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COLON TARGETED DRUG DELIVERY SYSTEMS: A NOVEL APPROACH TO DRUG DELIVERY

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Abstract: Targeted drug delivery leads to optimum therapy that meets the patient need by improving the safety and efficiency of the administered drug. Targeting drugs to the colon is one of the contemporary research areas in pharmaceutical sciences. Colon target drug delivery system has been gained great importance not only for the treatment of local diseases but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti- diabetic agents. This review article discusses, in brief, introduction to targeted drug delivery system, anatomy and physiology of the colon and approaches utilized for colon specific drug delivery. This article also discusses advantages & limitations of the different approaches & evaluation for site specific drug delivery to colon. It is a challenging area for future research and holds lots of promises for novel and efficient approach for targeted drug delivery system.

Keywords: Colon Targeted Drug Delivery System, Advantages, Limitations, Approaches, Evaluation.

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INTRODUCTION

To date, oral delivery is still the preferred route of drug administration, especially for chronic therapies where repeated administration is required. Oral administration offers patients less pain, greater convenience, higher likelihood of compliance, and reduced risk of cross infection and needle stick injuries. Thus, formulations of oral drug delivery continue to dominate more than half of the drug delivery market share. Despite these advantages, the oral route is not amenable to the administration of most protein and polypeptide drug available today, due to their high susceptibility to digestive enzymes in the gastrointestinal tract (GIT), poor absorption, and their limited ability to transport across the intestinal epithelial barrier. As a result, new strategies of drug delivery have been developed to overcome obstacles encountered by oral delivery. Among these strategies, colon-specific delivery has been extensively studied from the last two decades [1].

COLON TARGETED DRUG DELIVERY SYSTEM (CTDDS):

The colonic region of GIT is one area that would benefit from the development and use of such modified release technologies. Although considered by many to be an innocuous organ that has simple functions in the form of water and electrolyte absorption and the formation, storage and expulsion of faecal material, the colon is vulnerable to a number of disorders including ulcerative colitis, crohn's disease, irritable bowel syndrome and carcinomas [2]. Targeted drug delivery to the colon, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the GIT but rapidly releases in the colon following oral administration. Specifically delivering drug to the colon, a lot of benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases [3].

In addition to local therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded or poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. For successful colonic drug delivery it requires careful consideration of a number of factors, including the properties of drug, the type of delivery system and its interaction with the healthy or diseased gut. For instance, regardless of whether a local or systemic effect is required, the administered drug must first dissolve in the luminal fluids of the colon [2].

Colon an area where the protein drugs are free from the attack of numerous protease, is thought to be an ideal location to direct the drugs into the blood stream and the immune system [1]. The representatives of colon specific diseases are inflammatory bowel disease (IBD), including ulcerative colitis and crohn's disease, irritable bowel syndromes (IBS), constipation

and colorectal carcinoma. Most of the conventional drug delivery system for treating the colon disorders is failing as the drugs do not reach the site of action in appropriate concentrations. Thus, an effective and safe therapy of these colonic disorders, using site specific drug delivery system is a challenging task to the pharmaceutical technologists [4].

In the recent times the colon specific delivery is also gaining importance for the systemic delivery of protein and peptide drugs and local action drugs. The peptide and protein drugs are destroyed and inactivated in acidic environment of the stomach and /or by pancreatic enzymes in the small intestine [3].

Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed. Suppositories are only effective in the rectum because of the confined spread and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore oral administration is preferred, but for this purpose, many physiologic barriers have to be overcome. Absorption or degradation of the active ingredient in the upper part of the GIT is the major obstacle and must be circumvented for successful colonic drug delivery [4].

ADVANTAGES OF CTDDS [5]:

1) Delivery of drug in its intact form as close as possible to the target site,

2) The ability to cut down the conventional dose,

3) Reduced incidence of adverse side effects,

4) Due to negligible activity of brush border membrane peptidase and less activity of pancreatic enzymes,

5) Low hostile environment, the colonic transit time is long (20-30 hrs) and colonic tissue highly responsive to the action of absorption enhancers. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make the colon a promising site for the delivery of protein and peptide drugs for systemic absorption.

LIMITATIONS OF CTDDS [5]:

1) Multiple manufacturing steps.

2) Incomplete release rate.

3) The resident microflora could also affect colonic performance via metabolic degradation of the drug.

4) Non availability of an appropriate dissolution testing method to evaluate the dosage form *in-vitro*.

5) Bioavailability of drug may be low due to potentially binding of drug in a non-specific way to dietary residues, mucus or faecal matter.

FACTORS TO BE CONSIDERED DURING DESIGN OF CTDDS:

In order to get a CTDDS it is essential to familiarize with the various factors that influence the targeted drug delivery.

These factors are:

A. Anatomy and physiology of GIT

B. Anatomy and physiology of colon

C. Factors influencing bioavailability of drug in colon.[5]

A. Anatomy and Physiology of GIT [6]:

The GIT, also called the alimentary canal, is a muscular digestive tube that winds through the body. The GIT is a selective barrier between the environment and the systemic circulation, which functions to digest dietary food, to absorb nutrients, electrolytes and fluids, and to prevent the absorption of potentially harmful substances. The small intestine is the longest part of the GIT where most enzymatic digestion and virtually all absorption occur. Most digestive enzymes that operate within the small intestine are secreted by the pancreas peristalsis propels chime through the small intestine in about 3- 6 hrs. The large intestine is the last major subdivisions of the GIT. The digested materials that reach the large intestine contain few nutrients, but the residues remain here for 12- 24 hrs. Major regions of the large intestine are the cecum, colon, rectum and anal canal as shown in figure 1.
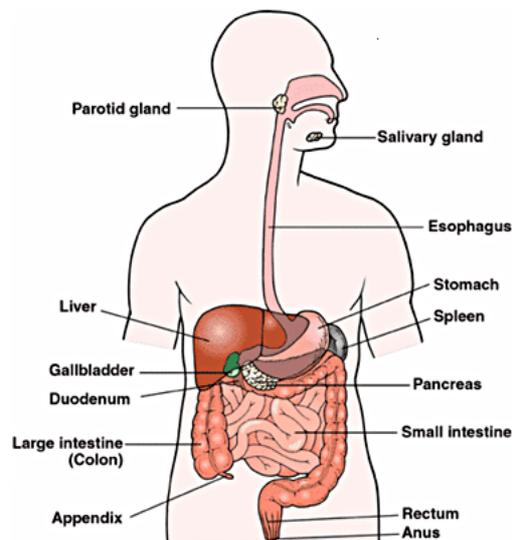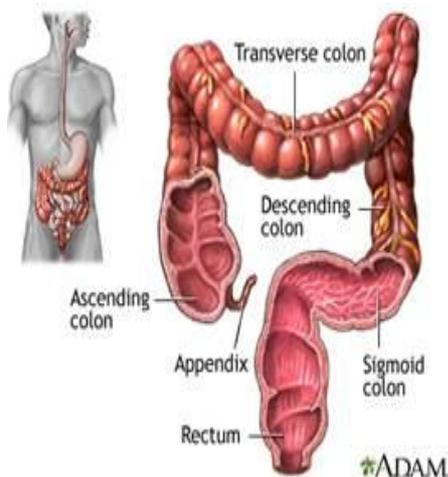
Fig. no. 1: GIT Tract

B. Anatomy and Physiology of Colon:

1. Structure of Colon [7,8]:

The colon forms the lower part of the GIT which extends from the ileo ceacal junction to the anus. The entire colon is about 5 feet (150 cm) long which is divided into following groups and shown in figure 2:

Fig. no. 2: Structure of Colon

a. Ascending Colon:

20- 25 cm long located behind the peritoneum hepatic flexure lies under right lobe of the liver.

b. Cecum (Proximal Right Colon):

6 X 9 cm pouch covered with peritoneum appendix a vermiform (worm like) diverticulum's located in the lower cecum.

c. Transverse Colon:

Lies anterior in abdomen, attached to gastro colic ligament splenic flexure near tail of pancreas and spleen.

Table 1: Length of different parts in Colon

Sr. No.	Large Intestine	Length (cm)
1	Cecum	6-9
2	Ascending Colon	20-25
3	Descending Colon	10-15
4	Transverse Colon	40-45
5	Sigmoid Colon	35-40
6	Rectum	12
7	Anal Canal	3

d. Descending Colon:

10- 15 cm long located behind the peritoneum. After it enters the true pelvis it is known as sigmoid colon.

e. Sigmoid Colon:

This part describes an S- shaped curve in the pelvis that continues downwards to become the rectum.

f. Rectum:

This is slightly dilated section of the colon about 13 cm long. It leads from the sigmoid colon and terminates in the anal canal.

g. Anal Canal:

This is the short passage about 3.8 cm long and leads from the rectum to the exterior.

The length of different parts of the colon is given in table 1.

2. Functions of the Colon [9]:

The major function of the colon is the consolidation of the intestinal contents into faeces by the absorption of water and electrolytes and to store the faeces until excretion. The absorptive capacity is very high; each day about 2000 ml of fluid enters the colon through the ileo-ceacal valve from which more than 90% of the fluid is absorbed.

3. pH in the Colon [10]:

The pH of the GIT is subjected to both inter and intra subject variations. Table 2 gives an overview of the pH of the GIT:

Table No. 2: Average pH in the GIT

Sr. No.	Location	pH	
1	Oral Cavity	6.2- 7.4	
2	Esophagus	5.0- 6.0	
3	Stomach	Fasted condition: 1.5- 2.0 conditions: 3.0- 5.0	Fed
4	Small Intestine	Jejunum: 5.0- 6.5 6.0- 7.5	Ileum:
5	Large Intestine	Right colon: 6.4 colon and left colon: 6.0- 7.6	Mid

4. Gastro Intestinal Transit: [11]

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. Diseases affecting colonic transit have important implications for drug delivery, diarrhoea increases colonic transit and constipation decreases it. However, in most conditions, transit time appears to remain reasonably constant. The transit time of small dosage forms in GIT are given in table 3:

Table 3: Transit time of dosage forms in GIT

Sr. No.	Organ	Transit time (hrs)
1	Stomach	<1 (fasting) >3 (fed)
2	Small intestine	3- 4
3	Large intestine	12

5. Colonic Absorption: [12]

The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10- 24 hrs). Drugs shown to be well absorbed include glibenclamide, diclofenac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil and atenolol.

Factors affecting colonic absorption:

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

b. Colonic residence time as commanded by GIT motility.

c. Degradation by bacterial enzymes and metabolite products.

d. Local physiological action of drug.

e. Selective and non-selective binding to mucus.

f. Disease state.

g. Transit through GIT.

6. Colonic Microflora: [13]

A large number of aerobic and anaerobic bacteria are present throughout the length of the GIT.

The bacterial count (Colony forming unit (CFU) /ml) in different regions of the GIT is:

a. Stomach- $0-10^3$ CFU/ml

b. Jejunum- $0-10^5$ CFU/ml

c. Ileum- 10^3-10^7 CFU/ml

d. Colon- 10^{11}-10^{12} CFU/ml

These bacteria carry out a variety of metabolic reactions like hydrolysis, decarboxylation, dealkylation and dehalogenation. The metabolic activity of the microflora can be modified by various factors such as age, GI disease, intake of drugs and fermentation of dietary residues. This may lead to inactivation of drugs and enhancement of the drug action and side effects.

Table 4(a) & 4(b) shows the various enzymes present in the human colon that metabolizes the drug.

C. Factors Influencing Bioavailability of Drug in Colon [14]:

There are basically three factors influencing bioavailability of drug in colon. These are:

1. Physicochemical parameters:

a. pKa of the drug, lipohilicity and gastrointestinal pH:

The pH partition explains the process of drug absorption from the GIT and its distribution across all biological membranes. The theory states that for drug molecules of molecular weight greater than 100, which are primarily transported across the bio membrane by passive diffusion, the process of absorption is governed by:

- The dissociation constant (pKa) of the drug

- The lipid solubility of unionized drug

Table 4(a): Drug metabolizing enzymes in the human colon that catalyze reductive reaction

Enzyme	Microorganism	Metabolic Reaction Catalyzed
Nitroreductase	E.coli, Bacteroids	Reduced aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E.coli	Reduced cleavage of azo compounds
N-oxidereductase, Sulfoxidereductase	E.coli	Reduced N-oxides and sulfoxides
Hydrogenase	Clostridia, Lactobacilli	Reduced carbonyl groups and aliphatic double bonds

Table 4(b): Drug metabolizing enzymes in the human colon that catalyze hydrolytic reaction

Enzyme	Microorganism	Metabolic Reaction Catalyzed
Esterases and Amidases	E.coli, P.vulgaris, B.subtilis, B.mycoides	Cleavage of esters or amidases of carboxylic acids
Glucosidase	Clostridia, Eubacteria	Cleavage of b-glycosidases of alcohols and phenols
Glucuronidase	E.coli, A.aerogenes	Cleavage of b-glycosidases of alcohols and phenols
Sulfatase	Eubacteria, Streptococci	Cleavage of o-sulfates and sulfamates

- The pH at the absorption site.

Since most of the drugs are weak electrolytes (weak acids or weak bases), their degree of ionization depends upon the pH of the biological fluid. If the pH on either side of the membrane is different, then the compartment whose pH favours greater ionization of the drug will contain greater amount of drug, and only the unionized form of drug, if sufficiently lipid soluble, can permeate the membrane passively until the concentration of unionized drug on either side of the membrane becomes equal i.e. until equilibrium is attained.

b. Drug Stability:

A drug for oral use may destabilize either during its shelf life or in the GIT. Two major stability problems resulting in poor bioavailability of an orally administered drug are: degradation of drug into inactive form and interaction with one or more different components either of the dosage form or those present in the GIT that form a complex which is poorly soluble or is un-absorbable.

2. Pharmaceutical Parameters:

a. Drug Candidate:

Drugs which show poor absorption in the stomach and intestine are most suitable for colon delivery. Drugs such as theophylline, nifedipine, ibuprofen and low molecular weight peptides have been shown to be effectively absorbed from the colon.

b. Drug Carrier:

The selection of carrier depends on the 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 influences the carrier selection.

3. Patient Related Parameters:

a. Gastric Emptying:

The passage from the stomach to the intestine is called as gastric emptying. It can also be a rate-limiting step in drug absorption. Factors which influence gastric emptying are volume of meal, composition of meal, emotional state, body posture etc.

b. Age:

In infants the gastric pH is high and intestinal surface and blood flow to the GIT is low resulting in comparison to adults. In elderly persons, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area and GI blood flow.

APPROACHES FOR TARGETING DRUGS TO THE COLON:

By definition, an oral colonic delivery system should retard drug release in the stomach and small intestine but allow complete release in the colon.

The system designed for the drug delivery in the colon may be single or multiple unit dosage form which is based on the core being coated with one or more successive layers.

Single unit colon targeted drug delivery systems may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Recently, much emphasis is being laid on the development of the multiparticulate dosage forms in comparison to single unit systems because of the potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [15, 16].

Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. The use of multiparticulate drug delivery systems in preference to single unit dosage forms for colon targeting showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GIT easily, leading to less inter and intra subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GIT and also ensure more uniform drug absorption [16, 17].

In general approaches used for colon targeted drug delivery are:

A. Primary approaches:

1. pH sensitive polymer coated drug delivery to colon

2. Delayed (time controlled release system) release drug delivery to colon

3. Microbiologically triggered drug delivery to colon

a. Prodrug approach for drug delivery to colon

b. Azo-polymeric approach for drug delivery to colon

c. Polysaccharide based approach for drug delivery to colon

B. Newly developed approaches:

a) Pressure controlled drug delivery system (PCDDS)

b) CODES[TM] (a novel colon targeted drug delivery system)

c) Osmotic controlled drug delivery to colon (OROS-CT)

A. Primary Approaches for CTDDS:

1. pH Sensitive Polymer Coated Drug Delivery to Colon [18]:

This approach has been based upon the fact that there is variation of pH gradient in the entire GIT that increases progressively from the stomach (pH 1.5-3.5) and small intestine (pH 5.5-6.8) to the colon (pH 6.4-7.0). pH sensitive polymers, especially with carboxyl group have been employed in colon targeting because they are insoluble at low pH but soluble at high pH values. Table 5 gives the list of various pH dependent polymers.

2. Delayed (Time Controlled Release System) Release Drug Delivery to Colon [18]:

This approach has been based on the transit time of the drug in the different regions of GIT. It involves delaying the release of drug until it enters into the colon. A lag-time of 5 hrs is usually considered sufficient since small intestine transit is about 3-4 hrs, which is relatively constant and hardly affected by the nature of formulation administered.

3. Microbially Triggered Drug Delivery to Colon [19]:

This approach has been based upon the fact that there is the presence of biodegradable enzyme in the colon that has been produced by colonic microflora. Thus by using the biodegradable polymers the colon targeting can be carried out.

a. Pro-drug Approach for Drug Delivery to Colon:

A prodrug is a pharmacologically inactive derivative of the drug molecule that becomes active only after it is metabolized by the body. Prodrug approach is an outcome of the covalent linkage of drug with carrier, thus upon oral administration the moiety remains intact in the stomach and small intestine but in the colon drug release is triggered by high activity of certain enzymes in comparison to stomach and small intestine.

b. Azo-Polymeric Approach for Drug Delivery to Colon:

Sub-synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. These have been evaluated for CDDS. These have been found to be similarly susceptible to cleavage by the azo-reductase in the large bowel. Coating of peptide capsules with polymers cross linked with azo-aromatic group has 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.

Table 5: Various pH dependent coating

Polymer	Threshold pH
Eudragit L-100	6.8
Eudragit S-100	7.0
Eudragit L-30 D	5.6
Eudragit FS-30 D	6.8
Eudragit L 100-55	5.5
Hydroxy Propyl Methyl Cellulose Phthalate	4.5-4.8
Hydroxy Propyl Methyl Cellulose Phthalate 50	5.2
Hydroxy Propyl Methyl Cellulose Phthalate 55	5.4
Cellulose Acetate Trimellate	5.0
Cellulose Acetate Phthalate	4.8

c.   Polysaccharide Based Approach for Drug Delivery to Colon:

Use of naturally occurring polysaccharides is attracting lot of attention for drug targeting to the colon since these polymers of monosaccharides are found in abundance, are inexpensive and are available in a variety of structures with varied properties. They can be easily modified chemically and bio-chemically and are highly stable, safe, nontoxic, hydrophilic, gel forming and biodegradable. These include naturally

occurring polysaccharides obtained from plant (guar gum, inulin) animal (chitosan) algal (alginates) or microbial (dextran) origin. These are broken down by the colonic microflora to simple saccharides. So these fall into the category of "generally regarded as safe" (GRAS).

B.   Newly Developed Approaches for CDDS [20]:

1.   Pressure-Controlled Drug Delivery Systems:

This approach relies on the strong peristaltic waves in the colon that lead to a temporarily increased luminal pressure. Takaya et al. (1995) have developed pressure controlled colon delivery capsules by using water insoluble polymer ethyl cellulose. The release of drug occurs following disintegration of water soluble polymer capsule as a result of pressure in the lumen of colon.

2.   Novel CTDDS (CODESTM):

CODESTM is 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 form site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with an acid soluble material Eudragit E and then subsequently over coated 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 passage through the alkaline pH of the small intestine. Once the tablet arrives in the colon the bacteria will enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.

3.   Osmotic Controlled Drug Delivery (ORDS-CT):

The OROS-CT system either comprises 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. Upon ingestion the hard gelatin shell dissolves the enteric coating delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH>7. As a result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon.

EVALUATION PARAMETERS FOR CTDDS [18]:

In vitro Evaluation:

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

1.   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. 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)

2.   In vitro enzymatic test: For this there are 2 tests:

a.   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.

b.   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. Example 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 vascularizes within 4 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 gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

1.   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.

2.   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 and gammascintigraphic studies (pharmacoscintigraphy).

LIMITATION AND CHALLENGES [21]:

1.   One challenge in the development of colon-specific drug delivery system is to establish an appropriate dissolution method in designing in vitro system. Due to the rationale after a colon delivery system is quite diverse. As, a site for delivery offers a near neutral pH, reduced digestive enzymes activity, a long transit time, and increased responsiveness to absorption enhancers, hence targeting is complicated, with reliability and delivery efficiency.

2.   Limiting factors for poorly soluble drug as the fluid contents in colon is much lower and it is more viscous than in upper part of GI tract, for successful delivery through this site, drugs require to be in solution form before it arrives to colon and/or it should dissolve in luminal fluid of colon.

3.   The resident microflora could also affect colonic performances via metabolic degradation of drug.

4.   Lower surface area and relative 'tightness' of the tight junction in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

FUTURE PROSPECTS [21]:

Recent reports indicate interest in colon as a site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for   oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines.

However, drug release is not the end point of oral delivery. The bioavailability of protein drugs delivered at the colon site needs to address. The use of drug absorption enhancers into the drug delivery systems is likely to enhance therapeutic efficacy. Studies on drug absorption by the intestinal system have focused on drug transporters that mediate drug influx and efflux and agents which can enhance drug absorption. The colon segment is designed by nature mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

CONCLUSION:

The discovery of novel drug delivery system brings the green revolution in colon targeting. It lights up the black box by curing diseases either by virtue of local absorption or systemic absorption. Successful colonic delivery could be achieved by protecting the drug from the upper GIT warriors. Various approaches have been designed for colonic drug delivery among these microbial triggered drug delivery appears more promising since there is an increased amount of bacterial population and associated enzyme activity in the colon represent a non-continuous event, independent of GI transit time.

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