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Review Article

COLON TARGETED DRUG DELIVERY AND NOVEL APPROACHES

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ABSTRACT

Now a day's oral drug delivery system is having a great potential advantages. Number of dosage form available in the market is for orally administration. Novel colon drug delivery system is developed for targeting the diseases associated with the colon like ulcerative colitis, Crohn's diseases etc.different types of approaches developed for drug targeting to the colon like Coating of the drug core with pH sensitive polymers, Time Controlled Release System, Pressure dependent systems,Microbially Triggered Drug Delivery system etc. the main mechanism of these system is protect the drug from acidic environment and release only at site of the colon. Now a day's sustained and controlled release colon drug delivery system has been developed for treating colonic disease. Colon drug delivery system increases efficacy and bioavailability of drug.

KEY WORDS: Colon drug delivery system, Anatomy, Advantages, Novel approaches.

INTRODUCTION

Oral rout is the simple and more convenient rout for administration of drugs. Now a day's most of the delivery systems available in the market are the oral drug delivery. Most of the techniques developed to the formulation of the colon drug delivery system. Colon drug delivery system is most useful for treating diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation. Colon drug delivery system is not useful for treatment of colon system. Oral route of administration is the great patient acceptance and ease of easy administration disease but also useful forsystemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents and delivery of low molecular weight compound .If the drug having high first pass metabolism or drug degraded in the stomach it is formulated for colon delivery because it protect from stomach environment. Drug released and absorbed once th system reaches the colon. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time Kumar (2013), Challa (2011), Singh (2010). The colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Colon is large amount of lymphoid tissue, e.g., Uptake of antigen into mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. Region of colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than stomach and Small intestine. Main applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction. Sustain release mechanism of colon drug delivery useful for improving drug efficacy by concentrating the drug molecules where they are need most. It is also minimize the side effect of the drug and increase stability of the drug in upper g.i.t. and stomach. The colon having high water absorption capacity, the colonic contents are

considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low Singh (2012),Anu (2013). Those drugs having poor bioavailability they are formulated for colon delivery for incerseing bioavailability. The colon has a long retention time and appears highly responsible to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release period's by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices Kumar (2013).The bioavailability of poorly soluble drugs in the colonic reasons can be enhanced due to following reasons:

1. Less hostile environment of the colonic region with less diversity and intensity of activity than the stomach and small intestine.
2. Proteolytic activity of colon mucosa is Comparative much less than that observed in the small intestine, thus colon drug delivery system protects the peptide drugs from hydrolysis, and enzyme degradation in duodenum and jejunum and eventually releases the drug ileum or colon which leads to greater bioavailability.
3. Colon has a longer residence time which is up to 5 days and is highly responsive to absorption enhancers Chandra (2013).

There are various techniques developed for formulation of colon drug delivery, which is colon drug targeting can be achieved, for example, formation of prodrug, coating with pH-sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems . Coating of the drugs with pH sensitive polymers provides simple approach for colon-specific drug delivery Gupta(2010) .The colonic region contains over 400 distinct species of bacteria a possible population of up to 1010 bacteria per gram of colonic contents which is responsible for absorption and metabolism of drugs Kolte(2012), Jawalkot(2013), Philip(2010).

2. NEED FOR COLON TARGETED DRUG DELIVERY:

2.1 For the treatment of various colonic diseases like,

- Ulcerative colitis
- Crohn's disease
- Colon cancer
- Irritable bowel syndrome
- Infections

2.2 For the treatment of nicotine addiction.

2.3 Disease sensitive to circadian rhythms such as asthma, angina and arthritis are
treated efficiently by colon targeting of drugs.

2.4 Delivery of drugs that are found to be absorbable in colon like steroids
thereby increasing drug efficiency and reducing dosing frequency.

2.5 For the absorption of protein and peptides due to less intensity of digestive
andProteolytic enzymes in the colon.

2.6 This site is used for delivery of drugs which undergo degradation in gastricand acidic environment of stomach and irritate to the gastric mucosa.

2.7 Required for minimising first metabolism of drugs Singh (2012), Chandra (2013), Kolte (2012).

3. GENERAL CONSIDERATIONS FOR DESIGN OF COLONIC FORMULATIONS:

The formulation for the colonic delivery after reaching into the colon provide a 'burst release' or to sustain/prolong release. The correct selection of a formulation approach is totally dependent upon several important factors like,

- Pathology
- Pattern of the disease or physiology
- Physiological composition of the healthy colon if the formulation is not intended for localized treatment,
- Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery and the desired release profile of the active ingredient.
- The pH gradient of the GIT.
- Drug dissolution and release rate of the drug in the colon.

Generally, due to presence of less fluid in the colon than small intestine, the dissolution and release rate from colonic formulations is slow because less fluid presence in the colon than small intestine and this may affect on the systemic availability of the drugs. In case of poorly water soluble require higher doses for therapy. Consequently, such drugs need to be delivered in a pre-solubilised form, or formulation should be targeted for proximal colon, which has more fluid than in the distal colon Kothawade (2011), Patel (2011).

4. COLON ANATOMY:

4.1 The GI tract is divided into three parts,

- Stomach,
- Small intestine
- Large intestine.

The large intestine extending from the ileocecal junction to the anus is divided in to three main parts.

- Colon,
- The rectum
- Anal canal.

4.2 The entire colon is about 5 feet (150 cm) long, and is divided in to five large segments.

- Peritoneal folds called as mesentery which is supported by ascending and descending colon.
- The right colon consists of the cecum, ascending colon, hepatic flexure and
- The right half of the transverse colon.

- The left colon contain the left half of the transverse colon, descending colon, splenic flexure
- And sigmoid.
- The rectum is the last anatomic segment before the anus.

4.3 The major function of the colon is,

- to provide suitable environment for the growth of colonic microorganisms,
- storage reservoir of faecal contents,
- Expulsion of the contents of the colon at an appropriate time
- Absorption of potassium and water from the lumen.

The absorptive capacity is very high; each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed Singh (2012).

Table 1: Measures of Different Parts of Colon Singh (2012).

Large Intestine	**Length (cm)**
Cecum	6-9
Ascending colon	20-25
Descending colon	10-15
Transverse colon	40-45
Sigmoid colon	35- 40
Rectum	12
Anal canal	3

Table 2: Gastrointestinal Transit Time of Contents Singh (2012).

Organ	**Transit Time (hr)**
Stomach	<1(fasting), >3(fed)
Small intestine	3-4
Large intestine	20-30

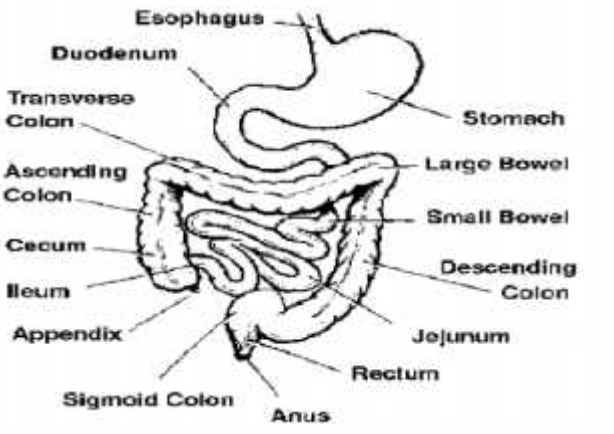

Fig. 1: Diagram of various regions in gastrointestinal tract Philip (2010).

5. NOVEL APPROACHES FOR CDDS:

1. Systems developed with pH sensitive polymer:

This delivery system utilizes specially for considering the pH of the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).In this delivery system included designing the formulation by using pH sensitive polymer to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.

1.1 Coating of the drug core with pH sensitive polymers:

Coating of the drug molecule with the suitable pH sensitive polymersthey can be delivered to the colon without absorbing at the upper part of the intestine which release only in the colon site. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed or sustained release and protect the active drug from gastric environment. The stability of polymers is most important because they 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 problem with this approach is that the intestinal pH may not be stable because it is affected by,

Enteric polymer	Optimum pH for dissolution
Poly vinyl acetate phthalate	5.0
Cellulose acetate trimelitate (CAT) 5.5	5.5
Hydroxypropyl methylcellulose phthalate (HPMCP)	5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	6.0
Methacrylie acid copolymer, Type C (Eudragit L100-55)	6.0
Methacrylic acid copolymer dispersion (Eudragit L30D-55)	5.0
Methacrylic acid copolymer, Type A	6.0
Eudragit®L-100 and Eudragist L12,5	-
Cellulose acetate phthalate (CAP) (Aquateric)	6.0
Methacrylic acid copolymer, Type B	7.0
Eudragist S-100 and Eudragit S12, 5	-
Shellac (Mar coat 125 & 125 N)	7.0

- Diet,
- Disease
- Presence of fatty acids,
- Carbon dioxide,
- Other fermentation products.

The polymers used for colon drug delivery are 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. Problem of premature drug release can be overcome by the use of Eudragit FS.

Table 3: Threshold pH of Commonly Used Enteric Polymer

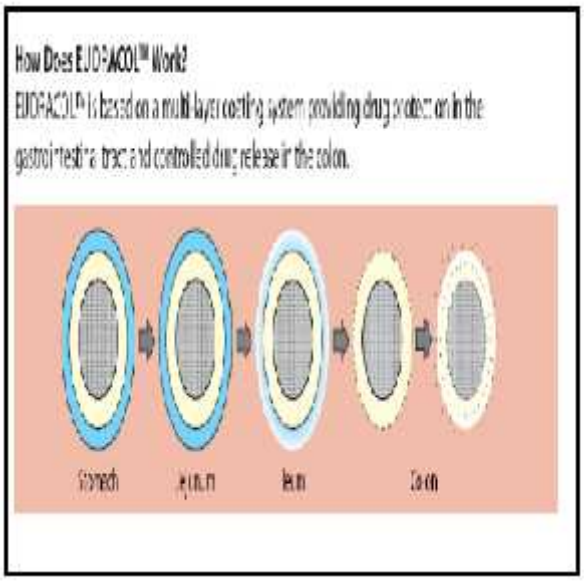

Fig. 2:Design and Working of Eudracol TM Patel (2011)**.**

1.2 Embedding in pH-sensitive matrices:

The drug molecules are embedded in the polymer matrix is the main mechanism of this method. Extrusion spheronization technique can be used to prepare uniform-size pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had an affected 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 Kothawade (2011), Patel (2011), Rajesh (2012).

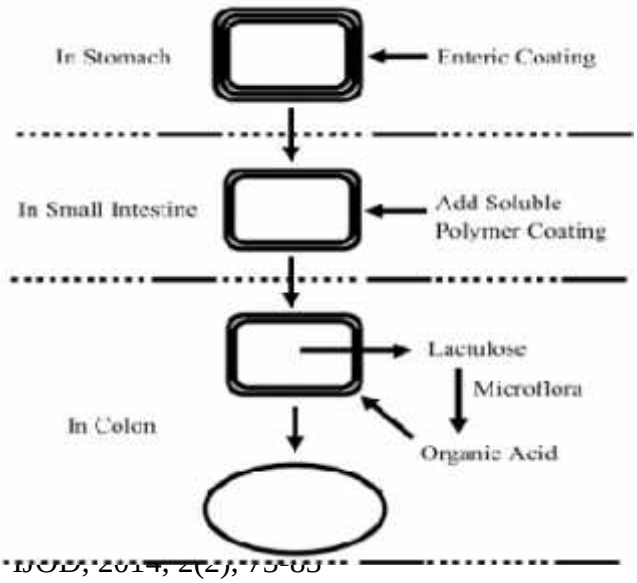

Fig. 3: Schematics of the conceptual design of CODES™ Philip (2010)**.**

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

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. Sometime in human beings large variations in gastric emptying time is observed therefore colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonic availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h.

However, the disadvantages of this system are:

i. Gastric emptying time varies due to 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 colonic disease.

Therefore, time dependent systems are not promising delivery system to deliver drugs to the 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. The time-release function (or timer function) shows more efficiently in the small intestine as compared to the stomach. In the small intestine drug carrier will be delivered to the target site, and drug release will begin at a predetermined time point after gastric emptying. On the other hand, in the stomach, the drug release should be suppressed by a pH sensitive function (acid resistance) in the dosage form, which would, reduces changes in gastric residence time. Enteric coated time-release press coated (ETP) tablets, are composed of three components,

- A drug containing core tablet (rapid release function),
- The press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function)
- And an enteric coating layer (acid resistance function).

The tablet does not release the drug in the stomach due coating with enteric coated polymer., the enteric coating layer rapidly dissolves After gastric emptying and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying Singh(2012), Rajesh(2012).

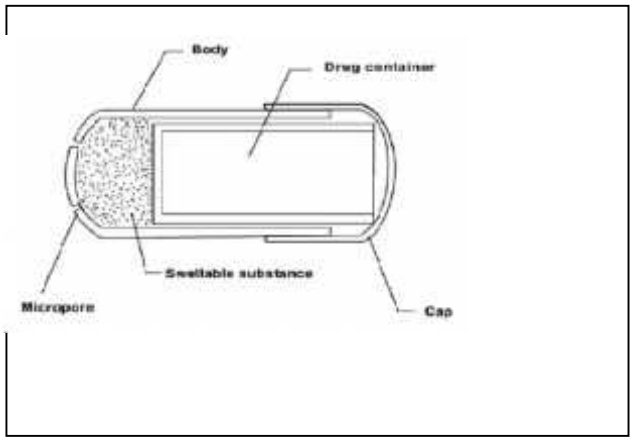

Fig. 4: Time-controlled capsule for colonic delivery Sangeetha (2011)

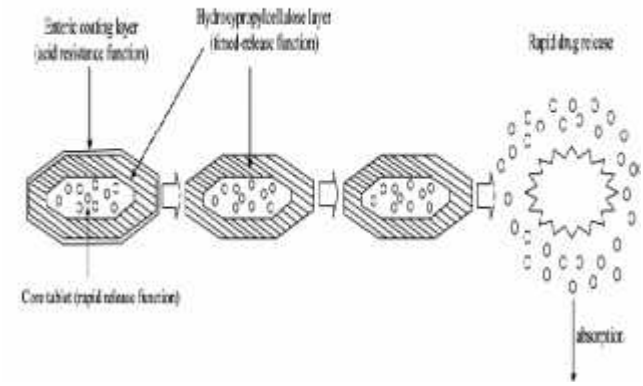

Fig. 5:Design of enteric coated timed-release press coated tablet (ETP Tablet) Sangeetha (2011).

3. Pulsincap:

Pulsincap® is the first formulation was developed by R.R.Scherer International Corporation, Michigan, US. It consists of half capsule body (non disintegrating) which is filled with drug content and 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. The length of the plug and its point of insertion into the capsule is controlled by the lag time. For water-insoluble drugs, a rapid release can be obtained by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glycerylmonooleate), and enzymatically controlled erodible polymer (e.g., pectin) Kothawade (2011) Patel (2011).

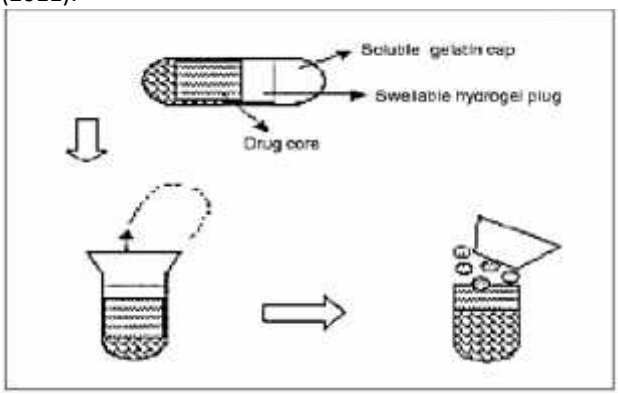

Fig. 6: Pulsincap system Danda (2013).

4. Chronotropic® system

The Chronotropic® system consists of a core containing drug which is coated by hydrophilic swellablehydroxypropylmethyl cellulose (HPMC) polymer, which is responsible for a lag phase in the onset of release. The variability in gastric emptying time can be overcome by outer gastric-resistant enteric film, and a colon-specific release can be obtained. The lag time is controlled by the thickness of coating layer and the viscosity grades of HPMC. The system is suitable for both tablets and capsules.

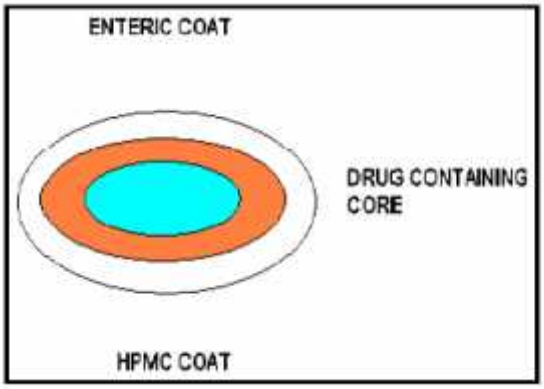

Fig. 7: **Design of Chronotropic® system** Patel (2011).

5. 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. Insoluble plug (lipidic) inside the capsule consisting of osmotically active agent and the drug formulation when this plug 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.

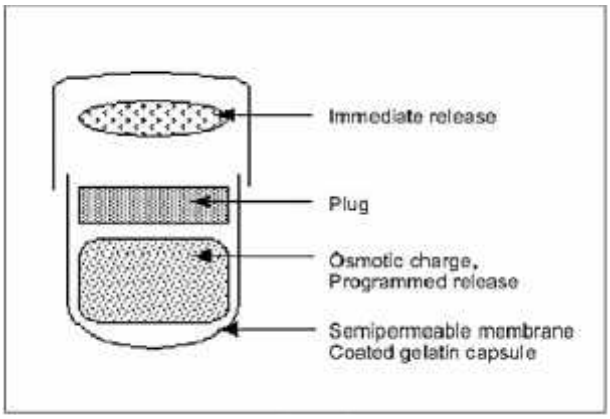

Fig. 8: Port system Danda (2013) **.**

6. Pressure dependent systems:

6.1 Pressure-controlled colon delivery capsule (PCDC):

Takaya et al. developed pressure controlled colon-delivery capsules prepared using Ethylcellulose this is insoluble in water. In this system, drug release occurs by the disintegration of water- insoluble polymer capsule because of pressure in the lumen of the colon. The most important factor for disintegration of the formulation is thickness of the Ethylcellulose membrane. The system also appeared to depend on capsule size and density. In pressure controlled Ethylcellulose single unit capsules the drug is in a liquid. When pressure-controlled capsules were administered to humans the Lag times is three to five hours in relation to drug absorption when pressure-controlled Capsules were administered to humans Singh (2012), Rajesh (2012).

6.2 Osmotic controlled drug delivery:

The OROS-CT (Alza Corporation) can be used to target the drug to the colon for the treatment of Disease. The OROS-CT system is single osmotic unit or 5-6 push-pull units, which diameter is 4 mm, encapsulated within a hard gelatin capsule. Each bi-layer push pull unit contains an,

- osmotic push layer
- a drug layer

Both layer surrounded by a semi permeable membrane. A small orifice is drilled through the membrane up to the drug layer. After the OROS-CT is swallowed, immediately the gelatine capsule containing the push-pull units dissolves. 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. The push pull unit enters the small intestine, at that time the coating dissolves in this higher pH environment (pH >7), then water enters the unit, causing the osmotic push compartment to swell, and immediate 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 semi permeable 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 release begins when the unit reaches the colon. OROS-CT units can able to maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon Singh (2012), Kumar (2013).

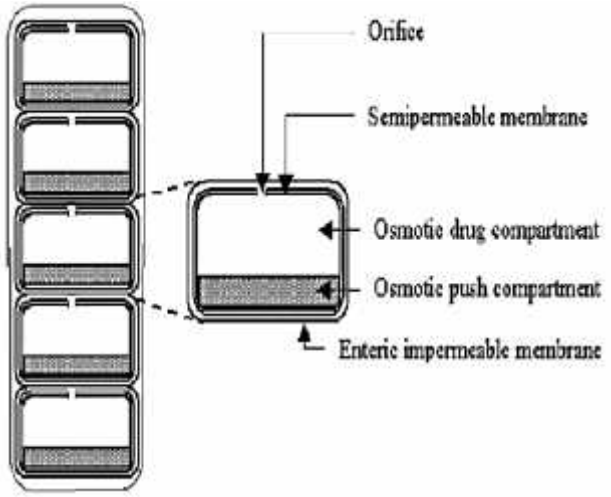

Fig.9: Osmotically controlled CDDs Danda (2013)**.**

7. Microbially Triggered Drug Delivery to Colon:

The microflora of the colon is in the range of 1011 -1012 CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteriaandruminococcus etc. This colonic microflora important for fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharidesetc.For this fermentation, the colonic microflora produces a large number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and ureadehydroxylase. 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 more site-specific approaches compared to other approaches Philip (2010), Dhir (2013).

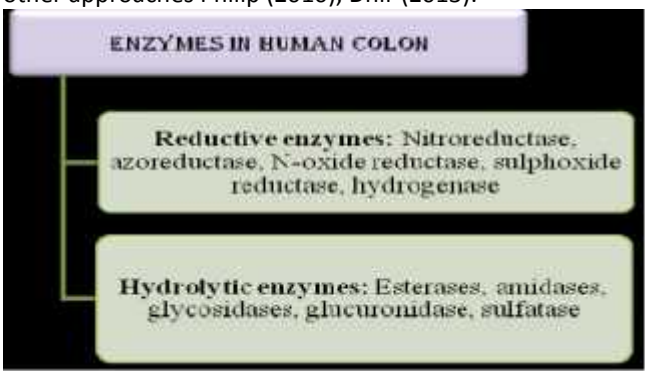

Fig. 10: List of reductive and hydrolytic enzymes in colon Mahajan (2013)**.**

7.1Prodrug Approach for Drug Delivery to Colon: Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, glactose, cellulose etc. Philip (2010), Dhir (2013).

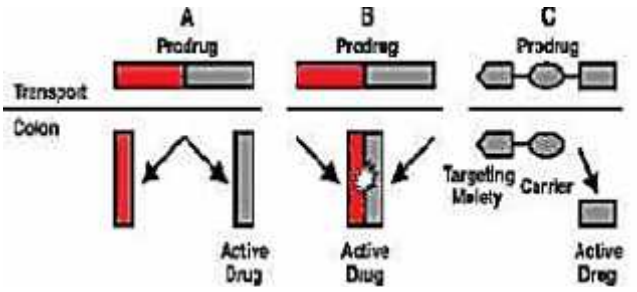

Fig. 11: Prodrug approach for CDDS

- **Azo-Polymeric Prodrug:**

Newer approaches are developed for the use of polymers as drug carriers for drug delivery to the colon. Both the synthetic as well as naturally occurring polymers have been used for this purpose. Semi synthetic polymers have been used to form polymeric prodrug. It is used with azo linkage between the polymer and drug. These have been evaluated for Colon Drug Delivery System. Various types' 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. Peptide capsules Coating with polymers cross linked with azo aromatic group has been found to protect the drug from digestion in the stomach and small intestine.

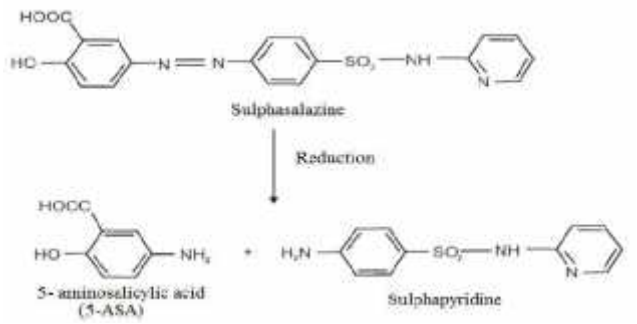

Fig. 12: Reduction reaction of sulphasazine in 5-ASA and sulphapyridine Gupta (2010) Dhir (2013)**.**

- **Polysaccharide Based Delivery Systems;**

Naturally occurring polysaccharides is used in colon targeting drug delivery system. The monosaccharides are found in abundance, they are having large advantages,

- have wide availability ,
- They are inexpensive
- They are available in a variety of structures with varied properties.
- They can be easily modified chemically, biochemically,
- They are highly stable,
- safe, nontoxic, hydrophilic
- Gel forming property and are biodegradable.

These include naturally occurring polysaccharides obtained from,

- plant (guar gum, inulin),
- animal (chitosan, chondrotinsulphate),
- algal (alginates) or
- Microbial (dextran) origin.

The polysaccharides can be broken down by the colonic microflora to simple saccharides Singh (2010).

Glycoside conjugation:

Steroid glycosides and the unique glycosidase activity are useful for a new colon targeted drug delivery system. Drug glycosides are hydrophilic in nature and thus, poorly absorbed in the small intestine. Once such a glycoside reaches the colon it can be break by bacterial enzyme. These bacterial enzymes are located at the brush border. In the plant kingdom numbers of compounds are found as glycosides. Certain drugs act as glycon and it can be conjugated to different sugar moieties which results in the formation of glycosides. Due to the hydrophilic and bulky nature of these glycosides, they do not penetrate the biological membrane upon ingestion Philip (2010), Dhir (2013).

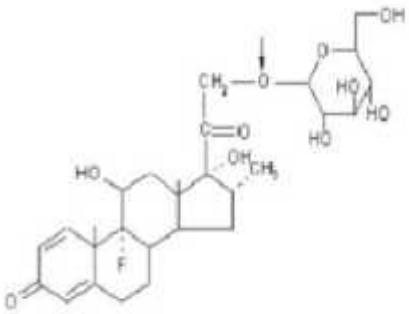

Fig.13: Glycoside Conjugate of Glycosides Kumar (2013)**.**

- **Glucoronide conjugates:**

Glucuronide and sulphate conjugation is most important for the inactivation of drug .It is also useful for clearance

of a variety of drugs. Lower GIT Bacteria of secrete glucuronidase and can deglucuronidate a variety of drugs in the intestine. In this deglucuronidation reaction results is the release of active drug and enables its re-absorption, glucuronideprodrugs would be expected to be superior for colon targeted drug delivery.

Cyclodextrin conjugate;

Cyclodextrins (CyDs) are cyclic oligosaccharides it consisted of six to eight glucose units through 1, 4 glucosidic bonds. They are utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The internal compartment of these molecules is lipophilic and the external compartment is relatively hydrophilic, to form inclusion complexes with various drug molecules. They are able to hydrolyzed and only slightly absorbed in passage through the stomach and small intestine; however, they are fermented by colonic microflora into small saccharides and thus absorbed in the large intestine Gupta (2010) Dhir (2013).

- **Dextran conjugate:**

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These glycosidic linkages are hydrolyzed by moulds, bacteria, and mammalian cells. These linkages hydrolysed by the enzyme dextranase. The dextranase activity is almost absent in the upper GIT, anaerobic gram-negative bacteria shows high dextranase activity, especially the Bacteroides, which are present in a concentration as high as 1011 per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon Patel (2011).

- **Amino acid conjugation:**

In the proteins and their basic units the hydrophilic nature of polar groups like NH2 and COOH present, they reduce the membrane permeability of amino acids and proteins. The conjugation of drug molecules with polar amino acids is the main mechanism of this method. Various prodrugs have been prepared. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicyluric Acid. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. The hydrophilicity and chain length of the carrier amino acid is increases and decreasing the membrane permeability of conjugates.

8. Polymeric prodrugs:

Polymericprodrugs with Azo-linked of 5-ASA were prepared and they are evaluated in simulated human intestinal microbial ecosystem. This ecosystem containing azo groups in the backbone were prepared and tested in vitro in a reductive buffer or in the bioreactor medium. It was demonstrated that for the hydrophobic polymer, reduction stops at the hydrazine stage whereas for a hydrophilic analogue reduction with formation of amine occurred. The amount of the drug released depends on the nature of the polymer and can approach that of low molecular weight prodrugs Singh (2012).

9. Bioadhesive systems:

Bioadhesion is a process by which a dosage form remains in contact with particular organ for an particular period of time. In case of poorly absorbed drug concentration of drug at that site is more because of the dosage form contact with that organ for particular time. 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 Gupta (2010).

10. **Hydrogels:**

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic monomer and enzymatically degradable azo aromatic cross-linkers. In the acidic pH, gels shows less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azareducatase, which ultimately release of drug Gupta (2010) Wasnik (2011).

11. Time Clock System:

It consists of a solid dosages form. The lipidic barriers inside this solid dosage form containing carnauba-wax and bee-wax along with surfactants, such as polyoxyethylenesorbitanmonooleate, these system coated with enteric coated polymer which is prevent premature release of drug in small intestine. The drug release does not dependent on the pH and the digestive state of the gut. The release mainly depends upon the thickness of the coat. As soon as the coat erodes or emulsifies in the aqueous environment after predetermined lag time, the core gets exposed to the colonic environment resulting in complete release of drug Kolte (2012).

12. Targit Technology:

In these approaches the pH sensitive polymer coated onto injection–molded starch capsules. It is specially designed for site-specific delivery of drugs to the colonic site. This system has been developed for the treatment of lower GI disease. The clinical data generated has showed its suitability in colon targeted drug delivery Kolte (2012).

13. COLAL-PRED system:

This system is developed by Alizyme for the treatment of ulcerative colitis. It is the combination of Alizyme's colonic delivery system, COLAL, and an approved generic steroid, Prednisolone sodium

metasulfobenzoate. It is effectively used in the treatment of ulcerative colitis without side effects of steroids Chandra (2013) .

14. Gas Empowered Drug Delivery System (GEDD):

It is a novel drug delivery system to colon .In these system mucoadhesive polymer polyethylene oxide is used for the colonic delivery of proteins and peptides by using N –trimethylated chitosan chloride as penetration enhancer and using co2 for providing driving force to push the drug substance to the absorbing membrane and also it degradation. The main function of mucoadhesive polymer is adhered to the mucous layer the permeation enhancer is used to open the tight junctions to promote paracellular pathway for drug absorption. CO2 also functions as permeation enhancer by opening the tight junctions mechanically. This system is successful in delivering the drug to the intestine because of the use of CAP (cellulose acetate phthalate) which protects the dosage form from the acidic pH of stomach Jawalkot (2013).

15. Ticking capsule:

These is chronotherapeutic provides controlling pulsatile drug release. Ticking capsules is divided into three compartments:

- Porous Si-based drug delivery module,
- Electronic control module (e.g. mucontroller)
- And Battery.

This ticking capsule useful in many human illnesses and their symptoms: Hypertension (early morning); arthritics pain (mid-afternoon); heart attack (early morning + late afternoon and asthma attack (night). It is recognizing intake into the body is limed to match the severity of the Symptom.

Fig.14: Design of ticking capsule system.

16. 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 .It contains a drug reservoir with a volume capacity of approximately 1 ml. The capsule having opening (9 mm in diameter) can be loaded with a liquid formulation (e.g. Solution, Suspension) or a particulate formulation (e.g., powder, pellets, in sit affects etc.) then the push-on Cap fitted on the opening with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high tensile strength polymer filament. A radioactive marker is placed inside a separate sealed tracer port, these markers responsible for real time visualization of the capsule location using the imaging technique of gamma Scintigraphy. When the capsule reaches the target location in the gastrointestinal tract, the contents are actively ejected by the external application of an oscillating magnetic field. The frequency of the magnetic field is set in 100 the low MHz region, low enough so that there is negligible absorption of the energy by the body tissues but sufficiently high enough to induce unable power in a tuned coil antenna embedded in the capsule wall. The magnetic field is used for inducing the power in the coil. Although the power is only a few tenths of a wall, the small size of the heater (less than 1mm3) means that heat build-up is extremely rapid. The heater resistor is in direct contact with the restraining filament, causing it to softer and breaks with the increase in temperature. This is turn, releases the spring and driver the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding GI fluids. The piston motion is stopped near the end of the capsule, which maintains a seal and presents contact of the internal electronic compartments with the GI fluids. The movement of the piston also operates a switch, which directs some of the electrical energy away from the heater and uses it to transmit a weak radio signal at a precise frequency. Detection of this signal externally confirms that the capsule has opened successfully.

Fig. 15: Design of Enterion capsule Chandra (2013).

17. Redox sensitive polymer coating:

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzesnonenzymatically by using enzymatically generated flavins are being developed for colon targeting. A common colonic bacterium, Bacteroidesfragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model azo compound Gupta (2010).

18. Multiparticulate systems:

Multiparticulates are used as drug carriers in pHsensitive, time-dependent and microbial control systems for colon targeting Kumar (2013) Wasnik (2011). Nanoparticles are now a day's become novel area for colon specific drug delivery system. These are novel approaches used to target drugs. These are small colloidal particles having size range about 200-300 nm made up of biodegradable and non- biodegradable polymers. The drug moiety can be dissolved, entrapped, or encapsulated in the nanoparticle matrix Mohanraj (2006).

They are several advantages,

- They results in more efficacy,
- reduced toxicity,
- better bio-distribution
- And improved patient compliance.

Microspheres are used for the delivery of proteins and peptides. The microspheres shield the drug from the acidic environment of stomach and target the drug to the desired site, and also improve drug absorption from paracellular route. The mechanisms of drug release from microspheres can be diffusion, degradation, hydrolysis or erosion.The drug encapsulated in microspheres having following advantages,

- Increased stability,
- Reduced toxicity
- And also targeted delivery to the site of action.

Examples are theophylline microspheres prepared by ionotropic gelation method using Ca-pectinate and Eudragit S100 for anti asthamatic activity Chandra (2013) Wasnik (2011).

6. CONCLUSION:

Colonic diseases treated effectively by designing the formulation for colon targeting. Novel approaches play important role in increasing the efficacy and bioavailability of drug at colonic site and also reduces side effect these approaches useful for those drug having high first pas metabolism and low bioavailability.

7. REFERENCES:

1. Anu, K. Priya, S.andSatinder, K.(2013). Colon targeted drug delivery system: a
2. Review. Novel Science.International Journal of Pharmaceutical Science., 2, 9-12.
3. Challa, T. Krishna, V. V. Allam, V. (2011).Colon Specific Drug Delivery
4. Systems: a Review on Primary and Novel Approaches. International Journal of Pharmaceutical Sciences Review and Research.,7, 171-181.
5. Chandra, D. Singh, A. P. Singh, P. K.andMaurya, J.K.(2013). A Review on Colon Specific Drug: Various Approaches including Novel Approaches and Evaluation. American Journal of PharmTech Research., 3, 82-104.
6. Danda, S.and Brahma, C. K.(2013).Colon Targeted Drug Delivery – a Review on
7. Primary and Novel Approaches. Journal of Global Trends in Pharmaceutical Sciences. 4,1174-1183.
8. Dhir, K. Singh, Kahlon H. and Kaur, S.(2013). Recent Approaches for Colon Targeted Drug Delivery System. International Journal of Pharmaceutical, Chemical and Biological Sciences. 3, 360-371.
9. Gupta, A. Mittal, A.and Gupta, A. K.(2010).Colon Targeted Drug Delivery Systems -A Review.International Journal of Pharmaceutical and Clinical Research., 2, 112-120.
10. Jawalkot, I. S. P. Jadhav ,P. D.Mane ,S. V.andKhade, M.M.(2013).Colon Targeted Drug Delivery System: a Review.IJPRBS., 2, 122-136.
11. Kumar, J. R. Muralidharan, S. Dhanaraj, S. A. and Umadevi, S.K.(2013).
12. Novel Drug Delivery Systems Colon Targeted: A Review. J. Pharm. Sci. & Res., 5, 42 – 47.
13. Kumar, R. Chandra, A. and Gautam, P.K.(2013). Modified Approaches for Colon Specific Drug Delivery System: A Review. Indian J. Pharm. Biol. Res., 1, 67-79.
14. Kolte, B. P. Tele, K. V. Mundhe, V. S.andLahoti, S. S. (2012). Colon Targeted
15. Drug Delivery System – A Novel Perspective. Asian Journal of Biomedical and
16. Pharmaceutical Sciences, 2, 21-28.
17. Kothawade, P. D. Gangurde, H. H. Surawase, R.K. Wagh, M.A. and
18. Tamizharasi, S.(2011)Conventional And Novel Approaches for Colon Specific
19. Drug Delivery: A Review. e - Journal of Science &Technology (e-JST)., 2, 33-
20. 56.
21. Mahajan, M. Kaur, S.and Kaur, R.(2013). An Itinerary to Access the Colon.
22. Journal of Drug Delivery &Therapeutics., 2,29-39.
23. Mohanraj, VJ and Chen, Y.(2006). Nanoparticles – A Review. Tropical Journalof Pharmaceutical Research.5 , 561-573.
24. Patel, A. Bhatt, N. Patel, K.R. Patel, N.M.and Patel, M.R.(2011). Colon Targeted
25. Drug Delivery System: A Review System.JPSBR., 1 ,37-49.
26. Philip, A. K.and Philip, B.(2010). Colon Targeted Drug Delivery Systems: A
27. Review on Primary and Novel Approaches .Oman Medical Journal.,25, 70-78.

28. Rajesh, A. Chaudhari, B.andSangeeta, A.(2012).Oral Colon Targeted Drug
29. Delivery System: A Review on Current and Novel Perspectives. Journal of Pharmaceutical and Scientific Innovation. 1, 6-12.
30. Sangeetha, G. Begum, M.J. Reddemma, S. and Rajendra, Y. (2011).Colon Targeted Drug Delivery System: A Review. International Journal ofPharmacy&Technology., 3, 1657-1672.
31. Singh, N. and Khanna, R. C. (2010).Colon targeted drug delivery systems – A Potential Approach. The Pharma Innovation., 1, 38-45.
32. Singh, K. I. Singh, J. Sharma, D. and Sharma, A. (2012). Colon Specific Drug Delivery System: Review on Novel Approaches. IJPSR., 3 ,637-647.
33. Wasnik, S.andParmar, P.(2011). The Design of Colon-Specific Drug Delivery
34. System and Different Approaches to Treat Colon Disease. International Journal of Pharmaceutical Sciences Review and Research. 6, 167-177.

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