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MEDICAL RATIONAL OF COLLOIDAL DRUG, GENE DELIVERY AND IT'S CHARACTERIZATION ASPECTS

DK. Sanghi[1] and *Rakesh Tiwle[2*]

[1]Principal of ShriLaxmanraoMankar Institute of Pharmacy, Amgoan, Gondia, Maharashtra, India- 441902.
[*2]Research Scholar of ShriLaxmanraoMankar Institute of Pharmacy, Amgoan, Gondia, Maharashtra, India- 441902.

ABSTRACT
The colon is a site where both systemic delivery and local delivery of a drugs can take place. Local delivery allows topical treatment of inflammatory like bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, by reducing the systemic side effects, codestm, and osmotic controlled drug delivery in this review article is focus on the colon targeted gene delivery system and it's evaluation parameters.

KEY WORDS: Colon drug delivery systems, Newly developed approaches, Evaluation of colon targeted drug delivery systems.

INTRODUCTION

Colon Targeted Drug Delivery Systems (CTDDS)

Since past 70 years, it has profound insights into the physiology, physical chemistry of organs, biology cells, membranes, compartments, cellular organelles and functional proteins related with the absorption processes of drugs in the gastrointestinal tract (GIT). Oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders [1]. Colonic delivery offers several potential therapeutic advantages as a site for drug delivery because 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, where poorly absorbed drug molecule may have an improved bioavailability, Reduced proteolytic activity in the colon, longer retention time, Reduced fluid motility and motility in the colon when compared with small intestine [2]. Targeting of drugs to the colon is of increasing importance for local treatment of inflammatory bowel diseases (IBD) of the colon such as ulcerative colitis and crohn's disease (CD). The prevalence of ulcerative colitis and CD ranges from 10 to 70 per 100,000 people, number of other serious diseases of the colon, e.g. cancer, colorectal might also be capable of being treated more effectively if drugs were targeted on the colon.

CTDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak, symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis [3]. Colonic drug delivery can be achieved by oral or rectal administration. To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage form must be formulated taking into account the obstacles of gastrointestinal tract [4].

Advantages of CSDDS [5]

1. It Improved drug utilization and bioavability.
2. Decrease in dose to be administered
3. Decreased side effects
4. It is a promising site for a drug which is unstable or poorly absorbed from upper GI tract
5. Target drug delivery
6. It maintain the drug accuracy

Benefits of Colonic Drug Delivery [6]

1. Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.

Corresponding Author:-**Rakesh Tiwle** Email:-rakesh_tiwle@rediffmail.com

2. The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.
3. The colon targeted drug delivery can also be used for chronotherapy for effective treatment of diseases like asthma, angina and arthritis.
4. Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
5. Local treatment has the advantage of requiring smaller drug quantities.
6. The colon is an attractive site where poorly absorbed drug molecules which improved bioavailability.
7. Bypass initial first pass metabolism.
8. Possibly leading to a reduced incidence of side effects and drug interactions.
11. Improve patient compliance.
12. Targeted drug delivery system.

Disadvantages of Colonic Drug Delivery

1. There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired [7]
2. The major disadvantage of colonic delivery of drug is poor site Specificity.
4. Nature of food present in GIT can affect drug pharmacokinetics. In diseased conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site [8]

Factors Affecting Colon Targeted Drug Delivery

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors

a. Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles.[9] Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.

b. pH of colon

The pH of GIT varies between different individuals. The food intakes, diseased state, influences the pH of the GIT.[10] This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems.

C. Colonic micro flora and enzymes

The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT. [11]The GIT contains a variety of microorganisms that produces many enzymes need for metabolism.

2. Pharmaceutical factors

a. Drug candidates

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc.[12] drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

b. Drug carriers

The various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient,[13] functional groups of drug molecule etc therefore selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used.

Polymers Used in Colon Targeting

Nowadays used in formulating various pharmaceutical products naturally polymer, which are include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides because it contain Polymer contain a large number of structural unit joined by same type linkage, form into a chain like structure.[14] In ancient time natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these polymer many therapeutic system of body namely controlled drug delivery systems [15]

Natural polymer

Chondrotinsulphate,Guar gum, Inulin, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Locust bean gum [16]

Synthetic polymer

Poly vinyl acetate phthalate.Shellac, Ethyl cellulose, Cellulosw acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit [17]

Factors to be considered in Designing CTDDS [18]

Formulations for colonic delivery are, in general, delayed-released dosage forms which may be designed either to provide a ‘burst release’ or a sustained / prolonged or targeted.

(A) Anatomy and physiology of colon

Most digestion and absorption occurs in the small intestine. The small intestine including 3 parts the duodenum, the ileum and the jejunum, enzymes and other substances made by intestinal cells, the pancreas, and the liver are secreted into the small intestine and breakdown starches, sugars, fats, and proteins.[19] Absorption of nutrients occurs through the millions of tiny fingerlike

projections called villi and the even tinier projections on the villi called microvilli. [20] The large intestine has 3 parts the colon, the cecum, and the rectum. The main function of the large intestine is to remove water and salts (electrolytes) from the undigested material and to form solid waste (feces) that can be excreted. In mammals colon is further subdivided into the ascending colon, the *descending colon*, transverse colon and the sigmoid colon. The colon from cecum to the mid transverse colon is also known as the right colon. The remainder is known as the left colon. The location of the parts of the colon are either in the abdominal cavity or behind it in the retroperitoneum. *Ascending colon*. The ascending colon is on the right side of the abdomen. It is the part of the colon from the cecum to the hepatic flexure.

Transverse colon

The transverse colon is the part of the colon from the hepatic flexure (the turn of the colon by the liver) to the splenic flexure (the turn of the colon by the spleen). The transverse colon hangs off the stomach, attached to it by a wide band of tissue called the greater omentum. [21] On the posterior side, the transverse colon is connected to the posterior abdominal wall by a mesentery known as the transverse mesocolon. The transverse colon is encased in peritoneum, and is therefore mobile.

Descending colon

The descending colon is the part of the colon from the splenic flexure to the beginning of the sigmoid colon. It is retroperitoneal in two-thirds of humans. In the other third, it has a (usually short) mesentery.

Sigmoid colon

The name *sigmoid* means S-shaped. The walls of the sigmoid colon are muscular, and contract to increase the pressure inside the colon, causing the stool to move into the rectum. pH of the colon High pH gradient exists between the different parts of GIT. pH gradient between saliva and gastric juice and between gastric juice and intestinal juice is considerably high but that between different parts of intestine is low.[22] The pH of the gastrointestinal tract is subject to both inter and intra subject variations like diet, diseased state, and food intake influence the pH of the gastrointestinal fluid. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. There is a fall in the pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

(B) Colonic micro flora

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, theses enzymes are derived from gut Micro flora residing in high number in the colon. Colon consists of a more than 500 different types of enzyme liberating symbiotic anaerobes.[25]These enzymes derived from microbes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent i.e. release drug from the polymeric prodrugs. There is a vast difference in the micro flora count of intestine and cecum.

Intestinal micro flora count: 103 CFU/ml, ***Colonic micro flora count:*** 1012 CFU/ml

During illness and antibiotic therapy there is reversible destruction of microbes. The most important anaerobic bacteria are bactericides, Eubacterium, Peptococcus, Peptostreptocococcus, Ruminococcus, Propionibacterium and Clostridium.

(C) Transit time to colon

Under the normal conditions transit time to colon is between 5 to 7 h. Stomach 2 h , Upper small intestine 1 h, Lower small intestine 2 h, So, overall transit time is approximately 5 h. But this transit time varies with fed and fasted state of GIT. Under fasted state transit time is between 3 to 5 h and in fed state it is between 6 to 10 h. The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors other than diet like mobility, stress, disease state and presence of other drugs. In the healthy young and adult males, dosage forms such as tablets pass through the colon in approximately 20-30 h, although the transit time of a few hours to more than 2 days can occur.[26] Diseases affecting colonic transit have important implications for drug delivery diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant. Average pH in the GI tract .

Classification or Pharmaceutical Approches of CTDDS

1) pH dependent systems.
2) Time dependent systems.
3) Bacterial enzyme dependent system.
4) Covalent linkage of a drug with a carrier
5) Redox release system.
6) Bioadhesive systems.
7) Coating with microparticles.
8) Osmotic controlled drug delivery.
9) Multiparticulate System

1) PH dependent systems

pH of human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. 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 or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. [27]

Disadvantages of pH dependent systems

Lack of consistency in the dissolution of polymer at the desired site. Moreover, many factors such as the presence of short chain fatty acids, residues of bile acids, carbon dioxide or other fermentation products can reduce the colonic pH to approximately 6 which can certainly affect the release of drug in the colon.

2) Time dependent systems [28]

Strategy of time released system is to resist the acidic environment of stomach and release the drug after predetermined lag time, after which release of drug take place. Factors affecting release from time dependent systems Residence time plays a key role here along with it Fed and fasted state of the subject and the interdigestive phase may prolong emptying time of stomach. Residence time of stomach 2 h small intestine approx 2 to 4 h.

Disadvantages of time dependent systems:

Individual to individual variation arises due to health, pathologic state, concomitant medication which causes Premature / Delayed drug release.

3) Bacterial enzyme dependent system

The bioenvironmental inside the human GIT is characterized by the presence of complex micro flora especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary component or other materials.[29] Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, have been exploited in designing drugs for colon targeting. Actually, upon passage of the CTDDS through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present that is quiet insufficient for cleavage of polymer coating.

4) Covalent linkage of the drug with a carrier

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. [30] This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug. The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon [31].

5) Redox sensitive polymers

Novel polymers that hydrolyzed nonenzymatically by enzymatically generated flavins are being developed for colon targeting. [32] Under anaerobic conditions, bacterial azo reduction by enzymatically generated reduced flavins where the initial substrate thought to be involved in cellular electron transport requires the presence of NADPH as its electron source. As NADPH is oxidized, the electron mediator (reduced flavins) acts as an electron shuttle from the NADPH dependent flavoprotein to the azo compound. Reduction of the azo bond to the hydroazo intermediate requires a low electron density within the azo region, and thus substitution of electron-withdrawing groups will favor this reaction.[33] Redox potential is an expression of the total metabolic and bacterial activity in the colon and it is believed to be insensitive to dietary changes. The mean redox potential in proximal small bowl is - 67 90 mv, in the distal small bowl is -196 97 mv and in the colon is -145 72 mv. Microflora-induced changes in the redox potential can also be used as a highly selective mechanism for targeting to the colon.

6) Bioadhesive systems

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects.[34] Dissolution of dosage form and simultaneous absorption from upper GIT lead to low intracolonic drug concentration as well as absorption of drugs result in the generation of side effects. Bioadhesion is a process whereby drug remains in contact with a particular organ for a longer period of time.It may be used for improved absorption of poorly absorbable drugs. Polymers: polycarbophils, polyurethanes and poloxamers.

7) Coating with microparticles [35]

It consists of small silica particles (5-10 μm in diameter) covalently linked to a drug.

8) Osmotic controlled drug delivery

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable The OROS-CT system can be 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.[36] Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after he OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves.[37] Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach and hence no drug is delivered. As the unit enter the small intestine, the coating dissolve in this higher pH environment *(pH >7),* water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the

semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine.

Drug Used in Colon Drug Delivery System

1. METRONIDAZOLE [38]

Chemical name: 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole or 2-methyl-5-nitro imidazole-1-ethanol
Derivatives: Hydrochloride, Benzoate and Mesylate
Empirical formula: C6H9N3O3
Molecular weight: 171.16
Appearance: White to offwhite, crystalline odourless powder
Melting point: Crystals- 158 to 160 0C
Solubility: Slightly soluble in water and ethanol, very slightly soluble in ether.

Mechanism of action

MTZ is a prodrug; it requires reductive activation of the nitro group by susceptible organisms. MTZ, taken up by diffusion, is selectively absorbed by anaerobic bacteria and sensitive protozoa. Once taken up by anaerobes, it is non-enzymatically reduced by reacting with reduced ferredoxin,[39] which is generated by pyruvate oxido-reductase. This reduction causes the production of toxic products to anaerobic cells, and allows for selective accumulation in anaerobes. MTZ metabolites are taken up into bacterial DNA, and form unstable molecules.[40] This function only occurs when MTZ is partially reduced, and because this reduction usually happens only in anaerobic cells, it has relatively little effect upon human cells or aerobic bacteria

Pharmacokinetics

Preparations of MTZ are available for oral, intravenous, intravaginal, and topical administration. Absorption: The drug usually is absorbed completely and promptly after oral intake, reaching concentrations in plasma of 8 to 13 mg/ml within 0.25 to 4 h after a single.[41]

Contraindications

- ✓ Patients with evidence of a history of blood dysterias should not receive MTZ
- ✓ sinceaccasionlly leucopenia has been observed during its administration.
- ✓ Active organic disease of the central nervous system.
- ✓ Pregnancy (first trimester)

Interactions

Alcohol: MTZ taken in combination with alcohol may produce abdominal cramps, nausea, vomiting, headache and flushing.
Disulfiram: In a clinical trial of combined therapy with disulfiram and MTZ in the treatment of chronic alcoholics, severe acute psychotic reactions occurred in 6 out of 29 patients.[42]
Warfarin: MTZ inhibits the breakdown of the more potent S-isomer of warfarin. This is the pharmacologically active metabolite of the racemic parent molecule. Therefore, the activity of warfarin is enhanced by MTZ [43]
Phenobarbitone: Decreases the effect of MTZ probably due to increased metabolism.
Cyclophosphamide and Carmustine: MTZ should used with caution in patients who are receiving cyclophosphamide or carmustine as a drug interaction shown in mice, leads to increased toxicity.

2. SATRANIDAZOLE [44]

Introduction

Chemical name: 1-methylsulfonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-
imidazolidinone.
Empirical formula: C8H11N5O5S
Molecular weight: 289.27 g/mol
Appearance: White to off white, crystalline odourless powder
Melting point: 184–189°C
Solubility: soluble in water and ethanol.

Mechanism of action

Satranidazole has been shown to damage DNA as a consequence of reduction of the nitro group. The features of the damage viz. helix destabilization, strand breakage and the release of thymine derivatives are typical of 5-nitroimidazole drugs. The lowered electron values for reduction in the presence of DNA are also characteristic of nitroimidazoles and indicate that an electron affinic reduced intermediate is capable of abstracting electrons from DNA, thereby oxidizing it, causing strand breaks presumably in the region of thymidine residues.

Excretion: Half-life: 14 h in human

Dosage and Therapeutic uses

It possesses potent antiprotozoal activity against Entamoebahistolytica, Trepenomavaginalis, and Giardia Amoebic liver abscess: 300 mg bid for 10 days (Adult dose). Giardiasis: 600 mg as a single dose (Adult dose). Trichomoniasis: 600 mg as a single dose (Adult dose).

Contraindications

Pregnancy and lactation.

Adverse effects

Headache, dry mouth, weakness and dizziness.

Interactions

STZ taken in combination with alcohol may produce abdominal cramps, nausea, vomiting, headache and flushing. May result in disulfiram-like reaction when used with alcohol.

Table 1. Transit time of different parts of GIT

Part of GIT	Transit time
Fasted state	10min – 2hr
Fed state	>2hr
Small intestine transit	3-4hr
Colon transit	20-35hr

Table 2. PH in different parts of Colon

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small intestine	6.6- 7.5
Colon **Ascending colon** **Transverse colon**	6.4 6.6 7.0

Table 3. Different micro flora, enzymes released and action

Microorganism	Enzyme	Metabolic reaction
Clostridia, Lactobacilli	Hydrogenase	Reduces carbonyl groups & aliphaticdouble bonds
E.coli, Bacteroids	Nitroreductase	Reduces aromatic & heterocyclic nitro compounds
Clostridia, Eubacteria	Glucosidase	Cleavage of bglycosidase of alcohols & phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of Osulphates&Sulfamates

Table 4. Drugs used in Colon Associated Disease Conditions

Target Site	Disease Condition	Symptoms	Drugs and Active Agents	Marketed Formulations
Systemic Action	Ulcerative Colitis	Fulminant Colitis, Pancolitis, Ulcerative proctits	Prednisolone Beclomethasone	Acticort Tab. Salbair B Cap.
Topical Local action	Irritable Bowel Syndrome	Abdominal pain or cramping, bloated feeling, flatulence, diarrhea or constipation people with IBS may also experience alternating bouts of constipation & diarrhea, mucus in stool	Dicyclomine Hyoscine Propantheline Cimetropium Tegaserod	Ah-Spas Tab Biscoats Tab. Pro-Banthine Cap. Zelnorm Tab.
	Ulcerative Colitis	Inflammation in the rectum, rectal bleeding, rectal pain	Mesalamine Sulfasalazine Mercaptopurine Balsalazide	Inflacol Tab. Saaz Tab 6-Mp Tab. Balacol Tab.
	Colorectal Cancer	A change in bowel habits, narrow stools, rectal bleeding or blood in stool, persistent abdominal discomfort, such as cramps, gas or pain, abdominal pain with a bowel movement, unexplained weight loss	5 Flourouracil, Leucovorin Cetuximab	Florac Inj. Leucorine Tab
	Diverticulitis	Formation of pouches (diverticula) on the outside of the colon due to bacterial infection	Metronidazole Clindamycin	Flygyl Tab. Dalacine Tab.
	Antibiotic Associated Colitis	Overgrowth of *Clostridium Difficile*and its subsequent Toxin production	Broadspectrum penicillins (e.g., ampicillin, amoxicillin)	Almox Tab

Table 5. pH in different parts of Colon

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small intestine	6.6- 7.5

Colon	
Ascending colon	6.4
Transverse colon	6.6
Descending colon	7.0

Table 6. List of marketed products of metronidazole Brand Name

Brand Name	**Dosage Form**	**Manufacturer**
Aristogyl®	200 mg, 400 mg tablets and 100 mg suspension	Aristo
Aldezole®	200 mg, 400 mg tablets, 200 mg suspension and 500 mg injection	Albert David
Compeba®	200 mg tablets	IDPL
Flagyl ®	200 mg, 400 mg tablets and 200 mg suspension	NPIL
Unimezol®	200 mg, 400 mg tablets and 200 mg suspension	Unichem
Metron®	200 mg, 400 mg tablets and 200 mg suspension	Alkem
List of combination products of metronidazole		
Metrohex®	1% metronidazole + 0.25% chlorhexidine gel	Dr. Reddy's Laboratory
Stedmox-M®	200 mg metronidazole + 250 mg amoxicillin capsules	Stedman
Gramogyl®	100 mg metronidazole +100 mg norfloxacin suspension	Ranbaxy
Metrokind-P®	1% metronidazole + 5% povidone Iodine gel	Mankind
Diof ®	600 mg metronidazole + 200 mg ofloxacintabletsn	Zuventus

Table 7.List of marketed products of satranidazole Brand Name

Brand Name	**Dosage Form**	**Manufacturer**
Satrogyl®	300 mg satranidazole tablets	Alkem
Satromax O®	300 mg satranidazole and 200 mg ofloxacin tablets	Indchem

Figure 1. Anatomy and physiology of colon

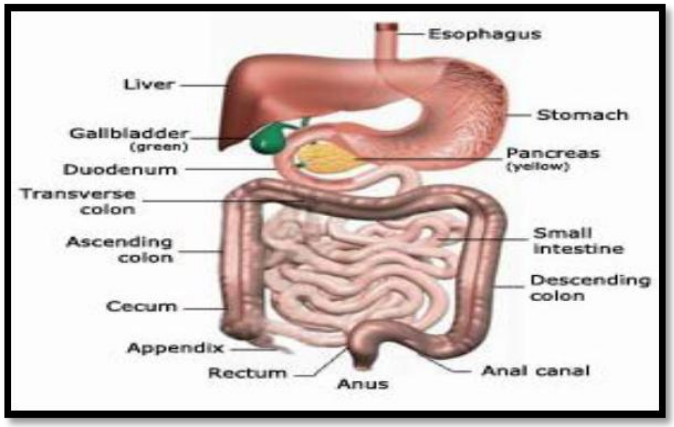


Figure 2. Covalent linkage of the drug along with carrier

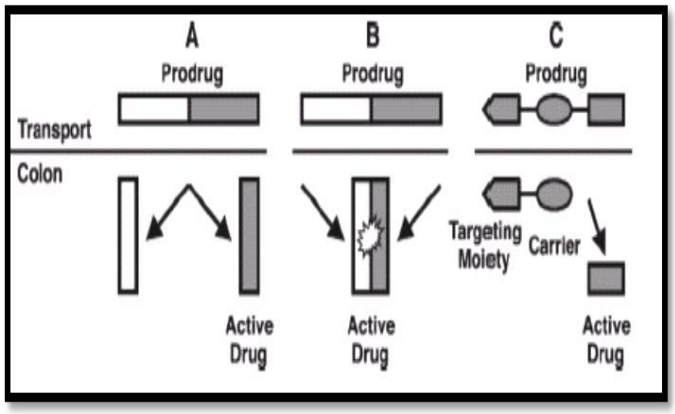


Figure 3(a). Drug release mechanism of port system

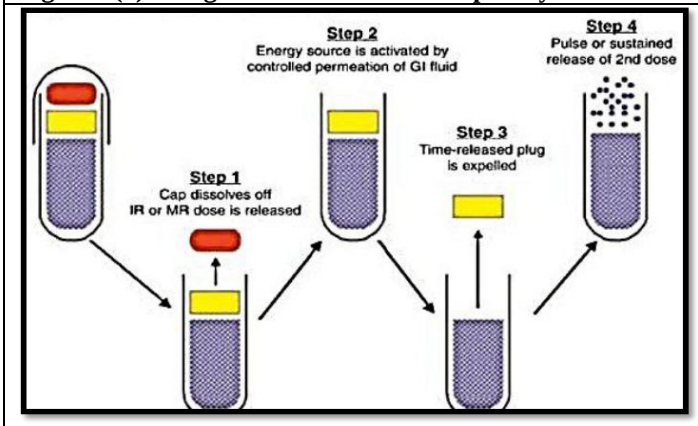


Figure 3(b). Osmotically controlled

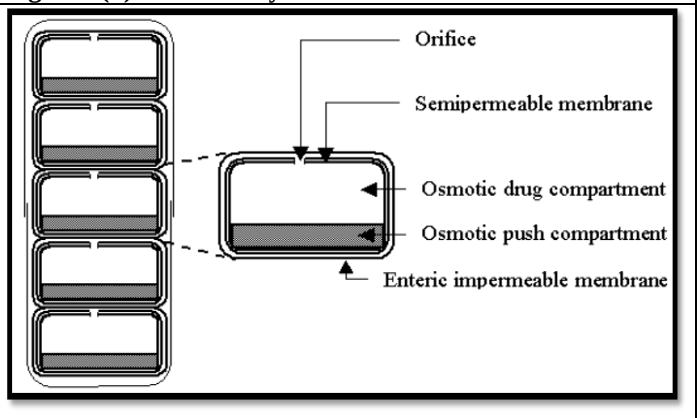


Figure 4. Multiparticulate system

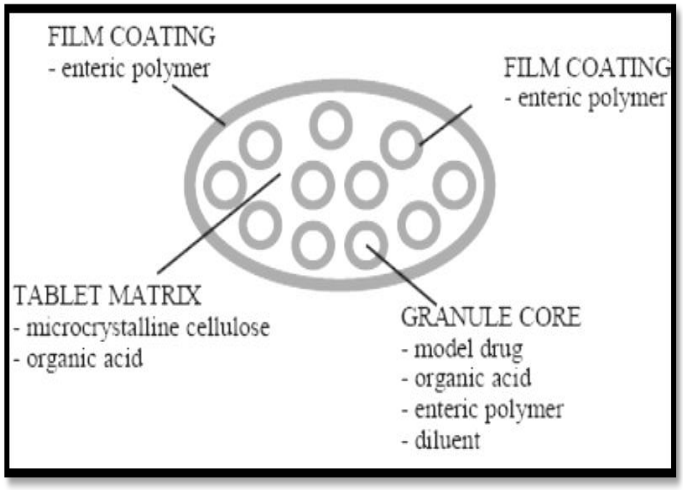


Figure 5(a). Structure of Metronidazole

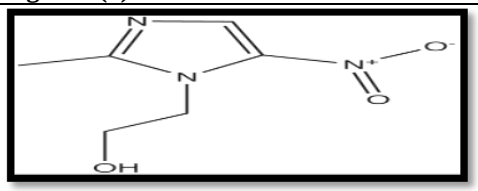


Figure 5(b). Structure of Satranidazole

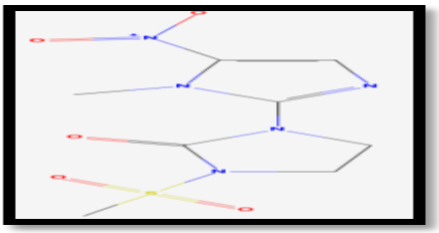


Figure 6. Delivery system of olsalazine

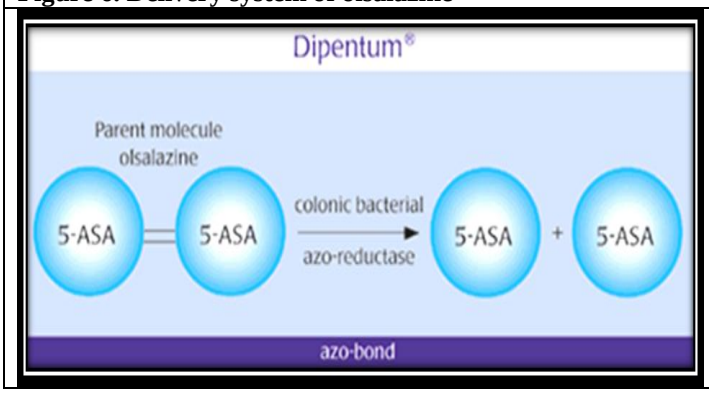
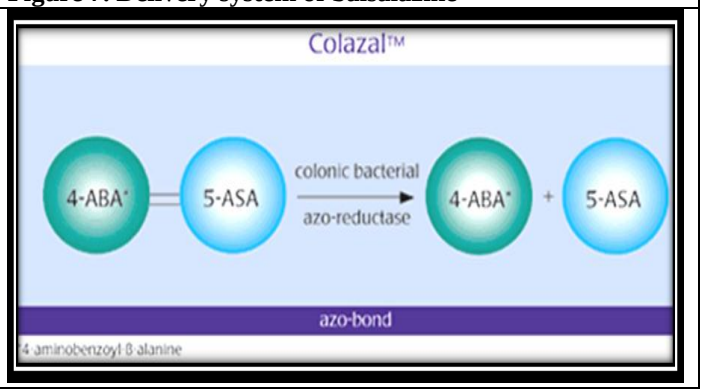


Figure 7. Delivery system of balsalazine



Evalutation Parameters

***In-vitro* dissolution test** [45]

The dissolution testing is done using the conventional basket method or dissolution apparatus. 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.

***In- vivo* evaluation** [46]

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 GIT of rat and rabbit is comparable to that in human.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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