COLON TARGETED DRUG DELIVERY SYSTEM

List of content

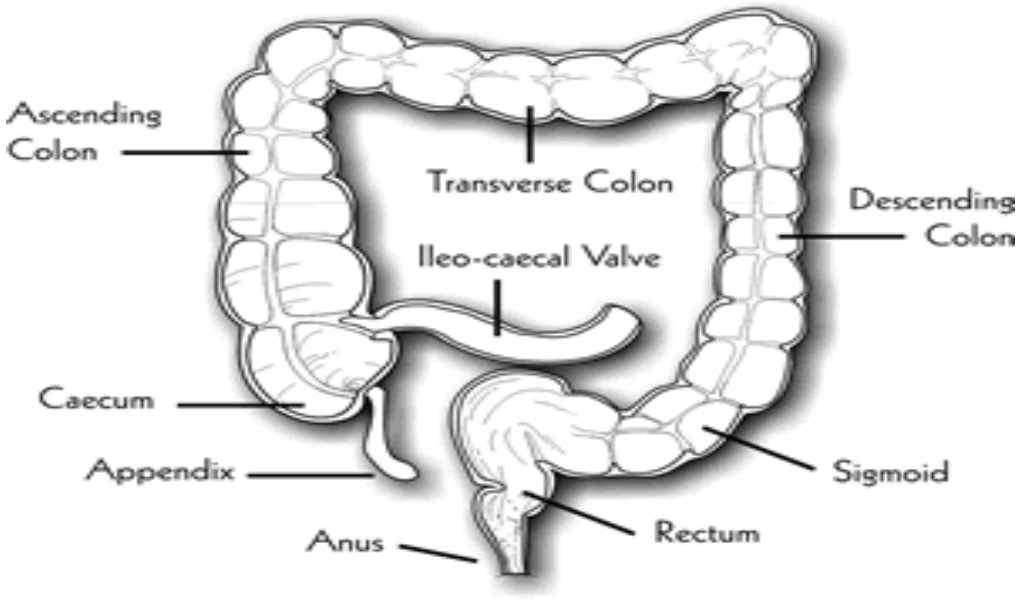
- **Anatomy of colon**
- **Introduction to colonic drug delivery system**
- **Factors governing colonic drug delivery**
- **Approaches for colonic drug delivery**

  A. Covalent linkage of drug with carrier

  B. Approaches to deliver intact molecule to colon
  1. **pH dependent approach**
  2. **Time dependent approach**
  3. **Microbially triggered drug delivery to colon**
  4. **Bioadhesive system**
  5. **Pressure controlled system**
  6. **Osmotic drug delivery**
  7. **Multiparticulate system**

- **Evaluation of colonic drug delivery**
- **References**

Anatomy of colon



Introduction to colonic drug delivery system:

- **By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e., colon).**
- **Colonic drug delivery system is targeted for topical/local as well as systemic effect.**

Effect	Disease conditions	Drugs used
Topical/local action	Inflammatory bowel disease, Irritable bowel syndromes and Crohn's disease	Hydrocortisone, Budenoside, Prednisolone, Sulphasalazine, Olsalazine, Infliximab Mesalazine, Balsalazide, 6-Mercaptopurine, Azathiorprine, Cyclosporine, etc.
	Amoebiasis	Metronidazole, Ornidazole, Tinidazole, Mebandazole, etc.
	Chronic pancreatitis, Pacreatactomy and Cystic fibrosis	Digestive enzyme supplements
	Colorectal cancer	5-Fluoro uracil
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

- **Systemic delivery of protein and peptide: The colon is believed to be a suitable site for absorption of peptides and protein drugs for following reasons:**

(i) Less diversity and intensity of digestive enzymes.
(ii) Comparatively
(iii) proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and eventually releases drugs in the ileum or colon which leads to greater systemic bioavailability.

- **<u>Chronotherapy:</u> Potential site for the treatment of diseases sensitive to circadian rhythms (asthma, hypertension, angina and arthritis). These diseases are characterized by night-time or early morning onset. For treatment of these diseases, it is therefore highly desirable to have a delayed-release delivery system that can provide nocturnal release of a drug, which in turn may provide considerable relief to the patients whilethey are resting.**
- **For the drugs that are absorbed through colon such as steroids.**
- **Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infections) whereby high local concentration can be achieved**
- **Minimizes side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption.**
- **The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.**
- **The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.**
- **Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.**
- **Drug directly available at the target site.**
- **Improved drug utilization: decreased dose to be administered.**
- **There is also an increasing interest in the colonic delivery for improving the oral bioavailability of drugs that are substrates of cytochrome P450 3A class, as the activity of this class of metabolizing enzymes is comparatively lower in the colonic mucosa than in the small intestine.**

➢ <u>Factor governing colonic drug delivery</u>

1. Physiological factors

2. Pharmaceutical factors

1. <u>Physiological factors:</u>

1. <u>Gastric emptying</u>

- **Drug delivery to the colon via the oral route depends on the gastric emptying and small bowel transit time.**

Fasted state	**10 min to 2 hour**
Fed state	**Higher than 2 hours**
Small intestinal transit	**3-4 hours**
Colon transit	**20-35 hours**

- **When the dosage forms reach the colon, transit depends on size. Small particles pass through the colon more slowly than the larger units. However, the density and size of larger single, units had no real effect on colonic transit.**
- **It has been shown that pellets move faster than do tablets through the ascending colon and therefore may be more favorable than tablets with respect to colonic drug absorption.**
- **Colonic transit time is only slightly affected by food but is reduced under stress. Although not significantly affected by most disease, the transit time is shorter in patients who complain of diarrhea and longer in patients with constipation.**

2. <u>Gastric and intestinal pH</u>

- **The pH of the gastrointestinal tract is subject to both inter- and intrasubject variations. Diet, diseased state, and food intake influence the pH of the gastrointestinal fluid.**
- **The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery. This can be achieved by using coatings that are intact at the low pH of the stomach but that will dissolve at neutral pH.**

Stomach	**Fasted state**	**1.5-2**
	Fed state	**2 - 6**
Small intestine		**6.6 - 7.5**
Colon	**Ascending**	**6.4**
	Transverse	**6.6**
	Descending	**7.0**

3. <u>Colonic microbial flora and enzymes</u>

- **The gastrointestinal tract contains a variety of microorganisms that participate in the metabolism of ingested material.**
- **The growth of the bacteria is regulated by gastric acids, peristaltic activity, and microbial interaction including bacterial metabolic byproducts.**
- **Administration of antibiotics as well as onset of disease and age can affect the metabolic activity of the intestinal microflora.**

- **Drug metabolizing enzymes in the human colon that catalyze reductive reactions**

Enzyme	Microorganism	Metabolic reaction catalyzed
Nitroreductase	E. coli, Bacteroids	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. Coli	Reductive cleavage of azo compounds
N –oxide reductase , sulfoxide reductase	E. coli	Reduce N-oxides and sulfoxides
Hydrogenase	Clostridia, Lactobacilli	Reduce carbonyl groups and aliphatic double bonds

- **Drug metabolizing enzymes in the colon that catalyze hydrolytic reactions**

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* glucuronidases of alcohols and phenols
Sulfatase	Eubacteria, Clostridia, Streptococci	Cleavage of O-sulfates and sulfamates

4. Colonic absorption

Factors affecting drug absorption from the colon

I. Physical characteristics of drug (pKa, degree of ionization)
II. Colonic residence time as dictated by gastrointestinal tract motility
III. Degradation by bacterial enzymes and byproducts
IV. Selective and non-selective binding to mucus
V. Local physiological action of drug
VI. Disease state
VII. Use of chemical absorption enhancers, enzyme inhibitors, bioadhesives.

5. **Gastrointestinal disease state**

DISEASE	EFFECT ON COLONIC ABSORPTION OF DRUGS
1. IBD (Crohn's disease & Ulcerative colitis)	Malabsorption lipophilic drugs Mucosa & submucosa gets thick & so reduces surface area, reduces diffusion
2. Diarrhea	Retention time reduces. Reduces drug absorption & release from dosage form
3. Constipation	Reduction in bowel movement, decreases the availability of drug at absorption site
4. Gastroenteritis	Diarrhea affects the performance of formulations

2. Pharmaceutical factors

1. Drug candidates

- The colon is a less hostile environment than the stomach and the small intestine. It has a longer retention time and is responsive to agents that cause an increase in the absorption of poorly absorbed drugs including peptides.
- Drugs that will benefit from colon targeting include those for the treatment of inflammatory bowel disease and irritable bowel syndrome.
- Drugs metabolized in the upper gastrointestinal tract also would be candidates for colon targeting.
- Drugs such as theophylline, nifedipine, ibuprofen, diclofenac, metoprolol, brompheniramine, pseudoephedrine, dinitrate, isosorbide, oxprenolol, and low-molecular-weight peptides and peptide-like drugs have been shown to be effectively absorbed from the colon.
- The permeability of the colonic epithelium may not be sufficient for achieving a transport rate required for therapeutic activity. This hurdle may be overcome by using penetration enhancers.
- They include chelating agents, non-steroidal anti-inflammatory drugs, fatty acids, and surfactants.

➢ Criteria for selection of drugs for CDDS

Criteria	Pharmacological class	Non peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Antisense oligonucleotide

Drugs poorly absorbed from upper GIT	**Antihypertensive and Antianginal drugs**	**Ibuprofen, Isosorbides, Theophylline,**	**Cyclosporine, Desmopressin**
Drugs for colon cancer	**Antineoplastic drugs**	**Pseudoephedrine**	**Epoetin, Glucagon**
Drugs that degrade in stomach and small intestine	**Peptides and Proteins**	**Bromophenaramine, 5-Flourouracil, Doxrubicin**	**Gonadoreline, Insulin, Interferons**
Drugs that undergo extensive first pass metabolism	**Nitroglycerin and Corticosteroids**	**Bleomycin, Nicotine**	**Protirelin, Sermorelin, Saloatonin**
Drugs for targeting	**Antiarthritic and Antiasthamatic drugs**	**Prednisolone, Hydrocortisone, 5-Amino-salicylic acid**	**Somatropin, Urotoilitin**

2. <u>Drug carriers</u>

- **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 the drug and the type of absorption enhancer chosen influence the carrier selection.**
- **Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond.**
- **The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.**

APPROACHES FOR COLON TARGATED DRUG DELIVERY SYSTEM.

A. Covalent linkage of drug with carrier

Prodrug approaches:-

- **Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site.**
- **This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.**
- **When synthesizing prodrugs, the choice of carrier depends on the functional group available on the drug molecule for conjugation with the carrier e.g., the hydroxyl group present on the corticosteroids can enter into a glycosidic linkage with various sugars and the carboxyl group of biphenylyl acetic acid forms an ester/amide conjugate with cyclodextrin.**
- **Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky to minimize absorption from the upper GIT, and if once in the colon, it is converted into a more lipophilic drug molecule, which is then available for absorption.**

1) Azo bond conjugate:-

- **These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction.**
- **The use of these azo compounds for colon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrugs.**
- **In the latter approach the drug is attached via an azo bond to a carrier. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora.**
- **Sulphasalazine, used for the treatment of IBD has an azo bond between 5-ASA and sulphapyridine (SP). In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier SP.**

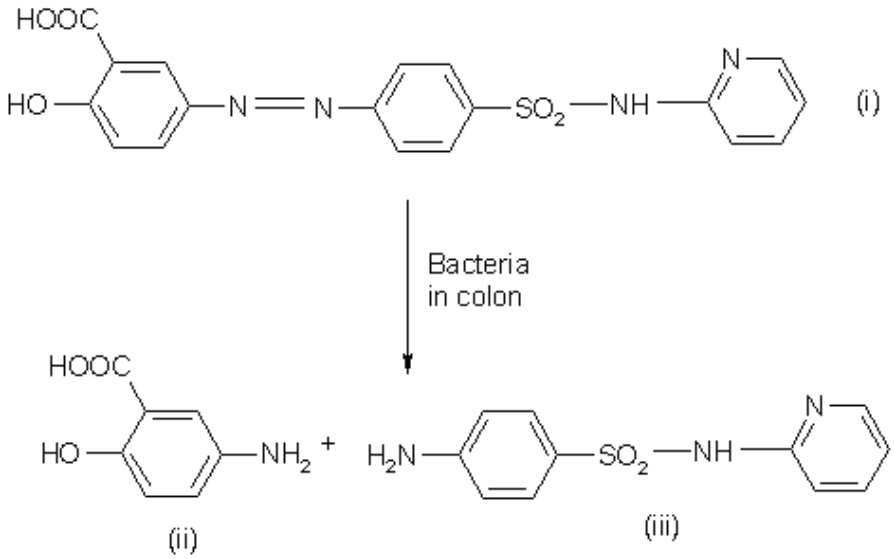


Figure: Hydrolysis of sulfasalazine (i) into 5-aminosalicylic acid (ii) and sulfapyridine (iii).

- **With the knowledge that the adverse effects associated with sulphasalazine are due to SP, an investigation started for the choice of a suitable carrier for 5-ASA with minimum adverse effects. SP was replaced by p-aminohippurate in ipsalazide and by 4-aminobenzoyl-b alanine in balsalzide.**

- **In another approach two molecules of 5-ASA have been joined together to form an ultimate prodrug disodium azodisalicylate (olsalazine), in which one molecule of 5-ASA is used as a carrier for the other. Under normal intact GIT conditions and bacterial flora, olsalazine delivers twice the amount of 5-ASA as compared to sulphasalazine.**

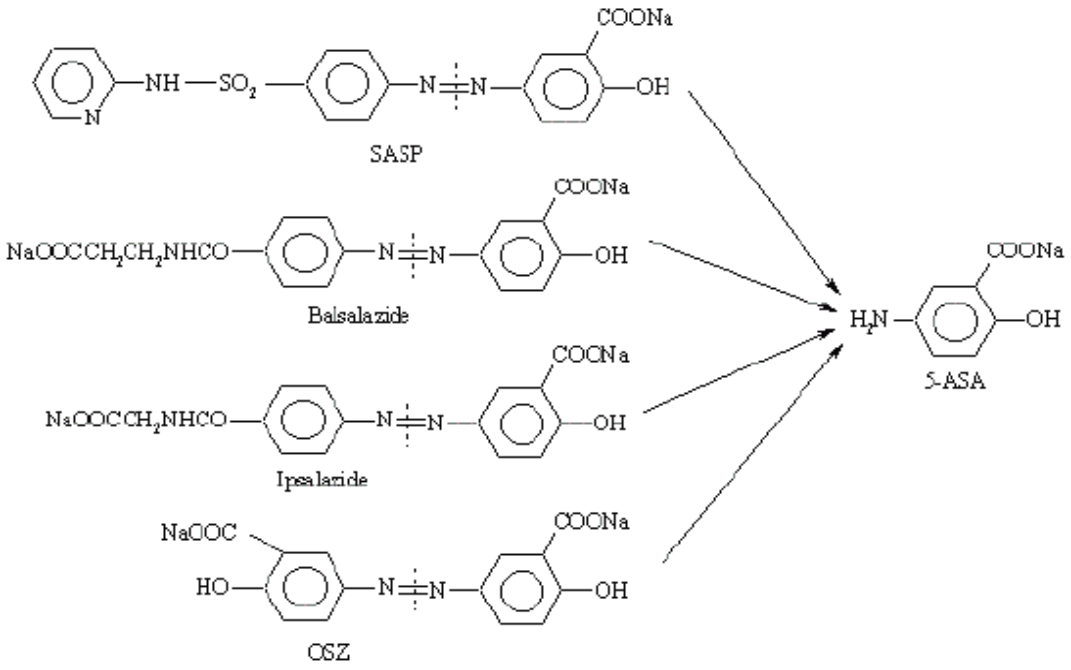


Figure: The chemical structure of SASP, balsalazide, ipsalazide and OSZ showing the site of bacterial cleavage leading to formation of the active agent 5-ASA.

2) Glycoside conjugation:-

- **Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system.**
- **Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycon and is linked to the sugar part, which forms the glycon part of the glycoside.**
- **Because they are bulky and hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidases, releasing the drug part from the sugar.**
- **The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers.**
- **The major glycosidase enzymes produced by the intestinal microflora are β -D-galactosidase, α -L-arabinofuranosidase, β -D-xylopyranosidase, and β –Dglucosidase**
- **These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily.**
- **Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone.**
- **Daxamethasone-21-β-glucoside, Prednisolone-21-β-glucoside.**

3) Glucoronide conjugates:-

- **Bacteria of the lower GIT secrete b-glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption.**
- **Example: Opiates, when taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS).**
- **A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon.**
- **When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel**

results in a diarrhea and The resultant diarrhea flushed out the drug/prodrug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn caused absence of withdrawal symptoms.

- **Budesonide-b-glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.**

4) Cyclodextrin conjugate:-

- **Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through α-1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability.**
- **The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules.**
- **They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed.**
- **This susceptibility to degradation specifically by colonic microflora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon.**
- **The a- and b-cyclodextrins are practically resistant to gastric acid, salivary, and pancreatic amylases. A clinical study has shown clear evidence that b-cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora.**

5) Dextran conjugate:-

- **Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolysed by moulds, bacteria, and mammalian cells.**
- **The enzyme responcible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the Bacteroides, which are present in a concentration as high as 10^{11} per gram in colon.**
- **This led to the use of dextran as carriers for drug molecules to the colon.**
- **In the colon, dextran's glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon.**

- **Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (−COOH).NASIDS ware directly coupled to dextran by using carboxylic groups of drugs**
- **Example: Naproxen-dextran conjugate.**
- **Glucocorticoids do not possess −COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid-dextran conjugates**

6) Amino acid conjugation:-

- **Due to the hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins.**
- **Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme.**

7) Polymeric prodrugs:-

- **Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose.**
- **Subsynthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.**

B. Approaches to deliver intact molecule to colon

1) pH dependent approach:-

- **This approach utilizes the existence of pH gradient in the git that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).**
- **By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site.**
- **The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.**

1. Coating of the drug core with pH sensitive polymers:-

- **The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.**

- **The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles.**

- **The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction.**

- **The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatin capsules.**

- **The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter- and intraindividual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine**

- **Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0(attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system. Problem of premature drug release can be overcome by the use of Eudragit FS.**
- **<u>Various pH dependent coating polymers:-</u>**

POLYMER	**THRESHOLD PH**
Eudragit L 100	**6.0**
Eudragit S 100	**7.0**
Eudragit® L-30D	**5.6**
Eudragit® FS 30D	**6.8**
Eudragit® L 100-55	**5.5**
Poly vinyl acetate phthalate	**5.0**
Hydroxypropylmethylcellulose phthalate	**4.5-4.8**
Hydroxypropylmethylcellulose phthalate 50	**5.2**
Hydroxypropylmethylcellulose phthalate 55	**5.4**

Cellulose acetate trimellate	**4.8**
Cellulose acetate phthalate	**5.0**

- **Examples:-**

Drug	Trade name	Coating polymer/formulation
Budesonid	Entrocort®	Eudragit® L 100-55, ethyl cellulose
	Budenofalk®	Eudragit® S (dissolution pH 7)
	Targit®	Coated starch capsule
Mesalazine	Claversal®	Eudragit® L 100(dissolution pH 6)
	Asacolitin®	Eudragit® S (dissolution pH 7)
	Salofalk®	Eudragit® S (dissolution pH 6)
	Pentasa®	Ethyl cellulose coated pellets
	Mesazal®	Eudragit® L 100(dissolution pH 6)
	Calitofalk®	Eudragit® L 100(dissolution pH 6)
	Asacol®	Eudragit® S (dissolution pH 7)
Sulfasalazine	Azulfidine®	CAP (dissolution pH 6.2-6.5)
	Colo –Pleon®	Eudragit® L 100-55 (dissolution pH 5.5)

2. Embedding in pH-sensitive matrices:-

- **The drug molecules are embedded in the polymer matrix.**
- **Extrusion spheronization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods.**
- **Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness. Citric acid promoted the pelletization process resulting in a narrower area distribution. However, EudragitS100 could not cause statistically significant delay in the drug release at lower pH.**

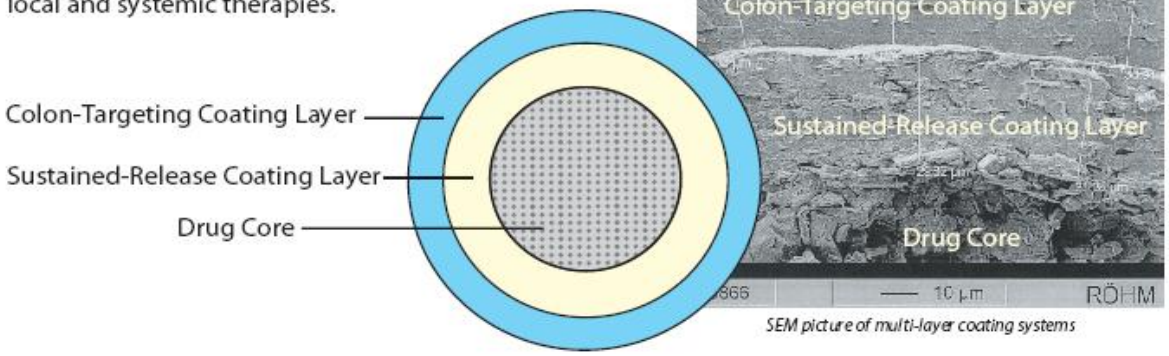
- **Some market formulations:-**

- **Asacol® Proctor & Gamble Pharmaceuticals, USA**

- **Delayed-release tablets containing mesalazine and coated with Eudragit®S-100 are marketed in a number of countries (Asacol). These tablets dissolve at pH 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon.**

- **Eudracol™**

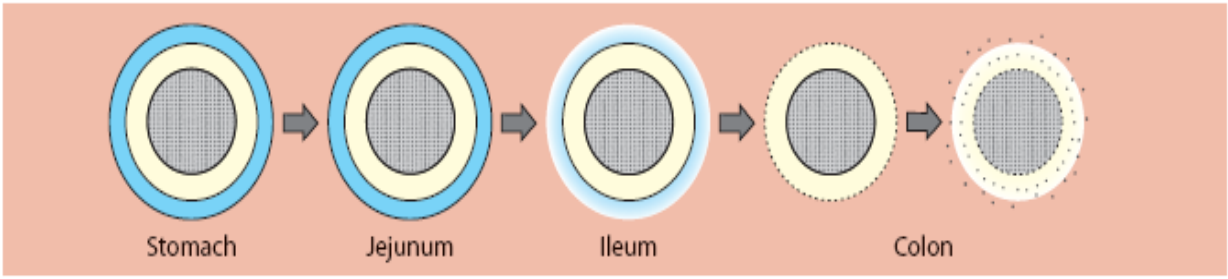
EUDRACOL™ is a colon-targeted, pH-triggered and sustained-release oral drug delivery technology for multi-unit dosage forms, for both local and systemic therapies.



SEM picture of multi-layer coating systems

How Does EUDRACOL™ Work?

EUDRACOL™ is based on a multi-layer coating system providing drug protection in the gastrointestinal tract and controlled drug release in the colon.



2) Time dependent delivery:-

- **It also known as pulsatile release, delayed or sigmoidal release system.**
- **This approach is based on the principle of delaying the release of the drug until it enters into the colon.**
- **Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place.**
- **The lag time in this case is the time requires to transit from the 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.**

- **Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms.**

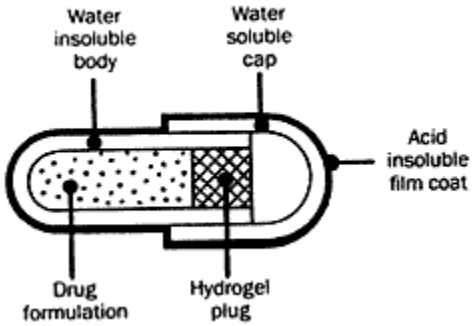
- **<u>Disadvantages of this system:-</u>**

  (i) Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
  (ii) Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
  (iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis.

- **Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases.**
- **Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon.**

1. <u>Pulsincap</u>

- **The first formulation introduced based on this principle was Pulsincap® developed by R.R.Scherer International Corporation, Michigan, US.**
- **It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying.**
- **When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell.**



Design of pulsincap system

- **The length of the plug and its point of insertion into the capsule controlled the lag time.**
- **For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material**

consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (eg, pectin).

- **These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastro-intestinal irritation.**

2. <u>Time clock</u>:-

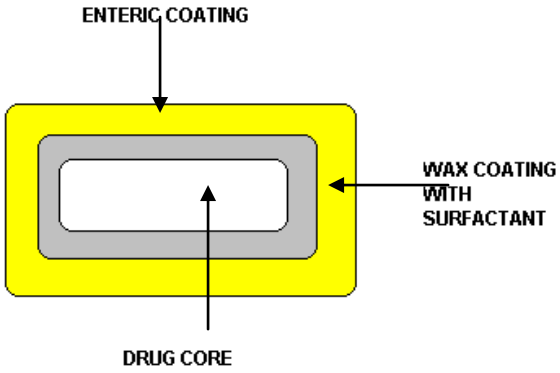


Figure: - Design of Time clock system

- **The Time Clock® system consists of a solid dosage form coated with lipidic barriers containing carnuba wax and bees' wax along with hydrophilic surfactants, such as polyoxyethylene sorbitan monooleate which improve adhesion to the core.**
- **Once in the contact with dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varing the thickness of the film. After the lag time, i.e.; the time required for rehydration, the core immediately releases the drug. This system has shown reproducible results in-vitro and in-vivo.**
- **Such systems are better suited for water-soluble drugs.**

3. <u>Time-Controlled- Explosion Drug-Delivery System (*Pulsatile System Based on Rupturable Coating*)</u>

- **It contains a four-layered spherical structure, with a core containing the drug, a swelling agent and a water-insoluble polymer membrane made of ethyl cellulose, Eudragit® RL.**
- **This system is characterized by rapid drug release with a programmed lag time. The penetration of GI fluids through the outer membrane causes the expansion of the swelling agent. The resulting stress due to swelling force leads to destruction of the membrane and subsequent rapid drug release.**
- **The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc.**

- **Drug release is not affected by pH and drug solubility but the lag time is a function of the thickness of the outer polymeric membrane.**
- **A rapid release after the lag phase was achieved with increased concentration of osmotic agent.**

- **<u>Advantages of this system:-</u>**
  - **(i) The release rate or pattern is minimally influenced by the solubility or dissolution rate of the drug**
  - **(ii) The release pattern is independent of pH of the dissolution medium, and**
  - **(iii) The drug is completely released.**

4. <u>Colon-Targeted Delivery Capsule based on pH sensitivity and time-release principles</u>

- **The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance.**
- **This capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer, and an enteric layer.**
- **After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released.**
- **Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer.**

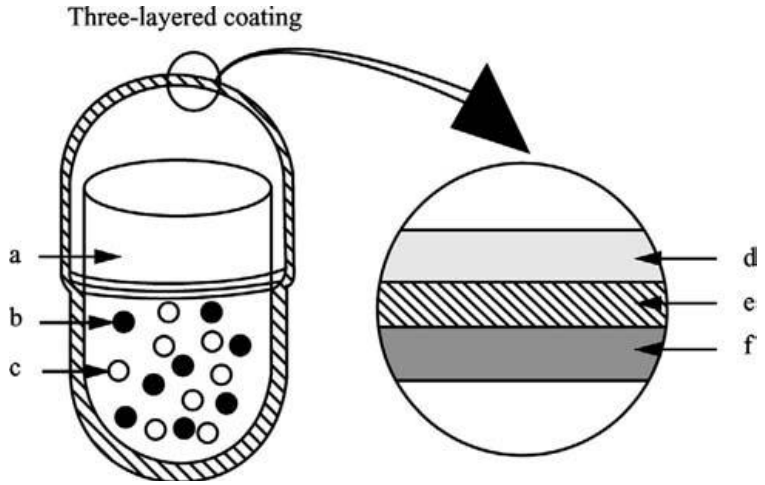
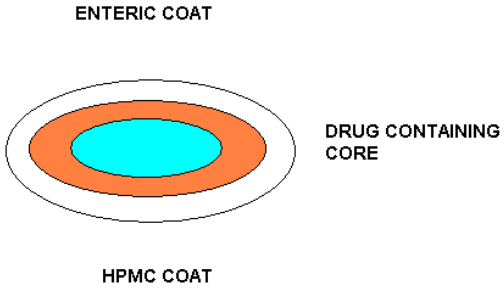


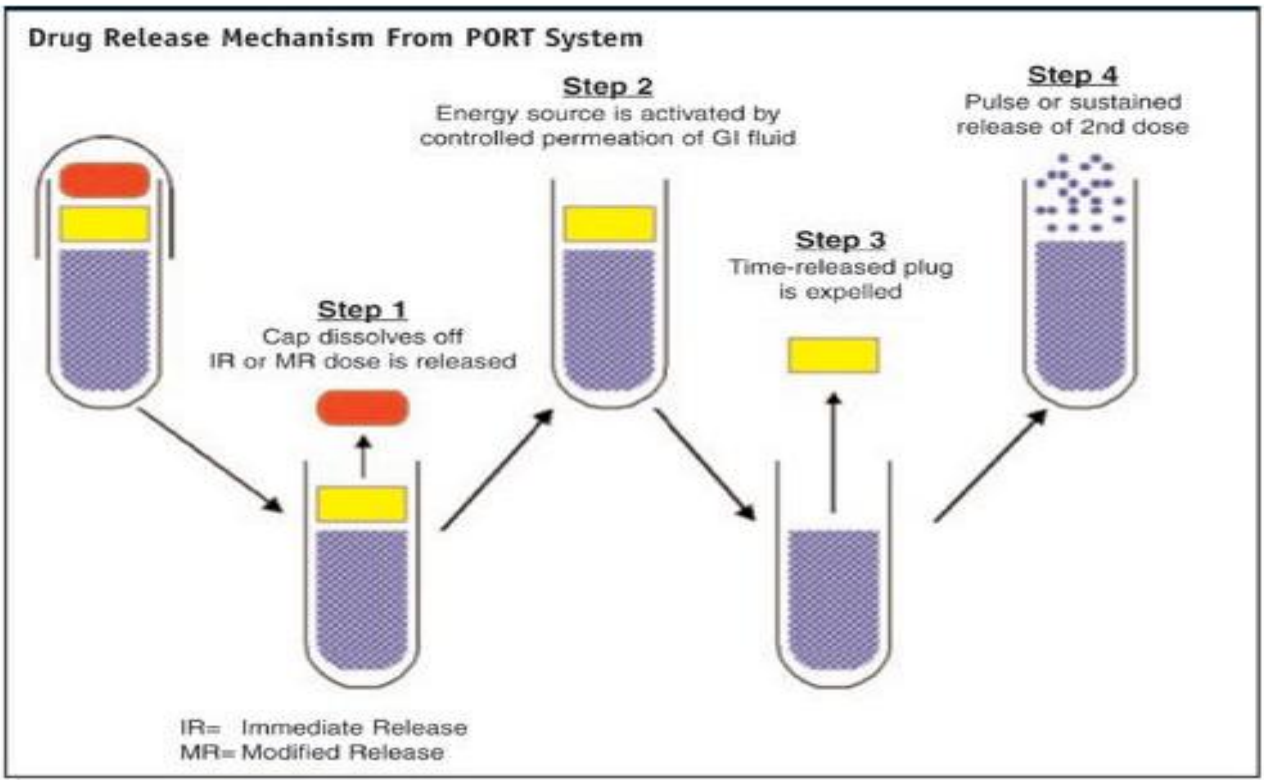
Fig. 4 Design of the colon-targeted delivery capsule: a) gelatin capsule; b) active ingredient; c) organic acid; d) enteric layer; e) hydrophilic layer; and f) acid-soluble layer.

5. Chronotropic® system



- **The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release.**
- **In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time.**
- **The lag time is controlled by the thickness and the viscosity grades of HPMC. The system is suitable for both tablets and capsules.**

6. PORT system:-



- **The Port system was developed by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of a gelatin capsule coated with a semipermeable membrane.**
- **Inside the capsule an insoluble plug (lipidic) consisting of osmotically 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.**
- **Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours.**

3) Microbially triggered drug delivery to colon

- **The microflora of colon is in the range of 10^{11} -10^{12} CFU/mL, consisting mainly of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc.**
- **This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri- saccharides, polysaccharides etc.**
- **For this fermentation the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.**
- **Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon- specific drug delivery seems to be a more site-specific approach as compared to other approaches.**
- **These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon.**
- **On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.**

Polysaccharide based delivery systems

- **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, have wide availability are inexpensive and are available in a verity of a structures with varied properties.**
- **They can be easily modified chemically and biochemically and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition biodegradable.**
- **These include naturally occurring polysaccharides obtained from plant (guar gum, inulin) animal (chitosan, chondrotin sulphate) 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).**

1. **<u>Coating with biodegradable polymers:-</u>**

- **The use of polysaccharides for coating purposes has been tried with limited success. Most of the non starch polysaccharides suffer from the drawback of lacking good film forming properties.**
- **Also, they tend to swell in the GI tract and become porous, resulting in the early release of the drug.**
- **Various biodegradable polymer used for coating are**

Class	Examples
Disaccharides	lactose
	Maltose
Oligosaccharides	Cellobiose
	Cyclodextrins
	Lactulose
	Raffinose
	Stachyose
Polysaccharides	Alginates
	Amylose
	Arabinogalactan
	Arabinoxylan
	Cellulose
	Chitosan
	Chondriotin sulphate
	Dextran
	Galactomannan (guar gum and their cross linked derivatives, locust bean gum)
	Inulin
	Karaya gum
	Laminarian
	Pectins and pectates, Methoxylated pectin, Amidated pectin
	Starch
	Xanthan gum
	Xylan
	Tragacanth gum

- **Earlier polymer cross linked with azo aromatic groups was used but due to potential carcinogenic activity now days natural polysaccharides are used.**

- **Natural polysaccharides generally undergo premature drug release so they are chemically modified or mixed with hydrophobic polymers. This polymer shows good film forming properties, reduced waters solubility resistant to pancreatic enzymes but they will undergo degradation due to bacterial enzyme.**

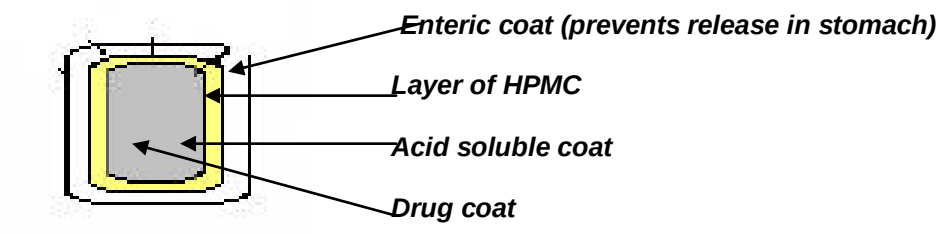
<u>COLAL</u>

- **COLAL involves coating of drug pellets, tablets or capsules with Ethylcellulose and (amorphous) glassy amylose. Amylose as such is normally resistant to environment of the stomach and the small intestine, but in its amorphous ("glassy") state, it is also resistant to degradation by salivary and pancreatic alpha amylases and digested by bacterial enzymes of the colon only.**
- **When coated pellets reach the colon, the coating is degraded, allowing the drug to be released.**

<u>COLAL-PRED system</u>

- **COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis (US). It has arisen from combining Alizyme's properitary colonic drug delivery system, COLAL, with an approved generic steroid (Prednisolone sodium metasulfobenzoate). It is an effective anti inflammatory treatment for UC without the typical side effects of steroids.**
- **COLAL-PRED has a coating that is broken down only in the colon, by locally occurring bacteria. This leads to topical delivery of prednisolone to the colon without significant systemic exposure so minimizing steroid related side effect**

<u>CODES™ technology (Yamanouchi Pharmaceutical Co., Ltd., Japan).</u>



- **Drug release from this system is triggered by colonic microflora coupled with pH-sensitive polymer coatings.**
- **In this approach, a core tablet is coated with three layers of polymeric coatings.**
- **The first coating (next to the core tablet) is an acid-soluble polymer, the middle layer is a barrier coat of HPMC interposed to prevent any possible interactions between the oppositely charged polymers and the outer coat is an enteric coating.**

- **The core tablet is comprised of a drug, one or more saccharides and other excipients.**
- **Examples of such saccharides include mannitol, maltose, stachyose, lactulose, etc.**
- **During its transit through the gastrointestinal tract, the CODES™ remains intact in the stomach because of the enteric protection, but the enteric and barrier coatings dissolve in the small intestine, where the pH is above 6.**
- **Upon entry into the colon, the saccharide inside the core tablet dissolves and diffuses through the coating.**
- **The bacteria enzymatically degrades the saccharide into organic acids.**
- **This lowers the pH level surrounding the system enough to affect the dissolution of the acid-soluble coating and subsequent drug release.**

2. <u>Embedding in biodegradable matrices and Hydro gels</u>:-

- **Polysaccharides retain their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharides and results in the degradation of the matrices.**
- **A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inuline, cyclodextrins, chondroitin sulphate, dextran and locust bean gum have been investigated for their use in colon targeted drug delivery systems.**
- **As these polysaccharides are usually soluble in water, they must be made water insoluble by cross linking or hydrophobic derivatisation. Very important is an optimal proportional of the hydrophobic and hydrophilic parts respectively and the number of free hydroxyl groups in the polymeric molecule.**
- **Hydrogels are usually formed by the covalent crosslinking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble.**
- **Heterogenous polymer mixtures may also be used to form hydrogels without the need for covalent crosslinking.**
- **Various hydrogels based on the azo polymeric networks have been developed for site-specific delivery of drugs to the colon.**
- **These have been evaluated for CDDS; various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large bowel.**
- **Coating of peptide capsules with polymers cross linked with azoaromatic 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.**

Various hydrogels for colon targeted drug delivery

Type of hydrogel	Material	Description
Azoaromatic hydrogels	Acidic co monomers	The gel structure remains intact in the stomach and liberates the drug upon arrival in the colon due to degradation of crosslinks.
	N,N-dimethylacrylamide, N,t-butylacrylamide and acrylic acid	In vitro and in vivo degradability dependa on the degree of the swelling of the gels.
Inulin hydrogels	Methacrylated inulin copolymerized with the aromatic azo agent BMAAB Or HEMA Or MA	Uptake of the water in the gel inversely proportional to the Methacrylated inulin feed concentration, the degree of substitution of the inulin backbone and the concentration of the BMAAB.
Dexatran hydrogels	Activated Dextran conjugated with 4-aminobutyric acid and crosslinked with 1,10 diaminodecane	Enhanced release of bovine serum albumin from the hydrogels by addition of dextranase in buffer solution

4) 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-polypropyline 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.

5) Pressure controlled system:-

- **The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents.**
- **In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis.**
- **These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems.**
- **The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents.**
- **In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces.**
- **It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems.**
- **Takaya et al. (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, 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 ethyl cellulose membrane is the most important factor for disintegration of the formulation. The preferred thickness of the capsule wall is about 35-60 µm. The system also appeared to depend on capsule size and density.**
- **In pressure-controlled ethyl cellulose single- unit 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.**

6) Osmotic controlled drug delivery:-

- **The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated with in a hard gelatin capsule.**
- **Each push-pull unit is bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane.**
- **In principle semipermeable membrane is permeable to the inward entry of water and aqueous gi fluids and is impermeable to the outward exit of the drug.**

- **An orifice is drilled into the semipermeable membrane to the drug layer.**
- **The outside surface of the semipermeable membrane is then coated by eudragit®S100 to 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.**
- **For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour 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 h in the colon or can deliver drug over an internal as short as 4 hour.**

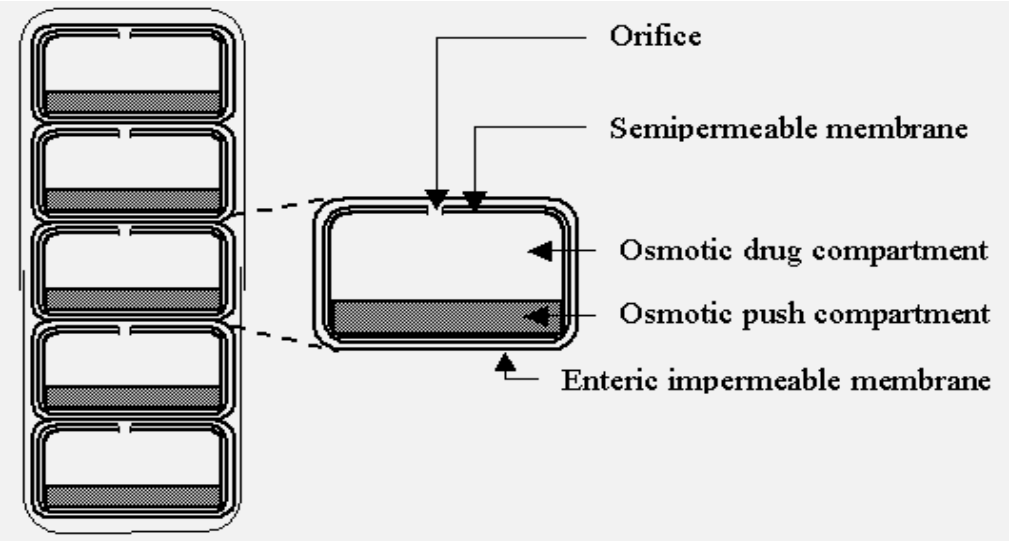


Figure: Cross section of the OROS-CT colon targeted drug delivery system.

7) Multiparticulate systems

- **Single unit colon targeted drug delivery system 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.**
- **Report suggests that drug carrier systems larger than 200 µm possess very low gastric transit time due to physiological condition of the bowel in colitis.**
- **And for this reason and considering the selective uptake of micron or submicron particles by cancerous and inflamed cells/ tissues a multiparticulate approach is expected to have better pharmacological effect in the colon.**
- **Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like,**

1. **Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time and hence increased bioavailability.**
2. **Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter- and intra subject variability.**
3. **Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption.**
4. **Reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.**

- **Multiparticulate approaches tried for colonic delivery include includes formulations in the form of pellets, Granular matrix, Beads, Micro spheres, Nano particles.**

DESIGN OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS

- **The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation, change in gastro luminal pH and enzyme population.**

a. pH and time dependent systems

- **One of the simplest approaches for designing pH dependent multiparticulate colon specific delivery system is to formulate enteric coated granules.**
- **Most commonly used pH-dependent coating polymers for peroral delivery are methacrylic acid copolymers, Eudragit L100 and Eudragit S100, which dissolve at pH 6.0 and 7.0 respectively. The combination of these two polymers in various ratios makes it possible to manipulate drug release within 6.0-7.0 pH range.**
- **Incorporation of organic acid in both the enteric coated granules as well as the tablet matrix retarded the *in vitro* release and *in vivo* absorption of the drug because of the prolongation in disintegration time of the core system due to the presence of the acid.**

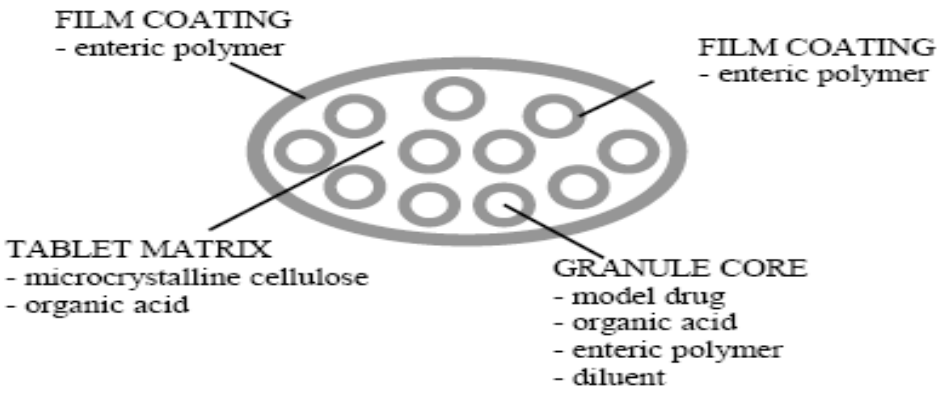


Figure 1. Structure of multiple-unit colon-specific tablet developed.

- **In another approach, 5-fluorouracil granular matrices were designed for release of the drug in the descending colon in a controlled fashion for the treatment of colorectal carcinoma.**
- **The Glyceryl plmitostearate matrices (retardant material) coated by Eudragit S100 and were then covered by a layer of chitosan HCl and loaded inside HPMC capsules coated with 30 D.**
- **Upon hydration, the capsule shell dissolves and the chitosan layer forms a gel (internal pH of 4.5), which generates an acidic environment around the Eudragit film so that it does not dissolve in the ascending colon.**
- **In the ascending colon, the chitosan HCl gel is degraded by the colonic micro flora, thereby exposing the Eudragit film to the colonic environment. But since the ascending colon is weakly acidic where pH is less than 7.0, the film coat still remains intact.**
- **However, on arrival in the descending colon where pH is greater than 7, the Eudragit film coat dissolves and the drug is released in a controlled fashion from the matrices.**
- **It is accepted that a colonic delivery system which is based only on GI transit time or pH of the GI tract would not be reliable because of the inherent variability of pH and emptying times from the GI tract.**

b. <u>Microbially controlled systems</u>

- **Amongst all the approaches used for colon targeting, a microbially controlled delivery system is the most appealing as it relies on the unique enzymatic ability of the colonic micro flora and enables a more specific targeting, independent of pH variations along the GI tract.**

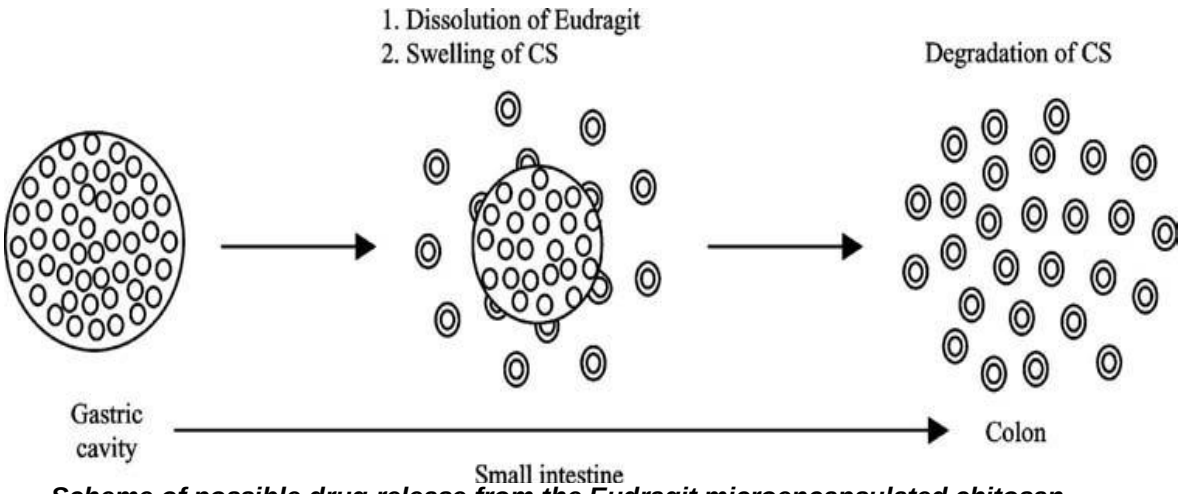
- **A multiparticulate system consisting of hydrogel beads was formed by chitosan and tri poly phosphate (TPP) for the delivery of protein.**

- **TPP was used as a counter ion to positively charged chitosan to form gel beads. The beads were loaded with bovine serum albumin (BSA), a protein that is liable to degradation in the upper parts of GI tract.**
- **The cross linking of chitosan with TPP resulted in reduced solubility of chitosan, thereby resulting in lesser protein release during upper GI transit. At the same time, the cross-linking and reduced solubility did not affect the degradability by microbial flora in the colon.**

- **The ability of amidated low methoxy pectin to form rigid gels with divalent cations has been exploited to produce calcium pectinate gel beads, intended for controlled release delivery of conventional drugs and also as a carrier for colonic delivery of proteins.**
- **To overcome the problem of high dissolution of pectin in the upper GI tract, pectin has been combined with calcium salts since calcium pectinate (the insoluble salt of pectin) is not degraded by gastric or intestinal enzymes but is capable of degradation by colonic pectinolytic enzymes.**

- **In another approach, chitosan microspheres coated with Eudragit L100 or S100 for the colonic delivery of metronidazole for the treatment of amoebiasis.**
- **The drug release take place after dissolution of the enteric coating in the small intestine and biodegradation of the chitosan in the colon due to presence of polysaccharides in the colonic contents.**
- **In order to prevent early loss of drug from microspheres, the chitosan is cross linked with glutaraldehyde.**

- **Lorenzo-Lamosa and coworkers manufactured a system in which chitosan microcores were entrapped within acrylic microspheres of Eudragit L-100 and Eudragit S-100, forming a multireservoir system. This system is designed to combine the specific biodegradability enforced by colonic bacteria with pH-dependent release of the drug sodium diclofenac.**
- **A continuous release for 8–12 h is obtained at the pH in which the Eudragit coats are soluble.**
- **Mechanism of release: dissolution of the Eudragit coating, swelling of the chitosan microspheres, dissolution of the drug, and its further diffusion through the chitosan gel cores.**



Scheme of possible drug release from the Eudragit microencapsulated chitosan microspheres.

c. <u>Microparticulate systems</u>

- **In the treatment of IBD, sustained release devices like pellets, capsules or tablets have less efficiency due to diarrhea, a symptom of IBD that enhances their elimination and reduces the total time available for drug release.**
- **It has been shown that drug carrier systems with a size larger than 200 µm would be subjected to speedy bowel evacuation due to diarrhea, resulting in a decreased GI transit time and decreased efficiency.**
- **Therefore, a multiparticulate system in the micron size range could be a useful option in the design of a suitable dosage form for IBD.**

- **<u>Typical formulation</u>**
- **Eudragit P-4135 F, a new pH-sensitive polymer was used to prepare microparticles of tacrolimus, an immunosuppressant drug, for colonic delivery.**
- **The use of Eudragit P-4135 F in the microencapsulation of 5-fluorouracil for the treatment of colorectal cancer has been reported.**
- **Eudragit P-4135 F belongs to the pH-sensitive Eudragit group of polyacrylates and possess a dissolution threshold pH slightly above 7.2.**
- **This is very useful as ulcerative colitis mainly affects the distal parts of the colon and an early drug loss towards the non-inflamed tissue would be undesirable. Eudragit P-4135 F might prove a useful alternative for systems intended for targeting to the distal colon.**

- **Since immune cells have an important pathophysiological role, they should be considered in the therapeutic strategy for patients with IBD.**

- **It is reported that biodegradable microspheres could be efficiently taken up by macrophages. Therefore, the direct uptake of anti-inflammatory agents loaded microspheres by macrophages would**

have a superior immunosuppressive effect and be more useful for treatment of patients with IBD.

d. Microparticulates in the delivery of peptides

- **The colon has always attracted attention as a potential site for the systemic absorption of peptide drugs on account of its lower proteolytic enzyme activity compared to the upper GI tract.**

- **Formulation 1**

- **A system consisting of insulin encapsulated by polyacrylates wherein the coating was meant to dissolve only in the colon.**

- **Formulation 2**

- **A terpolymer of styrene and hydroxyethyl methacrylate cross-linked with a difunctional azo-compound has also been reported for the delivery of insulin. The system depends on cleavage of azo bond by colonic microflora resulting in degradation of polymer and release of insulin.**

- **Formulation 3**

- **Insulin containing polyanhydride microspheres which were shown to adhere to the walls of the small intestine and release the insulin upon degradation of the polymeric carrier. This ensured protection of insulin from degradation in upper portion of the gastro-intestinal tract and release into distal portion of small intestine and proximal colon for systemic absorption.**

e. Nanoparticulate systems

- **Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting.**
- **Orally administered nanoparticles serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability. Nanoparticles have also been investigated for the delivery of protein and peptide drugs.**
- **For colonic pathologies, it was shown that nanoparticles tend to accumulate at the site of inflammation in IBD.**
- **This is because in case of colitis, a strong cellular immune response occurs in the inflamed regions due to increased presence of neutrophils, Natural Killer cells, macrophages and so on.**
- **It has been reported that microspheres and nanoparticles could be efficiently taken up by these macrophages.**
- **This results in accumulation of the particulate carrier system resulting in prolonged residence time in the desired area.**
- **However, an important area of concern is to prevent loss of Nanoparticle in the early transit through GI tract in order to optimize**

therapeutic efficacy. Moreover, particle uptake by Payer's patches and/or enzymatic degradation may cause the release of entrapped drug leading to systemic drug absorption and side effects.

- **In order to overcome this problem, drug loaded nanoparticles were entrapped into pH sensitive microspheres, which serve to deliver the incorporated nanoparticle to their site of action, thereby preventing an early drug leakage.**
- **The use of nanoparticles for bioadhesion purposes has also been investigated. Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion can be induced by binding nanoparticles with different molecules.**
- **For covalent attachment, the nanoparticle surface has to show free functional groups, such as carboxylic or amine residues.**

EVALUTION OF COLONIC DRUG DELIVERY SYSTEM:

1) 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 jejunal 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)**

1. <u>In vitro enzymatic test</u>

For this there are 2 tests:

i) 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

2) <u>In vivo evaluation</u>

- **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. Eg. 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.**

3) <u>Drug delivery index</u>

- **DDI is calculated pharmacokinetic parameters; following single or multiple doses of oral colonic prodrugs.**
- **DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug).**

- ***<u>High drug DDI value indicates better colon drug delivery.</u>***

- **<u>Relative Colonic Tissue Exposure to Drug (RCE)</u>**

- **RCE = <u>[AUC $_{(tissue)}$CD]</u> * <u>[DOSE $_{ref}$]</u>**

[AUC $_{(tissue)}$ref] [DOSE $_{cd}$]

Where,

$AUC_{(tissue)}$CD = area under curve of tissue drug conc. vs time after oral ingestion of colon delivery system

$AUC_{(tissue)}$ref = area under curve of drug conc. Vs time after administration of reference dosage form (i.v. or oral dosage form)

$DOSE_{cd}$ = dose of colonic delivery system

$DOSE_{ref}$ = dose of reference dosage form

- **Relative Systemic Exposure to Drug (RSE)**

- **RSE = [AUC $_{(blood)}$ CD] * [$DOSE_{ref}$]**
  [AUC $_{(blood)}$ ref] [DOSE $_{cd}$]

Where the terms are same as that of above equation for RCE but it is with the context of blood.

DRUG DELIVERY INDEX = [RCE]
[RSE]

Drug Delivery Index proportionate to better colonic drug delivery.

4) 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.**
- ***Principle* of 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**

- **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).**