

## RECENT ADVANCES IN COLON SPECIFIC DRUG DELIVERY SYSTEM

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### ABSTRACT

Colon specific drug delivery system are utilized to deliver the drug directly into the Colon. The colon specific drug delivery system provides optimum utilization of the drug. Colon specific drug delivery system are basically a form of Targeted drug delivery system. They are the better choice for Crohn's disease, Celiac disease, Ulcerative colitis, and in detection of GI bleeding. The recent development of the colon specific drug delivery system makes a dramatic change in colon specific drug delivery system. A new development in the colon targeted drug delivery system like Enterion capsule, (To detect the positioning of the disease) Swallowable Camera Capsule (To detect the images used to diagnose a number of disease) makes easy to diagnose a number of diseases and provides useful information regarding the

treatment of the disease. Now a days colon specific delivery system like "Robotic Beetle" is used to detect the small intestine Polyps & Tumor and provide direct therapy, some of colon specific drug delivery system are basically activated when they come in contact with Enzyme and provide Therapeutic Action.

**KEYWORDS:** Colon, Enterion, Approaches, Robotic etc.

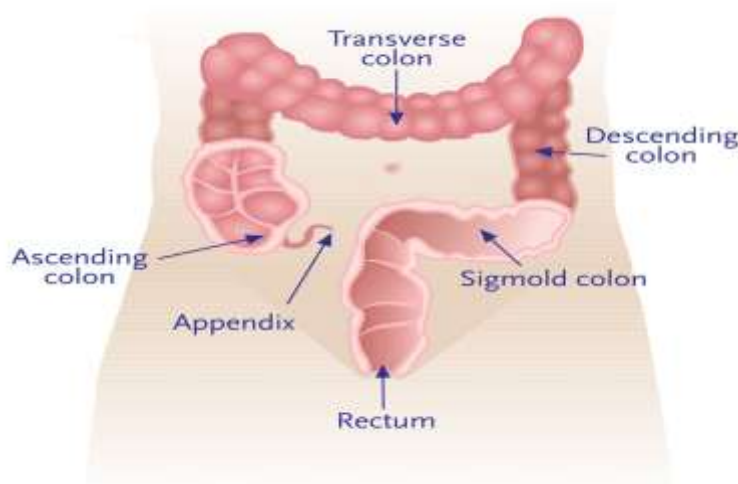
### INTRODUCTION

The colon is also called the large intestine. The ileum (last part of the small intestine) connects to the cecum (first part of the colon) in the lower right abdomen. The rest of the colon is divided into four parts.

- The ascending colon travels up the right side of the abdomen.
- The transverse colon runs across the abdomen.

- The descending colon travels down the left abdomen.
- The sigmoid colon is a short curving of the colon, just before the rectum.

The colon removes water, salt, and some nutrients forming stool. Muscles line the colon's walls, squeezing its contents along. Billions of bacteria coat the colon and its contents, living in a healthy balance with the body.<sup>[1,2]</sup>



**Structure of colon with their parts**

So the colon is a main part of our body and direct delivery of the drug in colon provide a colon targeted drug delivery system. In the recent years there is new development in field of colon specific drug delivery system. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents.<sup>[3]</sup>

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects.

The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative 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 duodenum

and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. the following are the diseases drugs and their target sites are given in the table.<sup>[4]</sup>

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

**colon targeting diseases, drugs and their sites**

### Advantages of colon specific drug delivery system

There are several advantages of colon targeted drug delivery system some of them are given below.

- Drugs are directly available at the target site.
- Comparatively lesser amount of required dose.
- Decreased side effects.
- Improved drug utilization.<sup>[5]</sup>
- Improved patient convenience and compliance.
- Reduction in fluctuation in steady state level.
- Increased safety margin.
- 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.

**Limitation of the colon targeted drug delivery system**

- One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system *in-vitro*. This is due to the rationale after a colon specific drug delivery system is quite diverse.
- The colon PH is neutral or near neutral. So at this PH there is reduction in the digestive enzyme activity. and before reaching the target site or at the colon the drug is required to travel through a long path way. so the targeting of the drug to the colon is very complicated process. the drug before reaching at the colon the drug first comes in the contact with the GIT so the large number of enzymes present in the GIT causes the absorption & deterioration.
- For site specific delivery of the drug, the drug should be available in the solution form. first it should dissolve in the luminal fluid. but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.
- In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

**General considerations for design of colonic formulations**

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

- a. Pathology and of disease, especially the affected parts of the lower GIT.
- b. Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery.
- c. The preferred release data of the drug.

Very common physiological factor which is considered in the design of delayed release colonic formulations is pH gradient of the GI tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH is  $6.6 \pm 0.5$ ) to the end of the ileum (pH is  $7.5 \pm 0.4$ ), a decrease in the cecum (pH is  $6.4 \pm 0.4$ ), and then a slow rise from the right to the left colon with a final value of  $7.0 \pm 0.7$ . Some reports suggested that

alterations in gastrointestinal pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations.<sup>[6]</sup>

### **Approaches of Designing of oral colon specific drug delivery system**

To achieve successful colonic delivery, a drug needs to be protected from absorption and or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. Colon targeting is naturally of value for the topical treatment of diseases of colon such as Chron's diseases, ulcerative colitis, colorectal cancer and ameobiasis. Peptides, proteins, oligonucleotides and vaccines pose potential candidature for colon targeted drug delivery.

### **METHODS**

The various strategies for targeting orally administered drugs to the colon include covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bioadhesive systems and osmotic controlled drug delivery systems. Various prodrugs (sulfasalazine, ipsalazine, balsalazine and olsalazine) have been developed that are aimed to deliver 5-amino salicylic acid (5-ASA) for localized chemotherapy of inflammatory bowel disease (IBD). Microbially degradable polymers especially azo cross linked polymers have been investigated for use in targeting of drugs to colon. Certain plant polysaccharides such as amylose, inulin, pectin and guar gum remains unaffected in the presence of gastrointestinal enzymes and have the way for the formulation of colon targeted drug delivery systems. Times dependent drug delivery systems have been developed that are based on the principle to prevent release of drug until 3-4 h after leaving the stomach. Redox sensitive polymers and bioadhesive systems have also been exploited to deliver the drugs into the colon.

### **Following are the some basic methods by which a colon specific drug can be designed**

- Embedding in matrices
- Embedding in biodegradable matrices and hydrogels
- Bioadhesive systems
- Osmotic controlled drug delivery
- Coating with microparticles
- Coating with polymers
- Coating with biodegradable polymers

- Coating with pH-sensitive polymers
- Time dependent approach
- Pressure dependent
- Azo bond conjugates the intestinal microflora
- Glycoside conjugates
- Amino-acid conjugates

### **Embedding in matrices**

The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the colon for liberation of entrapped drug.

### **Embedding in biodegradable matrices and hydrogels**

the polysaccharides are resistant to the digestive action of the microorganisms. 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 polysaccharidases and results in the degradation of the matrices. Common polysaccharides used are amylase, dextran, cyclodextrin, chytosan, pectin ,guar gum etc.

The commonly used hydrogels are azoaromatic hydrogels, inulin hydrogels,dextran hydrogels etc.

### **Bioadhesive systems**

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

### **Coating with microparticles**

Enta amoeba histolytica remains in the intestine and it requires high drug concentration for the treatment but coating of the drug 2-(4-aminophenoxyethyl)-5-nitro-1-methyl imidazole with silica particles shows that trophozoites phagocytosed the particles *in vivo* and *in vitro* , followed by rapid cell death due to the released drug.

**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 4 mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane.<sup>[7]</sup>

**Coating with polymers**

the drug molecule is intact with the suitable polymer in that manner that the drug release only in the colon instead of other part like small intestine and stomach.

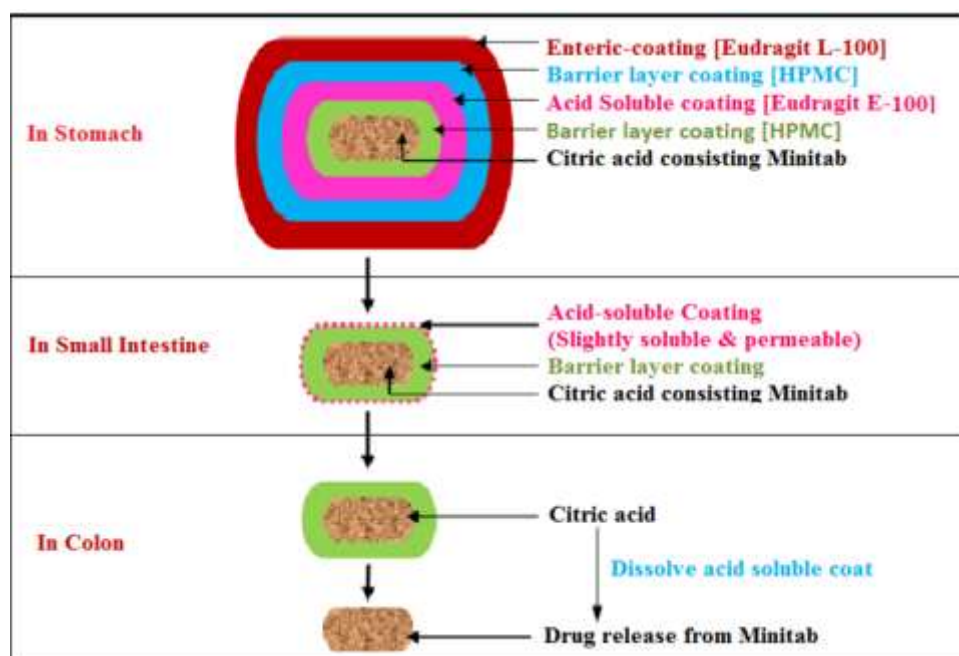
**Coating with biodegradable polymers**

The intestinal microflora has a large metabolic capacity and it appears that reduction of azo bonds is a general reaction of colonic bacteria. The azo polymers having a high degree of hydrophilicity were degraded by colonic bacteria. A large number of microorganisms are present in the colon. They are involved in the reduction of the dietary components. So the coating of the drug with biodegradable polymer is another approach. The microorganisms present in the colon cause the cleavage of the polymer at the alkaline pH and in the colon. Azo polymers are most widely used for this purpose.

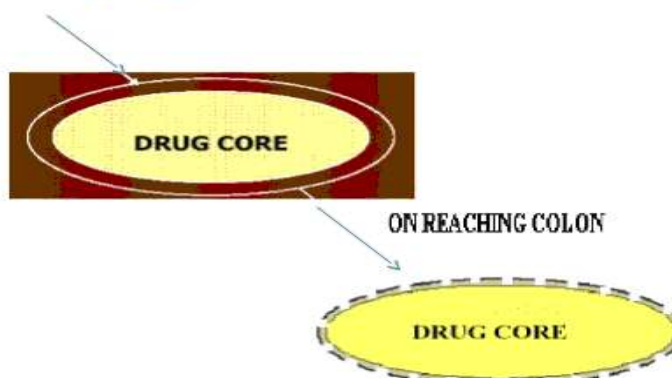
**Coating with pH-sensitive polymers**

The molecule is coated with the pH sensitive polymer so that the release of the drug only takes place at slightly neutral or alkaline pH but not release at acidic pH in stomach and small intestine. Polymers used are for eg. Eudragit, poly vinyl acetate phthalate, hydroxyl propyl methyl cellulose phthalate. Eudragit L and S are copolymers of methacrylic acid and methacrylate. 5-aminosalicylic acid is commercially available as an oral dosage form coated with Eudragit L and S. Colon targeted drug delivery systems based on methacrylic resins have been described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxene, Khan *et al.* prepared Lactose based placebo tablets and coated using various combinations of two methacrylic acid polymers, Eudragit L100-55 and Eudragit 100 by spraying from aqueous systems.<sup>[8]</sup>





### pH sensitive polymer



Mechanism of action of the controlled release colon specific drug coating with PH sensitive polymer is shown in the above diagram when the drug molecule comes in the contact with the colon the ph sensitive polymer get lysed and the drug is applicable to show its action.<sup>[9]</sup>

### Time dependent approach

The time-dependent approach is also known as pulsatile release, delayed, or sigmoidal release system. In this type the drug release in a system occur after a certain lag period which is related to the time spend by the drug in reaching from mouth to the colon. so the lag time is depend on the size of the drug and gastric emptying.<sup>[10]</sup>

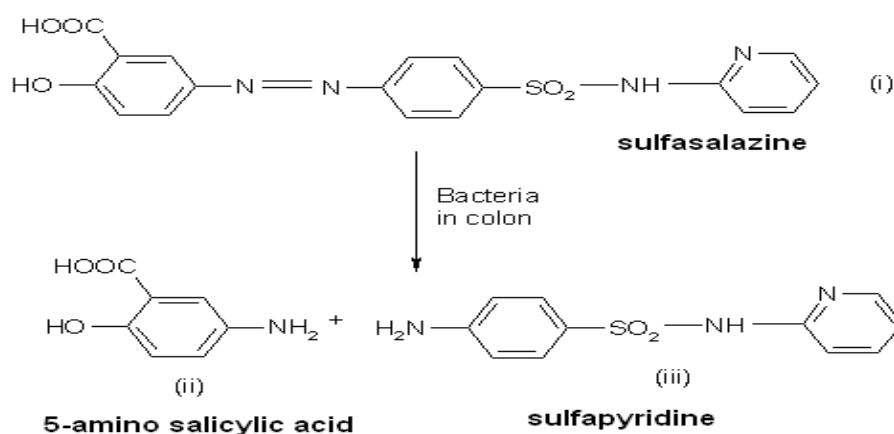


### Pressure dependent delivery

gastro intestinal pressure is used for this purpose in this type the pressure is generated by larger contraction of the muscles of the gastric part. so the molecule of the drug travels fastly in the gastric part and there is also increase in gastric intestinal motility so drug in short time reached to the colon and show effect. For this purpose the capsule shell are prepared of water insoluble polymer ethyl cellulose.

### Azo bond conjugates the intestinal microflora

It is characterized by a complex and relatively stable community of microorganism, they show various metabolic reactions including reduction of azo and nitro group.

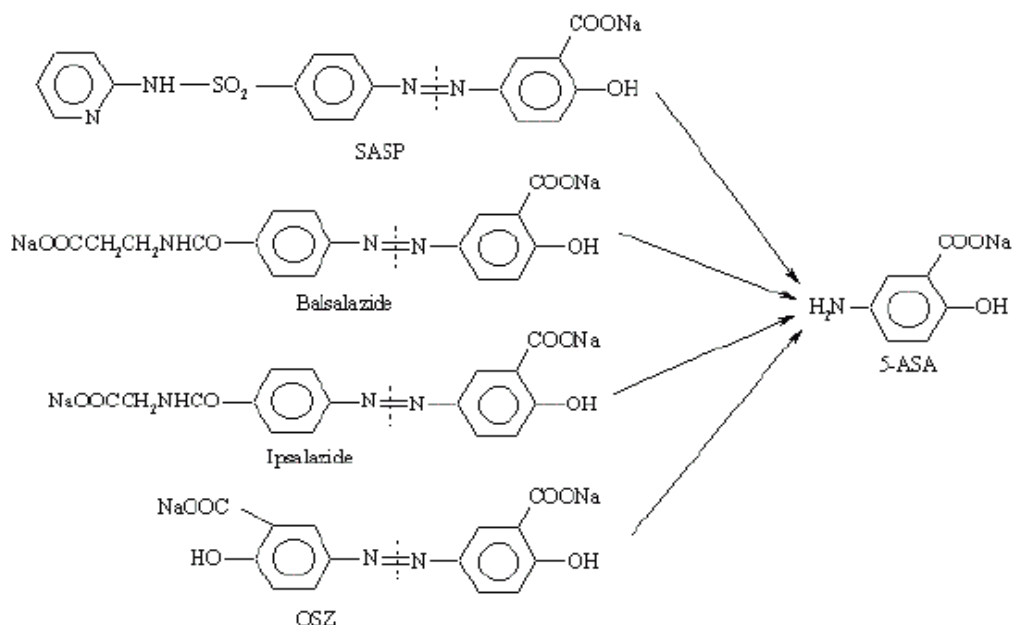


### Hydrolysis of sulfasalazine by azo reductase into sulfapyridine and 5-aminosalicylic acid

For example the drug sulfasalazine is used for the treatment of rheumatoid arthritis and anti-inflammatory diseases when the sulfasalazine is taken orally the azo reductase enzyme secretes by the bacteria causes the reduction of the sulfasalazine and the two species formed are sulfapyridine and 5-amino salicylic acid.

The same application is applied for the drug prontosil. the reduction of the drug prontosil by azo reductase form the active species sulfanilamide.

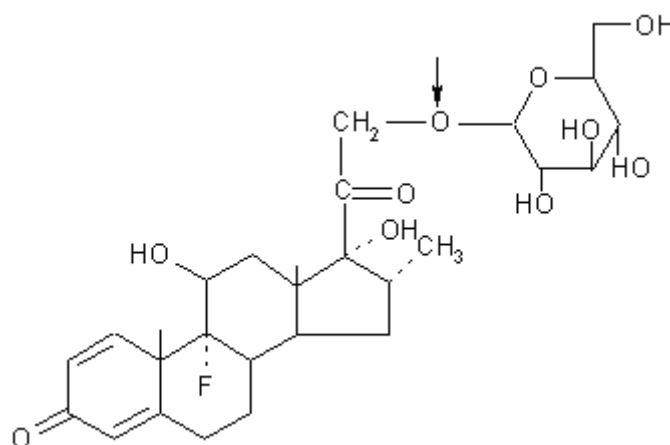
So the prodrugs are designed that when they come in contact with GIT they remain intact but when they comes in contact with in the colon the hydrolysis or break down of the drug take place. the hydrolysis is mainly carried out by the enzyme azo reductase following are the some example of the drugs which activated when they comes in contact with the colon.



**The chemical structure of sulfasalazine, balsalazine, osalazine cleavage leading to the formation of active species 5-amino salicylic acid**

### Glycoside conjugates

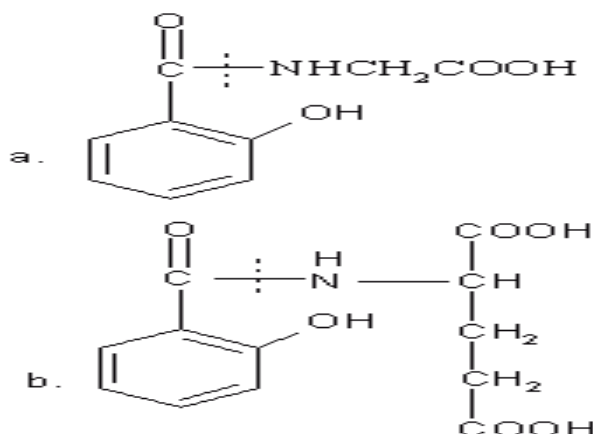
Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. The drug glycosides are mainly hydrophilic in nature so they are not absorbed by the small intestine but when they reach in the colon they are hydrolysed by the enzyme bacterial glycosidases.



**Dexamethasone-21-O-β-D-glucoside (Arrow shows site of action of glycosidase)**

### Amino-acid conjugates

protein is made up by two hydrophilic groups like  $-NH_2$  and  $-COOH$ . they reduce the cell membrane permeability. so various pro drugs are designed by the conjugation of the drug molecule with the amino acids.<sup>[11]</sup>



**Glycine and glutamic acid conjugates of salicylic acid. (a) Salicyluric acid. (b) Salicyl-glutamic acid conjugate (Dotted line shows the site of cleavage)**

### Techniques employed for the colon specific drug delivery system

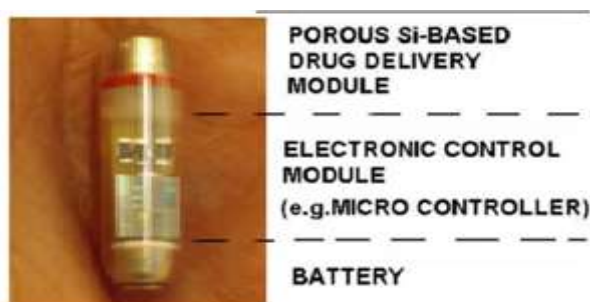
#### Target technology

As the name suggest target technology is designed to for site specific delivery in the colon. or for providing the targeted delivery of the drug in the colon. The technology is based on the application of pH Sensitive coatings onto injection-moulded starch capsules. this shows reliable in vivo performance. By this technique about 90% of the drug is released at the target site. target technology specially used for the treatment of the inflammatory bowel diseases.

#### Ticking capsules

It is a chronotherapeutic device controlled by electrical means and provide a pulsatile release of the drug. it consist of three parts.

- Porous Si-based drug delivery module
- Electronic control module (e.g. micro controller)
- Battery



**Design of ticking capsule**

As shown in the figure the drug is delivered through the upper part (porous si based drug delivery system). And the electronic controller module control the delivery and the pulsatile release of the drug.

### **Multi particulates**

Multiparticulates are used as drug carriers in pH-sensitive, time dependent and microbial control systems for colon targeting. multi particulate system offers advantage over conventional dosage form like capsule and tablet. they are.

- fewer adverse effects than single unit dosage form
- more predictable gastric emptying
- frequency of dose required is less
- increase patient convenience

A multi particulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. this system is prepared the drug loaded cellulose acetate butyrate. microsphere is loaded by an enteric coated polymer which prevents the drug release in the stomach and also causes the drug release in the intestine.

A Multiparticulate system combining pH sensitive property and specific biodegradability was prepared for colon targeted delivery of metronidazole. The Multiparticulate system was prepared by coating cross-linked chitosan microspheres exploring Eudragit L-100 and S-100 as pH sensitive polymers.

High-Amylose corn-starch and Pectin blend micro particles of diclofenac sodium for colon-targeted delivery were prepared by spray drying technique.

### **Microspheres**

Methotrexate is combined with cross link guar gum molecules to provide a sustained release action in the colon which is used in the treatment of the colorectal cancer. In this method glutaraldehyde is used as a cross linking molecule and guar gum is used as a microsphere. And the microsphere is prepared by emulsification method. In this method 79% of the drug releases at the colon part while in case of conventional dosage form the percentage is very low.

One another drug 5-fluorouracil is also used for the treatment of the cancer. In this method core microspheres of alginate were prepared by modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The results showed that this method had great potential in delivery of 5-fluorouracil to the colon region

### Enterion capsule Technology

The Enterion capsule has recently been developed by Phacton Research, Nottingham, UK, for targeted delivery of a wide range of different drug formulations into any region of the gut. It is a 32-mm long, round-ended capsule and contains a drug reservoir with a volume capacity of approximately 1 ml. with either a liquid formulation (e.g. Solution, Suspension) or a particulate formulation (e.g., powder, pellets, in situ affects etc.) through an opening 9 mm in diameter, which is then sealed by inserting a push-on Cap fitted with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high tensile strength polymer filament

A radio active marker is also used in this technique to determine the location of the capsule. when the capsule reaches the target site the drug is released by the action of the magnetic field. the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of the capsule, which maintains a seal and presents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully.<sup>[12]</sup>

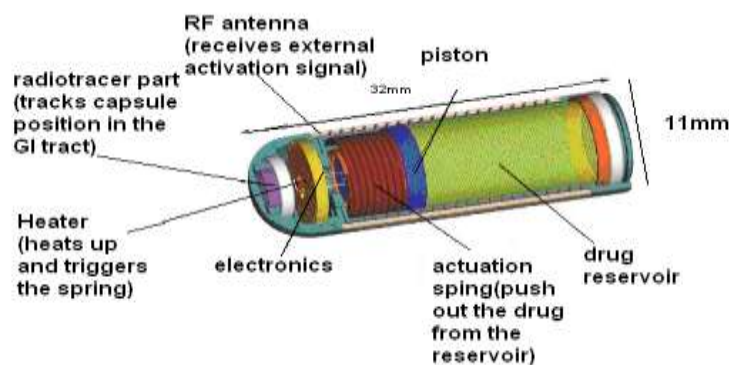


**Design of Enterion capsule**

The Enterion capsule is manufactured from medical grade plastics, and is approximately the size of a “000” capsule, with a drug reservoir of approximately 1ml. The Enterion capsule offers the opportunity to obtain data on the intestinal absorption of drugs in humans using a range of complex formulations both easily and efficiently. By delivering the drug in different physical forms into a specific region of the intestine, the respective contribution of intestinal permeability and/or in vivo dissolution to bioavailability is easily assessed.

Typically, the choice of formulation used in a study is driven by the key scientific questions of the project. A wide range of pharmaceutically relevant formulations can be loaded into the reservoir including.

- Active pharmaceutical ingredient (API)
- particulates
- pellets
- crushed tablets
- solutions
- suspensions.



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