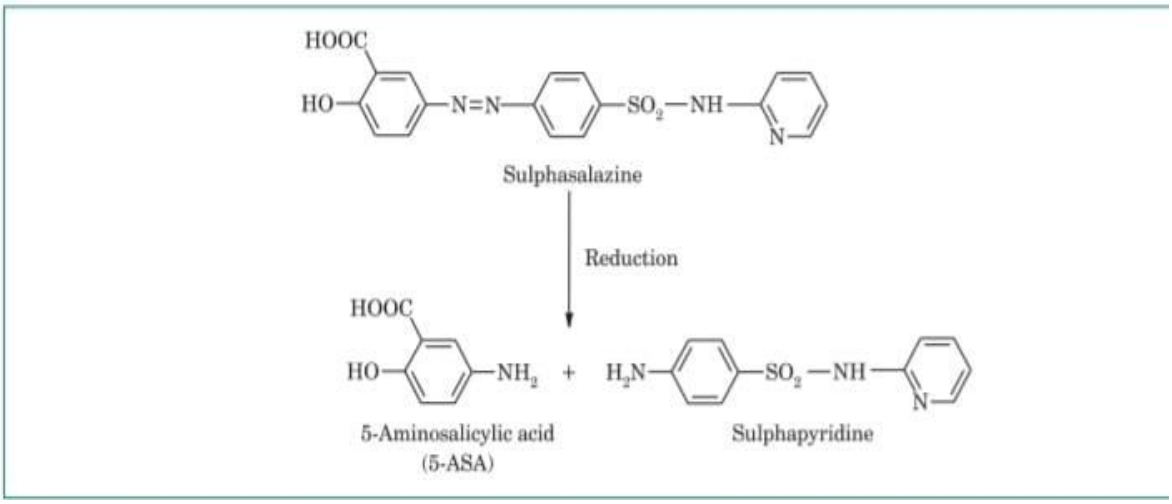
METHODS USED FOR DRUG TARGETTING TO THE COLON:

Formation of prodrugs:

Prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body [40]. Covalent linkage is formed be- tween 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. a) Azo bond conjugate: Sulfasalazine is mainly used for the treatment of inflammatory bowl diseases. It is 5-Amino Salicylic Acid (5-ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed, where it is re- duced by the anaerobic environment into 5-ASA and sulphapyridine as shown in Figure 2 [41]. Various studies are conducted on sulpha- pyridine which lead to the formation of other prodrug like Olsalazine, Balsalazine, 4-amino benzoyl-b-alanine [42]. Intestinal microflora produces glycosidase, one of prominent group of enzyme. Colon specific formulation of flurbiprofen had been evaluated by using azo-aromatic and pH-sensitive polymer and it was concluded that azo-aromatic polymer (poly-methylmethacrylate hydroxy

rthylmethacrylate:1:5) [43]. Mutual azo prodrug of 5-aminosalicyic acid with histidine, was synthesized by coupling L-histidine with Salicylic acid, for targeted drug delivery to the in flamed gut tissue [44].

b) 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 [45].

c) Cyclo dextrin 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 [46]. Ibuprofen prodrugs of a-, b-and g-Cyclodextrins were investigated [47]. Methotrexate prodrugs of a- and g-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 [48].

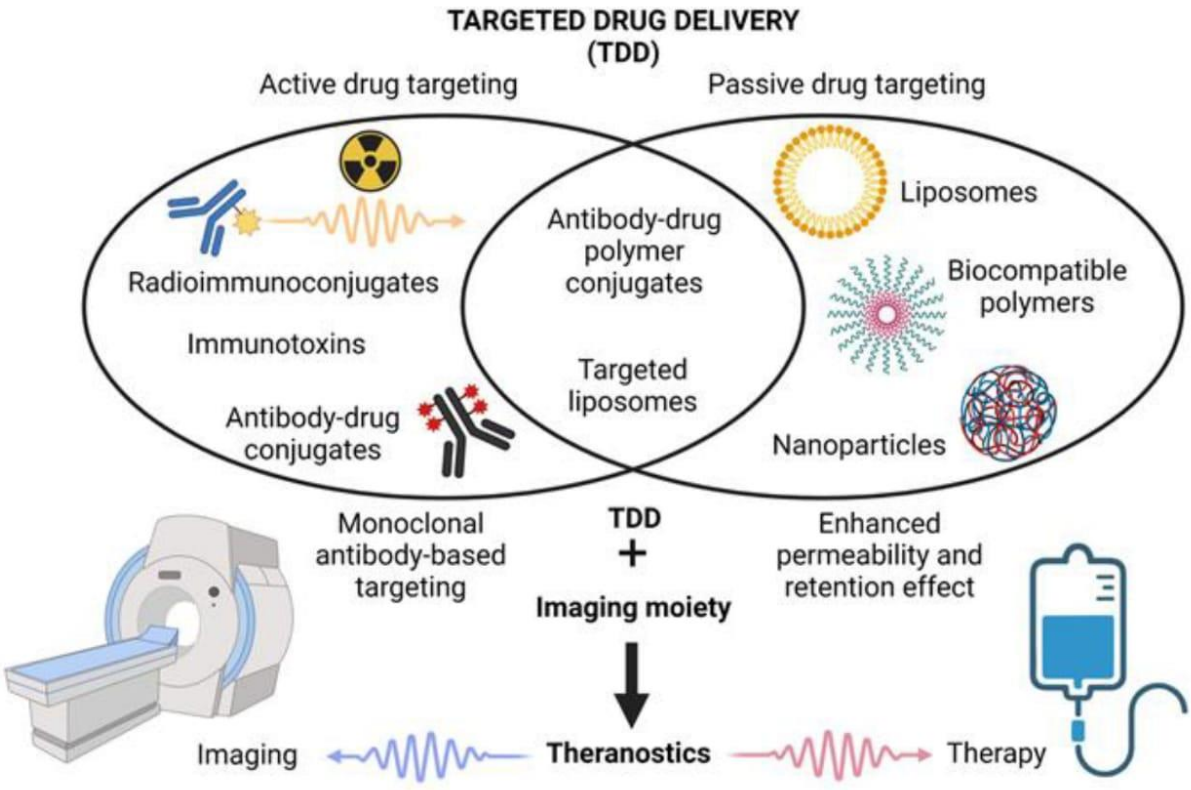
d) Dextran conjugates: Dextran ester prodrugs of metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone was synthesized and proved the efficacy of the

prodrugs for delivering drugs to the colon. Methyl prednisolone and dexamethasone were covalently attached to the dextran by the use of a succinate linker [49].

e) 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. Non-essential amino acids such as tyrosine,glycine, methionine and glutamic acid were conjugated to Salicylic acid.

MATERIALS AND METHODS:

The search was conducted electronically in Wiley online library, pubmed, google scholar from 1995 to 2014. The key words were colon targeted delivery system, novel approaches, microbial flora, pH dependent. The articles written in English were included in the review. A total of 1289 references were identified, after this 657 article were screened and 335 full text articles were studied for eligibility. Among which 72 articles were included matching the inclusion criteria. Finally 263 articles were excluded from this review process.



NOVEL APPROACHES FOR CTDD SYSTEM:

Hydrogels Based Approach:

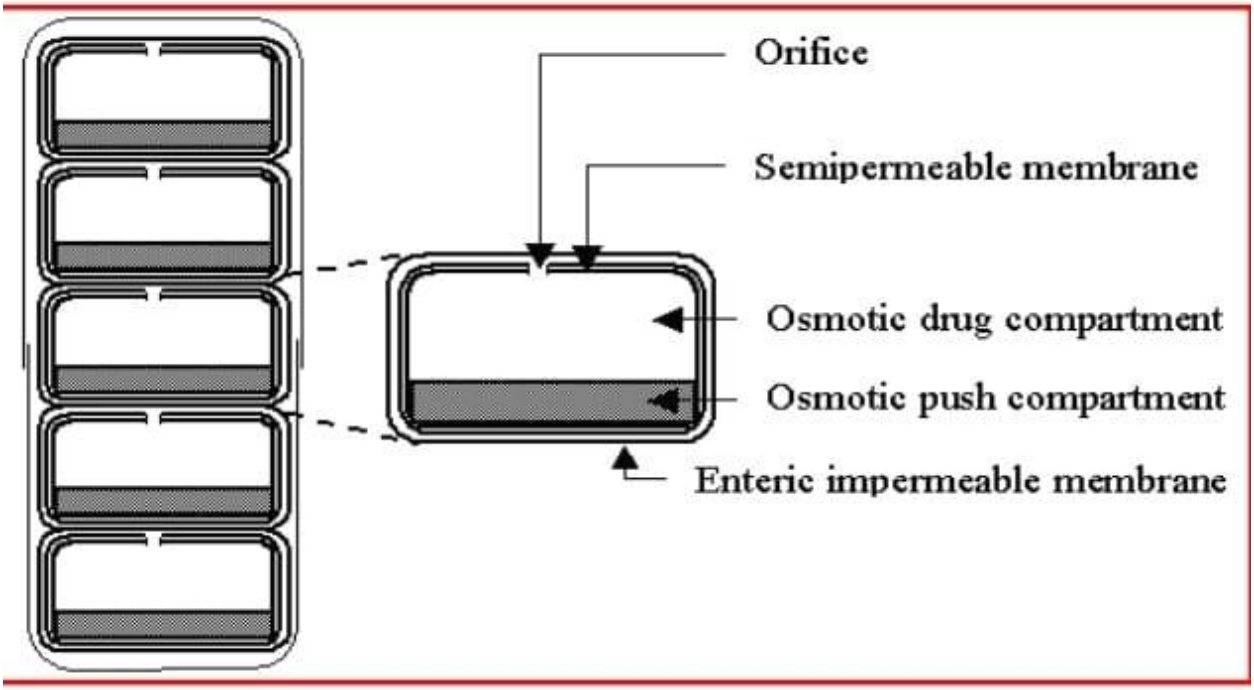
Hydrogels may be defined as the 3-D polymer network which is hydrophilic in nature and because of which it is able to swell in water or other biological fluids. It has the ability to retain a significant amount of fluid in the swollen state49. The property of water absorption of hydrogels is due to the presence of hydrophilic groups such as OH-, -CONH-, -COOH etc. 50.The hydrogels are used as delivery systems because of their ability to allow the passage of drug across its structure. The mechanism of drug release in this kind of systems is diffusion because hydrogels have good permeability for water soluble drugs 51. Hydrogels can be formulated in a number of physical forms like microparticles, coated films and nanoparticles. The commonly used hydrophilic polymers for hydrogels are poly ethylene glycol (PEG), poly vinyl acetate (PVA), poly acetic acid (PAA), Polymethacrylic acid, Polyacrylamide 52. These polymers can absorb water from a fraction to several thousand of their own weight 53. Diffusion controlled release is the considered the primary method of drug release from dosage form 54,55. The mesh size of hydrogels range from 5-100 nm which is much larger than the most drugs. In some cases diffusion of drugs is faster than the hydrogel distension, then swelling is considered the limiting factor for drug release and these systems are called as swelling controlled systems 56. Chemically controlled release is also identified where chemical reaction occurs within the gel matrix which controls the release mentioned in (Table 8). These can be further divided on the basis of the type of chemical reaction occurring during drug release57.Various stimuli sensitive hydrogels like pH, temperature sensitive hydrogels are prepared to target drugs or proteins to colon and other therapeutic agents to tumors58.

Bioadhesive Systems:

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for Bioadhesive systems. Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

Osmotic controlled drug delivery system (OROS-CT):

The OROS-CT (Alza corporation) (Figure 6) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable59. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule60. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable 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 semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hours post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon.[41-44] Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.



In-vitro Evaluation:

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 behavior of formulations at different pH levels. Dissolution tests of a colon- specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunum region of the small intestine, and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. Invitro 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:

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. ii. 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.

Clinical Evaluation:

High frequency capsule Colonoscopy and intubation are the techniques mostly used for the analysis of dosage form inside the body. High frequency capsules are the smooth plastic capsules taken orally. These contain small latex balloon, drug and radiotracer substance. The drug and radiotracer are released by an impulse, and the release is analyzed inside the different parts of GIT. By this technique the absorption properties of drugs in the colon are monitored.

Table 1: Various pharmaceutical approaches to colon targeted drug delivery systems.

Approach	Basic features
1. Covalent linkage of a drug with a carrier	
1.1. Azo conjugates	The drug is conjugated via an azo bond.
1.2. Cyclodextrin conjugates	The drug is conjugated with cyclodextrin.
1.3. Glycoside conjugates	The drug is conjugated with glycoside.
1.4. Glucuronate conjugates	The drug is conjugated with glucuronate.
1.5. Dextran conjugates	The drug is conjugated with dextran.
1.6. Polypeptide conjugates	The drug is conjugated with poly(aspartic acid).
1.7. Polymeric prodrugs	The drug is conjugated with polymer.
2. Approaches to deliver the intact molecule to the colon	
2.1. Coating with polymers	
2.1.1. Coating with pH-sensitive polymers	Formulation coated with enteric polymers releases drug when pH moves towards alkaline range.
2.1.2. Coating with biodegradable polymers	Drug is released following degradation of the polymer due to the action of colonic bacteria.
2.2. Embedding in matrices	
2.2.1. Embedding in biodegradable matrices and hydrogels	The embedded drug in polysaccharide matrices is released by swelling and by the biodegradable action of polysaccharidases.
2.2.2. Embedding in pH-sensitive matrices	Degradation of the pH-sensitive polymer in the GIT releases the embedded drug.
2.3. Timed released systems	Once the multicoated formulation passes the stomach, the drug is released after a lag time of 3-5 h that is equivalent to small intestinal transit time.
2.4. Redox-sensitive polymers	Drug formulated with azo polymer and disulfide polymers that selectively respond to the redox potential of the colon provides colonic delivery.
2.5. Bioadhesive systems	Drug coated with a bioadhesive polymer that selectively provides adhesion to the colonic mucosa may release drug in the colon.
2.6. Coating with microparticles	Drug is linked with microparticles.
2.7. Osmotic controlled drug delivery	Drug is released through semipermeable membrane due to osmotic pressure.

This approach chiefly involves the formation of prodrug,which is formocologically inactive derivative of a parent drug molecule that requires spountanious or enzymatic transformation in the biological environment to release the active drug.

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. (1995) have developed pressure controlled colon-delivery capsules prepared using an ethylcellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for disintegration of the formulation [25]. The system also appeared to depend on capsule size and density. 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. In pressure-controlled ethylcellulose singleunit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human [26].

Limitations and challenges in Colon Targeted Drug Delivery :

The colon is difficult to access due to its location at the distal portion of alimentary canal.

- Lower surface area and relative tightness of the tight junctions in the colon due to continuous blankets can restrict drug transport across the mucosa in to the systemic circulation20 .
- The reliability and delivery efficiency is also doubtful due to presence of wide range of
- pH values and different enzymes present in the GI tract which is encountered by the drugs before reaching the target site21 .
- Colonic contents are considerably viscous because of high water absorption capacity of the colon thereby decreasing the availability of most drugs to absorbtive membrane22 .
- Dissolution is minimal for poorly water soluble drugs because of less fluidity and more viscous contents in the colon than in small intestine23 .

- Drug transport across the mucosa into the systemic circulation is restricted due to lower¬ surface area and relative tightness of tight junctions in the colon21
- .

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine, Balsalazide.
Local action	Pancreatactomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements 5-Flourouracil.
Systemic action	To prevent gastric irritation	NSAIDS
	To prevent first pass metabolism of orally ingested drugs	Steroids
	Oral delivery of peptides	Insulin
	Oral delivery of vaccines	Typhoid

CONCLUSION:

Since past decades, considerable amount of research work has been proposed in the area of colon targeting. There are specific advantages and limitation for the system as mentioned earlier for the targeting drugs, specifically to the diseased colon are minimizing incidence of systemic side effects, lower dose of drug, delivery of the drug only when it is required and International Standard Serial Number (ISSN): 2249-6807 23 Full Text Available On www.ijipls.com holding of the dosage form in its intact form as close as possible to the target site to give maximum concentration drug. The novel approaches are more effective compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially activated system and others. Different polymers natural and synthetic are used to prepare CDDS by various approaches and are evaluated for their efficiency and safety. As concern to the evaluation there is no such standardized dissolution method established for possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, but still x-ray studies and gamma sintagraphy is the effective tool till date to correlate in-vitro/in-vivo data.The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. For colon targeted drug delivery four primary approaches were proposed for CDDS: prodrugs, pH and time dependent systems and micobletriggered drug delivery system. Of these first three approaches is not ideal for CDDS. Novel approaches developed for CDDS are more specific. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. For in vitro evaluation of a colon-specific drug delivery system, it seems that more than one testing method is necessary to characterize drug release and justify system design rationale. Considering the sophistication of colonspecific drug delivery systems and the uncertainty of current dissolution methods in establishing possible in vitro/in vivo correlation, challenges remain for pharmaceutical scientists to develop and

validate a dissolution method that incorporates the physiological features of the colon and yet can be used routinely in an industry setting for the evaluation of CDDS.

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