Review Article

Colon targeted drug delivery system: A review on current approaches

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ABSTRACT

The colon is the terminal part of the GIT which has gained as a potential site for delivery of various novel therapeutic drugs i.e. peptides. Colon targeted drug delivery system (CDDS) is an Promising tool for treatment of inflammatory bowel diseases such as ulcerative colitis, crohn's disease, colon cancer, amobebiasis by both systemic and topical delivery of dug. This article review a detailed study about disease of colon, diagnosis of diseases of colon, anatomy of colon, factors affecting drug absorption and different approaches of colon including some current approaches like Pulsinicap system, Port system, Probiotic approach, Chronotropic system, Colal-pred system, Enterion capsule Technology Muliparticulate system and some past studies on colon drug delivery with evaluation method for site specific drug delivery to colon.

1. Introduction

The oral route is considered to be most convenient for the administration of drugs to patients. Where drug normally dissolves in the gastro-intestinal (GI) fluids and is absorbed from these regions of the gastro-intestinal tract (GIT), and both process depends upon the physicochemical properties of the drug. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon such as colon cancer, ulcerative colitis, crohn's disease and inflammatory bowel disease whereby high local concentration can be achieved while minimizing side effects and also used in treatment of Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon. The colon specific drug delivery system (CDDS) should be capable of releasing the drug in to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the reaches the colon. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug molecule may have an improved bioavailability, CDDS has been employ to achieve following objectives i) Sustained delivery to reduce dosing frequency ii) Delay deliver of drug to achieve high concentration in treatment of disease of distal gut iii) to delay deliver to a time appropriate to treat acute phase of disease iv) deliver drug to that region that is less hostile metabolically, drug which is acid and enzyme labile such as proteins.

1.1 *Benefits of colon target DDS*

- Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn's disease etc.)
- By producing the 'friendlier' environment for peptides and proteins as compared to upper gastrointestinal tract
- Minimizing extensive first pass metabolism of steroids.
- Preventing the gastric irritation produced by oral administration of NSAIDS.
- Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.

1.2 *Limitation of colon target DDS*

- Difficult to access colon.
- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous

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than in upper GIT, which is the limiting factor for poorly soluble drugs.

- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.[1]

1.3 *Need for colon targeting drug delivery*

- Targeted drug delivery to the colon to ensure that direct treatment at the disease site (local delivery), at lower dosing and fewer systemic side effects [2].
- 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 [3].
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases [3].
- 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 [4].
- 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 [5].
- 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 [5].

1.4 *Anatomy of the Large Intestine*

The large intestine, which is about 1.5 m long and 6.5 cm in diameter, extends from the ileum to the anus. It is attached to the posterior abdominal wall by its mesocolon. Structurally, four major regions of the large intestine are the cecum, colon, rectum, and anal canal. The opening from the ileum into the large intestine is guarded by ileocecal sphincter, which allows passing of materials form small intestine into the large intestine. Hanging inferior to the ileocecal valve is the cecum, a small pouch about 6 cm long. The open end of the cecum attach with a long tube called the colon, which is divided into ascending, transverse, descending, and sigmoid portions. The ascending colon ascends on the right side of the abdomen, reaches the inferior surface of the liver and continues across the abdomen to the left side as the transverse colon. It curves beneath the inferior end of the spleen on the left side and passes inferiorly toward iliac crest as the descending colon. The sigmoid colon begins near the left iliac crest and terminates as the rectum. Rectum is 20 cm long last portion of the GI tract, lies anterior to the sacrum and coccyx. The terminal portion of the rectum is called the anal canal 2-3cm long. The mucous membrane of this portion is arranged in longitudinal folds called anal columns that contain a network of arteries and veins. The opening of the anal canal to the exterior, called the anus, is guarded by an internal anal sphincter of smooth muscle and an external anal sphincter of skeletal muscle. Large intestine promotes growth of various microorganisms by offering friendly environment which pay a key role in digestion of proteins, carbohydrates, into their simpler form, by secreting various enzymes. Large intestine help in maintaining optimum body water balance through the absorption of water, about 100-200mL fluid via osmosis, also absorbs ions like sodium, chloride and vitamins like B and K (Figure 1a and 1b).
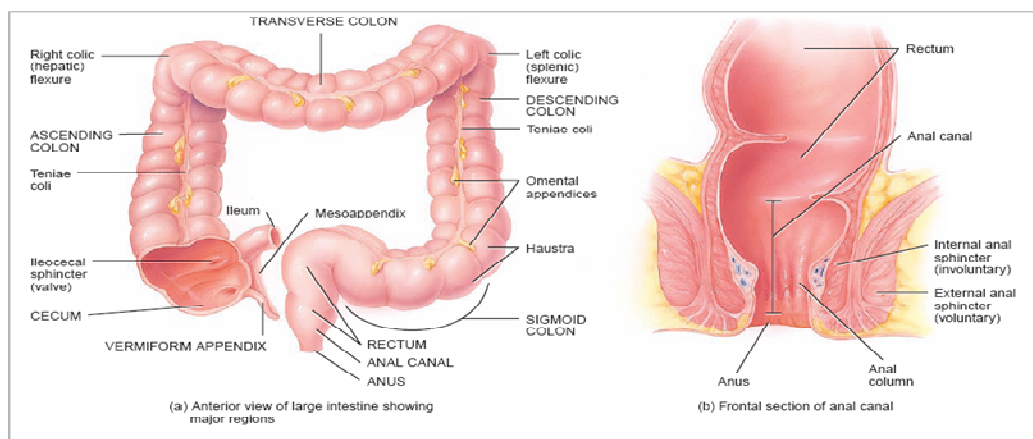

Figure 1a: Anatomy of the Large Intestine[6]

1.5 *Diseases of colon*

I.*Crohn's Disease*: Idiopathic chronic ulcerative inflammatory bowel disease, characterized by granulomatous infalammation.

Segment of terminal ileum or colon mostly affected or any part of GIT may associate with it. [7]

II. *Ulcerative Colitis***:** Acute and chronic ulcerative inflammation of mucosa and submucosa of rectum and descending part of colon some time entire length of colon may involve. Characterized by acute flare-up, diarrhoea, bleeding ulcer, pus discharge etc. [7]

III. *Amoebiasis***:** It is due to infection by Entamoeba histolytica. Primarily effects large intestine, ingestion of cyst form of parasite the cyst wall dissolved in the small intestine from where emoebae get liberate which pass in to large intestine and invade epithelium of the mucosa and then submucosa produce flask shape ulcer. [8]

IV. *Diverticulosis***:** It is outpouching or herniation of mucosa and submucosa with clinical symptoms like abdominal pain, constipation and intermittent bleeding. [9]

V. *Diverticulitis***:** It is inflammatous form of diverculi result in abdominal pain and constipation. [9]

VI. *Colon Bleeding***:** Vericosities of haemorrhoidal veinsm, there are of two types i) Internal pile: dilation of superior heammorrohoid plexus, ii) External pile: dilation of inferior plexus. These cause bleeding which commonly seen in stool. [10]

VII. *Salmonellosis***:** Generally cause by non-typhoidal salmonella after ingestion of contaminated food. Parasite infect the intestine and cause diarrhea and stomach cramp, physician give antibiotic which eradicate such infection. [11]

VIII. *Hirschsprung's disease***:** It is sever form of intestinal constipation in which bowel movement occurs once or twice in a week. [12]

IX. *Diarrhoea***:** Is an increase in the frequency, volume, and fluid content of the feces caused by increased motility of and decreased absorption by the intestines, and feces pass too quickly through the large intestine result in dehydration and electrolyte imbalances. Excessive motility may be caused by lactose intolerance, stress, and microbes that irritate the gastrointestinal mucosa, some time it self limited.

X. *Traveler's Diarrhoea***:** Bacteria such as enterotoxigenic Escherichia coli, enteroaggregative E. coli, Campylobacter, Salmonella, and Shigella are common causes of traveler's diarrhea which produce symptoms like loose stool, nausea, vomiting and fever. [13]

XI. *Coloractal Polyps*: polyps is any growth or mass protruding from the mucus membrane into the lumen, most common In large intestine and rectosigmoid colon than proximal colon. It can be both neoplastic and non neoplastic. [14]

XII. *Colon Cancer***:** Colon cancer is the fourth most common cancer globally with 639,000 deaths reported annually. [15]

1.6 Method of colorectal examination

II. *Digital rectal examination***:** The physician inserts a finger into the rectum to feel for polyps or other abnormalities.

III. *Fecal occult blood testing* **(FOBT):** A sample of feces is tested for examine microscopic amounts of blood. This could be an indication of a bleeding tumor, although there are many other causes of blood in the stool as well.

IV. *Barium enema***:** A suspension of barium sulfate is injected through the anus, which coats the rectum and colon and makes these areas appear opaque on an x-ray. When an x-ray is subsequently taken, abnormalities can be seen. In a double contrast barium enema, air is pumped into the rectum.

V. *Sigmoidoscopy***:** In this procedure a sigmoidoscope, which is a thin, lighted tube with a camera at the end, is inserted into the rectum and guided into the sigmoid colon. This test helps in detecting polyps, tumors, and other abnormalities in the rectum and sigmoid colon.

VI. *Colonoscopy***:** Complete examination of colon done by tube equipped with microscopic camera, highly sensitive for detection of polyps and carcinomas.

VII. **Fiberoptic colonoscopy:** Specific for distal colonic lesion, entire colon and rectum is examined. Like a sigmoidoscopy, the test is performed with a thin, lighted tube with a camera attached, but in a colonoscopy, the tube is guided further into the colon to visualize the entire colon. The colonoscope pumps air into the colon, while the video camera records the images on a screen for the doctor to see during the procedure. If polyps or other abnormal tissue are discovered, they can be removed and biopsied. [16]

VIII. *Colonic pH***:** It has been seen that the pH of gastrointestinal track drastically change from stomach to small intestine and large intestine as it given in table no 1. pH of GIT also affected by type of diet, food taken and disease state. Researcher taking benefits of these changes in pH for delivering the drug to the colon by using pH sensitive enteric coating polymer in order to achieve both local and systemic effect.

Table no: 1. Showing pH of gastrointestinal tract [17]

Region of Gastrointestinal tract	pH
Stomach	1.5 in fasting and 2-5 in fed condition
Small intestine	pH
Duodenum	6.1 in fasting and 5.4 in fed condition
jejunum	5.4
Ileum	7.8
Large intestine	5.5-7
Rectum	7-8

1.7 Transit through GIT

Orally taken dosage form first enters into stomach and small intestine and then reach colon. The nature and pH of the stomach affect the drug release and absorption. In order to successfully deliver tablet to colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Gastrointestinal transit varies from 1 hr to 3 hrs depending upon the condition fasting or non-fasting respectively. Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form. The mean transit time of the dosage form is about 3-4 hours in order to reach the ileocecal junction and the time period is consistent. During this time the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. Total time for transit tends to be highly variable and influenced by number of factors such as diet particularly dietary fiber content, mobility, stress, disease condition and drugs. The colonic transit time is ranging from 20 to 30 hours, can be increase in presence of active disease 50 to 70 hours. Longer residence time with subsequent longer transit time and the contact of dosage form with micro flora in colon govern the release and improve absorption of drug from dosage form. [18]

1.8 Colonic Absorption:

Absorption of drug through colon follow both paracellular and tarncellular routes.

- Paracellular route
  Here the drug molecule absorb through the colonocytes.
  Lipophilic drug absorb through this route.
- Transcellular route
  Here drug molecule transport through the tight junction between the colonocytes.
  Hydrophilic drug absorb through this route.

1.9 Drug which well absorbed

- glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol and oxyprenolol.

1.10 Drug which poorly absorbed

- *furosemide, pyretanide, buflomedil*, atenolol. [19]

1.11 Factor affecting drug absorption

1. **Physiochemical properties of drug**
   a. *Drug solubility and dissolution rate*
      For absorption of hydrophobic drug such as griseofulvin, spironolactone dissolution of drug is the rate determining step and the rate of drug permeation across the biological membrane is the rate determining step in absorption of hydrophilic dug.

   b. *Particle size and effective surface area*
      Particle size and surface area is inversely proportional each other e.g.; smaller the particle size greater its surface area. There are two types of surface area i) Absolute surface area is the total area of solid particle, ii) Effective surface area is the area of solid surface actually expose to dissolution media. According to Noyes Whitney theory of dissolution it has been clear that solid particle which has larger surface area has high dissolution rate.

   c. *Polymorphism*
      Is the phenomena where crystal which exist in more than one crystalline form is called polymorphism, and they differ from each other with respect to their physical properties like solubility, melting point, density, hardness, compression characteristics. Stable form of polymorph has less aqueous solubility since it is at lowest energy state and has highest melting point. Meta stable form has highest energy state and lowest melting point hence has high aqueous solubility and better bioavailability. Amorphous form has greater aqueous solubility than crystalline form because it has highest energy state:
      Amorphous > Metastable > Stable

   d. *Pseudopolymorph*
      Where solvent molecule are incorporate in crystal lattice of solid are called solvate, solvate can be exist in different crystalline form called Pseudopolymorphs, when solvent is association with the drug is water the solvate known as a hydrate. Anhydrous form of drug has greater aqueous solubility than hydrate, because hydrate already in association with waters therefore less energy for crystal to break.

   e. *Drug lipophilicity*
      Lipophilic drug better absorb than hydrophilic drug.

   f. *Drug stability*
      Poor bioavailability is due to degradation of drug in to inactivate form or drug interaction between excipients and formation of complex due to interaction between GI contain which is poorly absorbed from GI.

2. **Patient related factors**

a. *Age*
Infants has high gastric pH and intestinal surface area and low blood supply to GI result in altered absorption than elderly patient which has low gastric pH and intestinal surface area.

b. *Gastric emptying time*
Passage of food from stomach to the small intestine is called gastric emptying. Several factors which effect gastric emptying time are following:

• *Meal volume*
Larger the bulk of meal longer the gastric emptying times.

• *Composition of meal*
Fatty meal delayed gastric emptying time.

• *Physical state of meal*

Solid meal takes longer time to emptying stomach.
• *Body posture*
Lying right side favored gastric emptying time.
• *Emotional state*
Stress and anxiety promote gastric motility whereas depression retard it.

c. *Drug*
Antacids, anticholinergic, narcotic analgesic, retard gastric emptying whereas metoclopramide, domperidone promote gastric emptying time.

d. *GI pH*
There is different in hydrogen ion concentration between the stomach and colonic fluid, which effect absorption of several drugs.

Table: 2. Effect of drug pk$_a$ and GI pH on Drug Absorption [20]

Drug	pK$_A$	Site of absorption
Weak acidic drug	**pK$_a$> 8.0**	Unionisezd at all pH, absorbed through entire length of GI
pentobarbital	8.1	
hexobarbital	8.2	
Moderately Weak acidic	**pK$_a$ 2.5 to 7.5**	Unionisezd at gastric pH but ionized at intestinal pH, better absorbed from stomach.
Cloxacillin	2.7	
Asprin	3.5	
Stronger acid	**pK$_a$ < 2.5**	Ionized at all pH, poorly absorbed from GI
Disodium cromogylate	2.0	
Very weak base	**pK$_a$ < 5.0**	Unionisezd at all pH absorbed through entire length of GI
oxazepam	1.7	
diazepam	3.7	
Moderately Weak base	**pK$_a$ 5 to11.0**	Ionized at gastric pH, relatively unionized at intestinal pH, better absorbed from intestine
Reserpine	6.6	
Heroin	7.8	
Stronger base	**pK$_a$ >11.0**	Ionized at all pH, poorly absorbed from GI
Guanethidine	11.7	
mecamylamine	11.2	

e. *Disease state*
It has been seen that presence of following disease can affect drug release and absorption in gastrointestinal tract.

Table no 3: Effect of disease on drug absorption. [21]

Disease	Colonic absorption
Diarrhea	Hypermotility and frequent passage of hypertonic liquid feces significantly rdeuces drug absorption and release.
Colon cancer, Inflammatory Bowel Diseases (crohn's disease and ulcerative colitis)	Diarrhoea, fever, anaemia, obstruction of lymphatic drainage and hyperplasia of lymphoid tissue, which are observed in this condition may affect the drug release and absorption. The inflammatory response extends from mucosa to serosa through intestinal wall. Impairment of lymphatic drainage causes malabsorption of fats and highly lipophilic drugs. Thickening of mucosa and submucosa may reduce surface area and obstruct diffusion.
Constipation	Decreased peristaltic movement of bowel decreases diffusion and availability of drug at absorption sites. Severe constipation reduces bowel movement once or twice a week and interferes with the movement of formulations.
GIT infections	protozoal and bacterial infections causes extremely low transit time and increased mucus production, interferes with localization of drug and absorption. Toxins produced may obstruct diffusion process.
Cardiovascular disease	Intestinal edema decrease blood flow to GI result in poor absorption.

2.1 Drug candidates for colon targeting

- It should poorly absorb form stomach and small intestine.
- It should be compatible with carrier molecule and easily biotransform in large intestine
- It should be stable at alkaline pH of GIT.
- It should have both local and systemic effects.
- Drug use in treatment of various intestinal disorders such as ulcerative colitis, amoebiasis and colon cancer, inflammatory boweldisease,diarrhea.

2.2 Colonic Microflora

Over 400 different species of bacteria found in human colon with population of 10^{11} to 10^{12} CFU/ml. The main species include Bacteroides, Bifidobacterium, Eubacterium, and

Lactobacillus proximal colon contain highest growth of microbial load they produce reductive and hydrolytic enzyme which ferment carbohydrate, protein, bile acid, steroid. The non-starch polysaccharides are fermented during transit through colon via enzymatic action of α-L-arabinofunosidase, β-D-fucosidase, β-D-galactosidase, β-D-glucosidase and β-xylosidase. Polysaccharide enzymatic breakdown is greater in proximal colon than distal colon, while is negligible in stomach and small intestine. The end products of fermentation include short-chain fatty acid, carbon dioxide, hydrogen, methane, and hydrogen sulfide. The highest level of short-chain fatty acid is produced at right colon which is responsible for lowering colonic pH.

1. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.,
2. Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc.[15]

Table no: 4 Drug criteria for colon targeted (. [22, 14] Peptide drug *)

Sr No	Criteria	Pharmacological class	Drug and active agent
1	Local effect in colon	Anti-inflammatory Drugs	Oxyprenolol, Metoprolol, Nifedipine, Diclofenac sodium, Amylin[*], Oligonucleotide[*], Antisense[*].
2	Drug poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbides, Theophylline, Cyclosporine A[*], Desmopressin[*]
3	Drugs for colon cancer	Antineoplastics	Pseudoephedrine, Epoetin[*], Glucagon[*].
4	Drugs that degrade in stomach and small intestine	Peptides and Proteins	Bromophenaramine, 5flurouracil, Doxorubicin, Gonadoreline[*], Insulin[*.], Interferones[*].
5	Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Nimustine, Bleomycin, Nicotine, Dexamethasone, Molgramoatim, Protirelin[*], Sermorelin[*], Saloatonin[*].
6	Crohn's Syndrome	5-aminosalicylic acid, corticosteroids	Sulfasalazine, Olsalazine, Mesalazine, Hydrocortisone, Budenoside, Prednisolone
7	Ulcerative colitis	5-aminosalicylic acid, Purine antagonist,	Sulfasalazine, Balsalazine, Mesalamine, Mercaptopurine
8	Irritable bowel syndrome	Antispasmodic, Antidiarrheal, Anticholinergic, Antidepressant	Loperamide, Osmotic laxative, Dicyclomine, Mebeverine, Hyoscyamine, Amitriptyline
9	Diverticulitis	Nitroimidazole	Metronidazole, Bactrim, Sulfatrim, Flagyl.
10	Antibiotic associated colitis	Lincosamide, Aminopenicillin, Dihydrothiazine	Clindamycin, Ampicillin, Amoxicillin, Cephalosporinr
11	Hirschsprung's disease	Glycopeptide, Nitroimidazole, Antidiarrheal	Loperamide, Metronidazole Vancomycin

Table no: 5. Various Metabolic Reaction Catalyzed by Various Enzyme [17]

Enzymes	Microorganism	Metabolic Reaction Catalyase
Nitroreductase	E. coli, Bacteroids	Reduce aromatic and hetrocyclic nitro compounds
Azoreductase	Clostridia, Lactobacili, E. coli.	Reductive cleavage of azo compounds
N-Oxide reductase, Sulfoxide reductase	E. coli	Reduce N-Oxides and Sulfoxide
Hydrogenase	Clostridia, Lactobacili	Reduce carbonyl groups and aliphatic double bonds
Esterases and amidases	E. coli, P. vulgaris, B. subtilis, B, mycoides.	Cleavage of esters or amidases of carboxylic acid
Glucosidase	Clostridia, Eubacteria.	Cleavage of, β-glycosidase of alcohols and phenols
Glucuronidase	E. coli, A. aerogenes.	Cleavage of, β-glycosidase of alcohols and phenols
Sulfatase	Eubacteria, Clostrida, Streptococci.	Cleavage of O-sulfates and sulfamates.

2.3 *Approaches for colon drug targeting*

1. *Prodrug approaches*

i. *Azo bond conjugate*

In this approach drug has been conjugated by azo bond. The azo bond is stable in the upper GIT and is cleaved in the colon by azoreductases produced by the microflora. These azo compounds are extensively metabolized by the intestinal bacteria, by intracellular enzymatic components and extracellular reduction. Sulphasalazine, used for the treatment of IBD saulphasalazine(5-ASA)is composed of sulphapyridine. This has antibacterial activity and 5-ASA which has anti-inflammatory activity and both drug link with azo bond. In the colon, the azoreductases cleave the azo bond releasing the drug, and the carrier sulphapyridine. [23]

ii. *Glycoside Conjugated prodrug*

Enzyme Glycosidases produce by various human microfloraare β-D- galactosidase, α Larabino furanosidase,β-D-xylopyranosidase,and β-D glucosidase. These glycosidase enzymes are located at the brush border of colon. Natural occurring drug contain glycosides and aglycon part in their structure, after oral administration when they reach in colon glycosidases act on it and release pharmacological active aglycon. Glycosides are hydrophilic and poorly absorb from GIT because of this properties it use as the carrier for delivering drug to colon. Drug targeted by this approach are lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone. Daxamethasone-21-β-glucoside. Study were carried out using two prodrug Daxamethasone-21-β-glucoside, prednisolone-21-β-glucoside and unmodified steroids dexamethasone and prednisolon in rate. It has been seen that both modified form of steroids reach to the cecum whereas unmodified analog get absorbed in small intestine. [24]

iii. *Glucuronid Conjugation Prodrug*

Glucuronide conjugation is the major metabolic pathway of drug. β-Glucuronidaes secretedfrom large intestine deglucuronide various drug. This concept of metabolisum is use for delivering drug to colon where drug is couple with glucuronid gonjugation after oral delivery when it reach in to colon the

conjugation is specifically cleaved by β- Glucuronidaes and release active drug molecule. Colon targeting study has been carry out using glucuronid conjugation of narcotic analogs nalaxone and nalmefene which indicate that such conjugation useful in treatment of constipation cause by opiate. [25]

iv. *Dextran conjugated prodrug*
Dextran is the carbohydrate and colonic flora use it as the energy source. Dextran hydrogel is used in colon site specific delivery of drug, various prodrug of dextran is synthesized with NSADS using ester link between the Dextran and -COO group of drugs molecule. After oral administration of as it reach in to the colon enzyme Dextanase present in human colon break the ester linkage of such conjugation and liberate free drug. [26]

v. *Cyclodextrine conjugation*
Cyclodextrines are cyclic oligosaccharide consists of six to eight glucopyranose unit jointed by α (1→4) glucosidic linkage arrange in cyclic conformation, it have ability to form inclusion complex with may drugs since it interior portion of molecule is lipophilic and external portion is hydrophilic. Cyclodextrine is non toxic and bulky molecule it absorption is limited from the GIT hence it used as the carrier for some durg which unstable in stomach and intestinal environment. There are three analogs of cyclodextrine, α–cyclodextrine, β–cyclodextrine, γ–cyclodextrine. α–cyclodextrine, β–cyclodextrine are more stable to gastric, slivery and pancreatic enzyme as well as gastric pH they slowly digest in small intestine but completely degrade by colonic microflora. Study has been carried out by administration of cyclodextrin conjugate of anti-inflammatory drug biphenyl acetic acid in rat. After oral administration it has been found that cyclodextrine form of biphinayl acetic acid were selectively reach in to the colon and release drug without absorb form upper GIT. [27]

vi. *Protein conjugate*
Protein are hydrophilic in nature due to presence of polar group like -NH$_2$ and -COOH, and they are responsible for reducing the membrane permeability of various proteins, various prodrugs have been prepared with conjugation of such polar amino acids for site specific colon drug delivery. Study has been carried out for colon specific drug delivery of salicylic acid, study involved oral, intaravenous, intaracaecal and rectal administration of salicylic acid prodrug conjugate with glycylglycine in rabbit. Salicylic acid demonstrate in blood after 2hours by oral route, and unchanged salicylic acid glycylglycine conjugate was found in the blood followed by intravenous route where as free salicylic acid was found in the blood sample followed by intracaecal route. Form above study it has been prove that interstitial microflora is responsible for cleaving of such conjugation, such concept is useful in delivering drug to colon. [28]

2.4 *Polymeric approach to deliver intact drug molecule to colon*

I. Coating with pH sensitive polymer
When we want to formulate dosage form with aim that it selectively release drug in colon at that stage eudragit is one of the choice for coating tablet core. Basically it is poly(meth)acrylate base polymers and these are co-polymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (R). Eudragite polymers are available in a wide range of different physical forms (aqueous dispersion, organic solution, granules and powders). For achieving local treatment of bowel disorders such as Crohn's disease, ulcerative colitis or intestinal cancer drug needed to deliver at inflammatory site in colon without loss in upper GI this is accomplish by coating the tablet core with pH dependent polymer eugragit S100 but this type of formulation lead to premature drug release in distal part of small intestine this problem is over come by coating with solution containing mixture of both eudaragit L100 and eudragit S100. A study has been performed using 10% coating solution of ratio 1:4 of eudragitL100 and eudragit S100, these are anionic polymer and at low pH value it is impermeable to water and the ratio of carboxylic group to ester group is 1:1 for eudragit L100 and 1:2 for eudragit S100 they are soluble at pH>5.5 and pH> 7.00 respectively. Such polymer coat remain intact in stomach pH but as the reaches to distal part of small intestine where the pH is 7.5 at this pH value polymeric coat start depleting release small amount of drug but as it enter into colon the entire coat get dissolved lead to release higher amount of drug, premature release of drug is the major limitation of this approach and it can be control by Optimization of polymeric coating thickness. [29]

Table no: 6. pH dependent Polymers [30]

Polymer	Dissolution pH
EudragitL–100	6.0
EudragitS–100	7.0
EudragitL–30D	5.6
EudragitFS–30D	6.8
EudragitL10055	5.5
Eudragit S 12,5	>6.0
Polyvinyl acetate phthalate	5.0
Hyddroxy Propyl Methyl Cellulose Phthalate	4.5 to 4.8
Hyddroxy Propyl Methyl Cellulose Phthalate 50	5.2
Hyddroxy Propyl Methyl Cellulose Phthalate 55	5.4
Cellulose acetate Trimelliate	4.8
Cellulose acetate Phthalate	5.0

Table no: 7 pH Dependent formulation [31, 32].

Drug	Polymer	Dosage Form	Disease
Tegaserod maleate	Eudragit L100, Eudragit S100	Tablet	IBD
Prednisolone	Eudragit L100, Eudragit FS, Eudragit P4135 F	Tablet	Ulcerative colitis

II. *Based on pH sensitive hydrogel*

pH sensitive polymers contain pendant acidic such as carboxylic acid and sulfonic acid or basic such as ammonium salt group which can either accept or donate proton, depending upon pH of the surrounding environment, Poly(acrylic acid) become ionized at high pH Hydrogels made of poly(methacrylic acid) (PMA) grafted with poly(ethylene glycol) (PEG) have unique pH-sensitive properties. At low pH, acidic protons of the carboxyl groups of interact with the ether oxygen of PEG through hydrogen bonding, and such complexation results in shrinkage of the hydrogels. As the carboxyl groups of PMA become ionized at high pH, the resulting controlled by the crosslinking density.

The resulting decomplexation leads to swelling of the hydrogels. This principle can be applied for colon specific drug delivery system. Hydrogels made of polyanions (e.g. PAA) crosslinked with azoaromatic crosslinkers were developed for colon-specific drug delivery. Swelling of such hydrogels in the stomach is minimal and hence, the drug release is also minim as the hydrogel passes down the intestinal tract due to increase in pH cause ionization of the carboxylic groups lead to swelling which is further control by cross-links in hydrogel. The azoaromatic cross-links of the hydrogels are degraded by azoreductase produced by the microbial flora of the colon (Figure 1b)
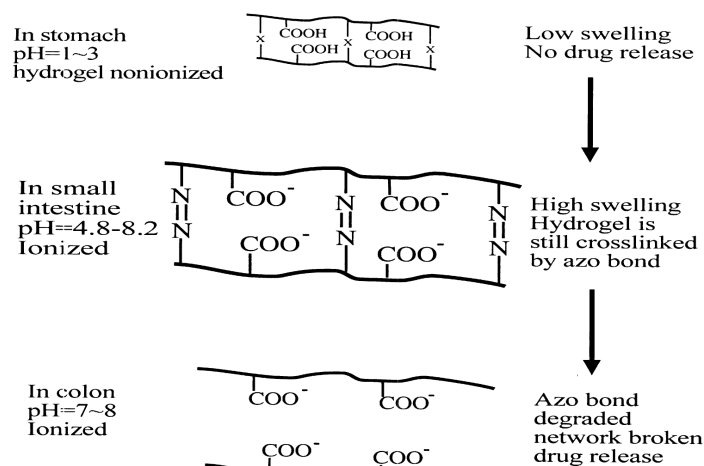

Figure no: 1(b)[33]

Table: 8. Marketed Hydrogel Based system[36, 37]

Drug	Polymer used	Approach used	Method of preparation
Satranidazole	Chitosan	pH sensitive	Cross linking method
5fluorouracil	Methacryloyloxy azobenzene	Degradation by azoreductase	Polymerisation

Azo-polysaccharide gel were prepared and in vitro evaluation of such formulation has been seen that hydrogel degraded by both reduction of azo linkage and enzymatic degradation of polysaccharide backbone. [34]. Dextran hydrogel were by crosslinking with diisicyanate for colon target which remain unaffected by stomach pH and these hydrogel swell and degrade by colonic microflora dextranase and release drug in cecum. [35]

III. *Bioadhesive polymer*
Bioadhesion is the new concept in colon drug delivery system, where the system get adhering to the mucus membrane of the colon, here the polymer swell and get adhere, adhesion involve formation of chemical or physical bonding between the polymer and surface of mucus membrane, improvement in both topical and systemic treatment in colonic inflammatory disease is achieve by localized drug delivery there by improving drug resident time. Polymer such as polycarbophils, polyurethane and polyethylene oxide. Prednisolone pellets containing different carbomers, including Carbopol 971P, Carbopol 974P and Polycarbophil AA-1, with or without organic acids, were produced by extrusion-spheronization technique and coated with a new enteric double-coating system, which dissolves at pH 7 and release the drug. [38]

IV. *Redox sensitive polymer coating*
This is novel polymer that degrades non enzymatically by enzyme secreting redox mediators, benzyl viologen and flavin mononucleotides are the redox mediators and act as electron shunt between intracellular enzyme and extracellular substrate which change in redox potential lead to cleaving of bond result in drug release form the polymer. The redox potential in proximal small intestine is about –67±90mv, in distal part of small intestine is about –196±97mv and in colon is –145±72 mv, colonic microflora cause change in the redox potential. This concept is used in targeting the colon. Under anaerobic condition bacterial azo reduction by enzymitically generated reduced flavins where the initial substrate thought to be involved in cellular electron transport requires presence of NADPH as its electron source NADPH oxidized the electron mediator (reduced flavins) acts as an electron shuttle from the NADPH dependent flavoprotein to the azo compound. Molecular modeling of low molecular

weight azo compound revealed that reduction of the azo bond to hydro-azo intermediate require a low electron density within the azo region thus substitution of electron withdrawing group will favor this reaction. [39]

V. *Embedded in biodegradable polymer matrix*
This are polysaccharide base polymer its monomer remain unaffected and resistant to digestive enzyme present in upper GI track, tablet coated with polysaccharide the remain intact when expose to stomach and small intestinal environment as they reach in colon the microflora present in colon (α-L-arabinofunosidase, β-D-fucosidase, β-D galactosidase, β-D-glucosidase and β-xylosidase) act on polysaccharide and degrade the tablet matrix and release the drug. Large number of polysaccharide has been investigated for their used in colon targeted drug delivery system are amylase, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans and locust bean gum, these polysaccharide are inexpensive, nontoxic and water soluble they must make water in soluble by crosslinking or hydrophobic derivatization. Very important is an optimal proportional of hydrophilic and hydrophobic part respectively and number of free hydroxyl group in polymeric molecule [40]. Guar gum and xanthan gum were used as the matrix former for preparing ibuprofen tablet. [57]

VI. **Time dependent colon drug delivery**
Pulsatile release systems are formulated to undergo a lag-time of predetermined span of time of no release, followed by a rapid & complete release loaded drugs(s). The approach is based on the principle of delaying the time of drug release until the system transits from mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. This system offers many advantages over conventional oral drug delivery systems like patient compliance, reduced dosage and dosage frequency, avoidance of side effects, avoidance of peak and valley fluctuation, nearly constant drug level at the target site. [41]

2.5 Novel Approaches for colon targeting

I. *Osmotic drug delivery*

Here the drug release form the device is achieved through an orifice by osmotic pressure generated in side the device. Metronidazole based on osmotic drug delivery system were formulate, this system consist of drug, osmogen (mannitol and fructose) this core were prepare by direct compression which were coat with semipermiable membrane which made by cellulose acetate, PEG400, guar gum, acetone, methanol, coating thickness of 90µm. This further coated with enteric polymer eudragit S100. During transit through GI this system remain intact in stomach due to coating of enteric polymer, but dissolve in small intestine pH and intestinal fluid enter into the tablet core react with osmogen and buildup osmotic pressure, as it reaches to colon the guar gum which is pore former is degrade by colonic microflora forming pore and due to osmotic pressure core break result in drug release in colon.[42]. OROS–CT in which drug core is surrounded by semipermiable membrane and it is coating with enteric polymer. Delay drug release after 2-4 hr to prevent drug release in upper GI, this maintain constant drug release upto 24 hours and it is use in treatment of ulcerative colitis, crohn's disease, idiopathic proctitis. [43]
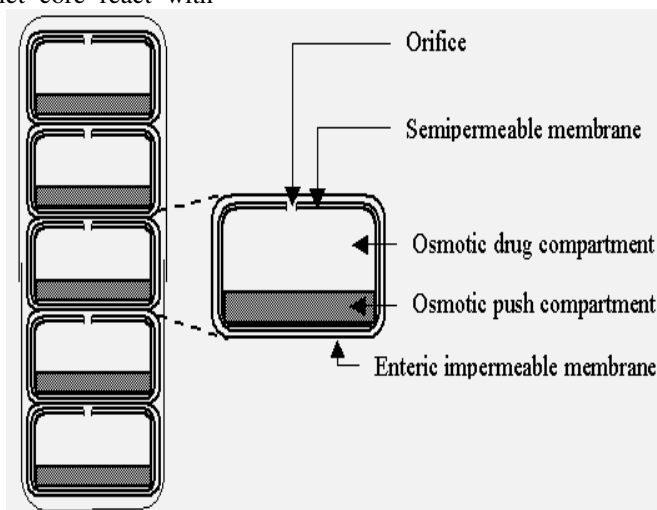

Figure no 2. OROS-CT

II. *Pulsincap*

Developed by R.R.Scherer. A capsule which consist of non disintegrating body part and water soluble cap, body part filled with drug molecule which is than sealed by water insoluble hydrophilic hydrogel and finally covered by water soluble cap, a hole is drill into the cap which is than sealed by enteric polymer. As the capsule enter into small intestine enteric polymer dissolved and intestinal fluid enter into the capsule because hydrophilic nature of hydrogel it absorb water and start swelling and eject. Lag period in drug release is determined by length of the hydrogel used. [44]

Table no: 9: Polymer for hydrogel

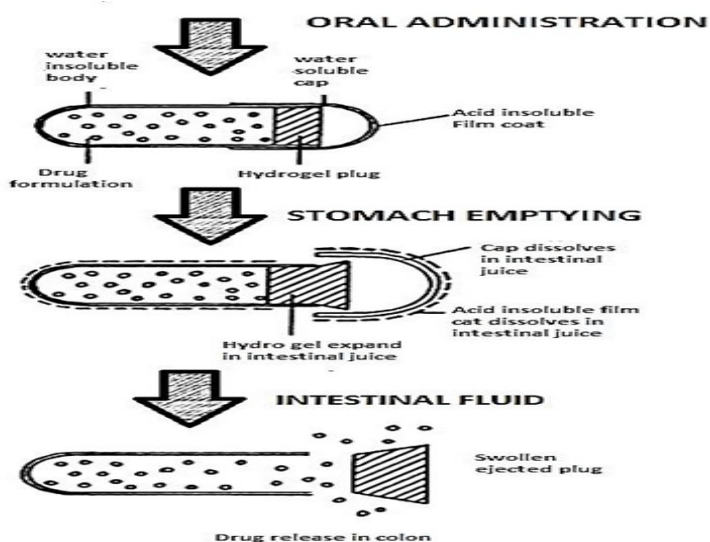| Hydrophilic swellable polymer	Erodible polymer	Congealed melt polymer	Biodegradable polymer
Polymethacrylates	HPMC, PVA, Polyethelen oxide.	Saturated polyglycolated glyceride, glyceryl monooleate	Pectin

Figure No 3; **Pulsincap mechanism of drug release**

III. *Port system*
The Port® developed by Port Systems, LLC it consists of a hard gelatin capsule which is coated with a cellulosic semi permeable membrane. Inside the capsule there was an insoluble plug and an osmotically active agent along with the drug formulation .When such contact with the aqueous medium, water diffuses across the semi permeable membrane of the device, resulting in increased inner hydrostatic pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness. The drug release pattern of port system is given in Figure 5.
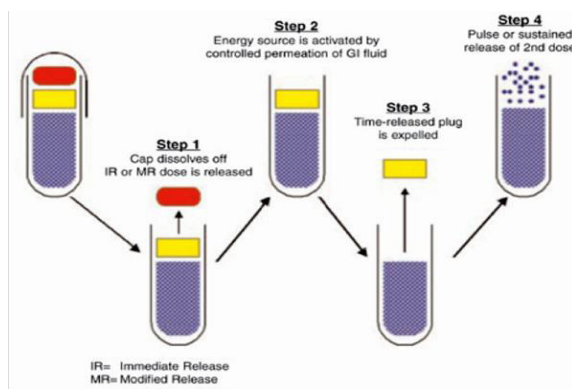

Figure no 5. Port sys[45]

IV. *Probiotic approach*
In this approach three components are desirable namely probiotic strain, microbially digestible carrier and triggering temperature. Probiotic strain include inactive microflora like bifidobacterium and lactobacillus species. At body temperature these strains get active start digesting the carrier and release drug at desirable place. Study has been carried out to evaluate in vitro release of diclofenac with or without probiotic using guar gum as carrier, it was found that 54.47% drug release achieve in absence of probiotic where as 73.01% in presence of probiotics. [46]

V. *Gas Empowered Drug Delivery System* (**GEDD**)

It is also a novel drug delivery system to colon which is designed to target the proteins and peptides to the intestinal region by using mucoadhesive polymer polyethylene oxide and TMC as penetration enhancer using CO_2. By the presence of mucoadhesive polymer the drug remains adhered to the mucous layer and the permeation enhancer is used to open the tight junctions to promote parcellular pathway for drug absorption. In this system the CO_2 gas is used as driving force to push the drug substance to the absorbing membrane and also it covers the dosage form completely to protect it from enzymatic and proteolytic degradation. CO_2 also functions as permeation enhancer by opening the tight junctions mechanically. This system is successful in

delivering the drug to the intestine because of the use of CAP (cellulose acetate phthalate) which protects the dosage form from the acidic pH of stomach.[47]

VI. *Chronotropic system*

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time and the drug releases at once after this lag time. Such system is beneficial in treatment of disease which affected by circadian rhythms asthma, rheumatoid arthritis and hypertension chronotropic study has been performed on guar gum crosslinked with ammonium ibuprofen tablet and it found that ammonium suppress drug release by reduced swelling of guar gum.[48]

VII. *Enterion capsule Technology*

Developed by Phacton Research It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. The capsule can be loaded with either a liquid formulation (e.g. Solution, Suspension) or a particulate formulation (e.g., powder, pellets, in sit affects etc.) through an opening 9 mm in diameter, which is then sealed by inserting a push-on Cap fitted with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high tensile strength polymer filament. A radioactive marker is placed inside a separate sealed tracer port to allow real time visualization of the capsule location using the imaging technique of gamma Scintigraphy. When the capsule reaches the target location in the gastrointestinal tract, the contents are actively ejected by the external application of an oscillating magnetic field. The frequency of the magnetic field is set in the low MHz region so there is negligible absorption in body tissue but sufficiently high to induce drug release. The power induced in the coil by the magnetic field is fed to a tiny heater resistor located within a separate sealed electronics compartment inside the capsule. the small size of the heater (less than 1mm3) means that heat build up is extremely rapid. The heater resistor is in direct contact with the restraining filament, causing it to softer and breaks with the increase in temperature. This is turn, releases the spring and driver the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of the capsule, which maintains a seal and presents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully[49].

VIII. *Colal-Pred*

This system is designed by Alizyme for the treatment of ulcerative colitis. It is the combination of Alizyme's colonic delivery system, COLAL, and an approved genericsteroid, Prednisolon sodium metasulfobenzoate. It provides the effective treatment of ulcerative colitis without the side effects of steroids. There is no competitor of this product yet in the market. COLAL-PRED has a coating which is break only in colon use in topical deliver of prednisolone in ulcerative colitis. Its colon targeting is done by coating it with such substances which get degraded by the colonic bacteria. [50]

IX. *Multiparticulate system*

Today researcher is more emphasis in development of multiparticulate dosage forms due to their potential benefits like increased bioavailability, reduced systemic side effect, it includes for pellets, granules, microparticulates and nanoparticles, such systems reach colon quickly and retained in colon for longer period of time. Such system easily cross gastro-intestinal tract due smaller particle size commonly used multiparticulate systems for colon target include pellet, granule, beads, microspheres and nanoparticles[51].

Table: 10. **Nanoparticles Based System** [52]

Drug Used	Polymer Used	Method of preparation	Disease
5fluorouracil	Soyalecithin, Dynasan114 and Dyanasin 118	Solid lipid nanoparticles	Colon cancer
Tripeptide, LysProVal	Alginate and Chitosan	Doubleemulsion/Solvent evaporation	IBD

Table no 11. Microsphere Base Colon Targeted System [53, 54, 55]

Drug	Polymer Used	Method of preparation	Disease
Theophyline	Ca–Pectinate, Eudragit S100	Ionotropic gelation method	Antiasthmatic activity
Indomethacine	Eudragit L100, Eudragit S100	Solvent evaporation method	Rheumatoid disroders
Acelofenac	Guar Gum	Emulsification	Rheumatoid arithritis

X. Combination of different approaches of CDDS

An oral colonic drug delivery system of 5-ASA was developed using combination of pH dependent, time-based and enzyme degradable approaches. The pellets core of 5-aminosalicylic acid(5-ASA) were coated with three functional layers i.e., the outer layer of Eudragit L 30D-55 for protection against gastro-intestinal fluids, the intermediate layer of ethyl cellulose to inhibit the drug release during passage through the small intestine and the inner film was coated with pectin which swell and get degrade by colonic microflora. In vitro release studies indicated that the coated pellets completely protected the drug release in 0.1M HCl while the drug release was delayed for three to four hours in pH 6.8 phosphate buffer. [56]

Table no 12.CDDS Based System [57]

Drug	Polymer	Dosage Form	Disease
MebeverineHCl	Eudragit RL100, Ethyl cellulose.	Tablet	Spasmolytic

3. Evaluation of colon targeted drug delivery system

3.1 *In-vitro* evaluation

No standardized evaluation technique is available for evaluation of CDDSas an ideal *in vitro* model should possess *in-vivo* conditions of gastro-intestinal tract such as pH, volume, stirring, bacteria, enzymes, enzyme activity and components of food. These conditions are influenced by diet & physical stress. The *in-vitro* evaluation of colon targeted drug delivery systems includes the *in-vitro* dissolution study & *in-vitro* enzymatic test

3.2 *In-vitro dissolution test*

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behavior of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 to simulate large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems.

3.3 *In-vitro* enzymatic test

There are 2 tests for the in-vitro enzymatic test.

a) The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.

b) Drug release study is performed in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier.

In vitro enzymatic dissolution study of tablet made by natural guar gum and xanthan gum has been carried out in presence of galactomannase enzyme and in both present and absence of caecal rate content.[58], [59].

3.4 *In- vivo evaluation*

The *in-vivo* evaluation of the CDDS is done in dogs, guinea pigs, rats & pigs as they resemble the anatomic and physiological conditions, microflora of human GIT. The distribution of various enzymes in gastro-intestinal tract of rat and rabbit is comparable to that in human.

I. *γ- saintigraphy*

γ-saintigraphy is an image modality which enables the in vivo performance of drug delivery system to be visualized under normal physiological conditions in a non invasive manner. Through scinitigraphy imaging, the following information regarding the performance of a colon specific drug delivery system within human Gastro-intestinal tract can be obtained, the location as a function of time the time and location of initial and complete system disintegration, the extent of dispersion the colon arrival time, stomach residence and small intestine transit time. Studies has been carried out in human subjects using technetium-99m-DTPA as tracing agent in sodium chloride core tablet and compression coated with guar gum act as protecting coat against upper Gastro-intestinal tract environment, and it has been observed that the tablet remain intact in stomach and intestinal pH but as it enter in

ascending colon it get degrade by colonic microflora and the release drug. [60]

II. *Roentgenography*

This technique involve incorporation of radio opaque material instead of drug such as barium sulfate, which visualized by taking X- rays of abdomen after oral administration. It is possible to observe movement, location and the integrity of the dosages after oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time intervals. [61]

4. Conclusion

The colonic region of the gastro-intestinal tract 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. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific 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.

Conflict of interest statement

We declare that we have no conflict of interest.

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