AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Potential Approaches of Colon Targeted Drug Delivery System: A Review

Chandrakant S. Satpute*, Prashant K. Pagare, Varsha M. Jadhav, Vilasrao J. Kadam

1. Department of Quality Assurance, Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D., Belapur, Navi Mumbai-400614, Maharashtra, India

ABSTRACT

Targeted drug delivery to the colon is more desirable for local treatment of a variety of bowel diseases and systemic delivery of protein and peptide drugs. Targeting depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site. To achieve the delivery of intact drugs to the colon, different primary as well as potential novel approaches are used. To achieve the maximum site specific delivery of drugs to colon, combination of two or more approaches are preferred over individual approaches. Because of limited success of primary approaches newly developed approaches are preferred.

Keywords: Potential approaches of colonic drug delivery, colon specific drug delivery, newly developed approaches for CDDS.

*Corresponding Author Email: chandrakant.satpute@yahoo.co.in

Received 9 July 2012, Accepted 21 July 2012

Please cite this article in press as: Satpute CS *et al.*, Potential Approaches of Colon Targeted Drug Delivery System: A Review. American Journal of PharmTech Research 2012.

INTRODUCTION

Targeted drug delivery to the colon is more desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, and systemic delivery of protein and peptide drugs. The deliveries of drugs to the colon via gastrointestinal (GI) tract require the protection of a drug from being released in stomach and small intestine. It can be achieved by the use of drug delivery system (DDS) that can protect the drug during its passage to colon and the drug must be released in the colon from the Drug Delivery System. Targeting depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site. Delivery of drugs via colon offers many therapeutic advantages. Drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes, are protected. Sustained release of drugs into colon can be useful in the treatment of certain diseases. The colonic delivery is also useful for the systemic absorption of drugs like Nifedipine, Isosorbide, and Theophylline. The colon is the most suitable site for absorption of peptides and protein drugs for the following reasons:

- Less degradation by digestive enzymes
- Proteolytic activity of colon mucosa is less than that observed in small intestine, thus colon drug delivery system (CDDS) protect peptide and protein drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and releases the drug into the ileum or colon which produces greater systemic bioavailability.[1]

The colon has a long residence time which is up to 5 days and hence it is highly responsible for enhancement of absorption. The human colon has about 400 different species of bacteria as resident flora. The reactions carried out by this gut flora are azoreduction and enzymatic cleavage i.e. glycosides.

Criteria for Selection of Drug for CDDS

The best candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea and colon cancer are ideal candidates for local colon delivery. Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drug depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example,

aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.[3]

Need of Colon Targeted Drug Delivery[4]

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

APPROACHES USED FOR SITE SPECIFIC DRUG DELIVERY TO COLON

Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:

A) Primary approaches of colon specific drug delivery system:

***1.* PH- dependent delivery**

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve in the lower small intestine and the site-specificity of

formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileocecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.[5, 6]

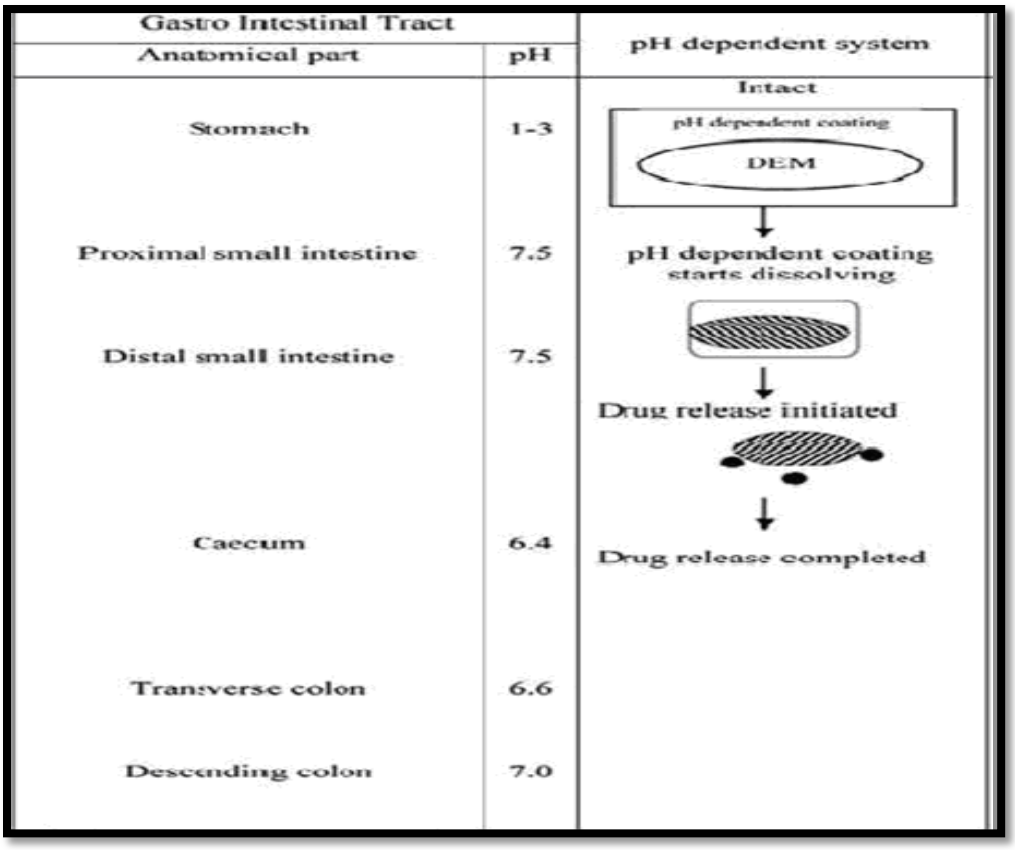

Figure 1: Schematic presentation of pH dependent release[5]

Most commonly used pH dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S, more specifically Eudragit L and S. Colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxen. Dissolution studies performed on the mesalazine tablets further confirmed that the release profiles of the drug could be manipulated by changing the Eudragit L100-55 and Eudragit S100 ratios within the pH range of 5.5 to 7.0 in which the individual polymers are soluble respectively, and a coating formulation consisting of a combination of the two copolymers can overcome the issue of high GI pH variability among individuals.[7]

***2.* Time dependent delivery**

Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time based. In this system, the site of drug release is decided

by the transit time of a formulation in the GIT, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. On an average, an orally administered dosage form takes about 3 hrs to travel through the length of the small intestine to the beginning of the colon.[2] Compared to gastric emptying rate; the small intestinal transit time is relatively consistent.[8]

There has always been a controversy about the usefulness of pH dependent polymers for colon targeted delivery due to high pH variability of GI tract. To overcome this problem time controlled systems are used along with pH dependent systems.[6] Time controlled delivery has been achieved by applying coats onto drug containing cores which delaying the release through different mechanisms or alternatively based on capsule-shaped and osmotic devices.[10]

The formulation is comprised of three parts:

- A central core containing the drug and swelling excipients,
- An inner semi-permeable polymer membrane containing a plasticizer which allows water influx but prevents the outward diffusion of drug and
- An outer enteric-coating which dissolves at or above pH 5.5. The outer enteric coat keeps the tablet intact until it reaches the small intestine.

Upon arrival in the small intestine, the enteric coat dissolves allowing for GI fluid to diffuse through the semipermeable membrane into the core. As a result, the core swells during the transit of the tablet through the small intestine. Finally, after a consistent period of 4-6 h transit in the small intestine, the swollen core burst the semi-permeable membrane releasing the drug in the colon. However, the disadvantages of this system are -

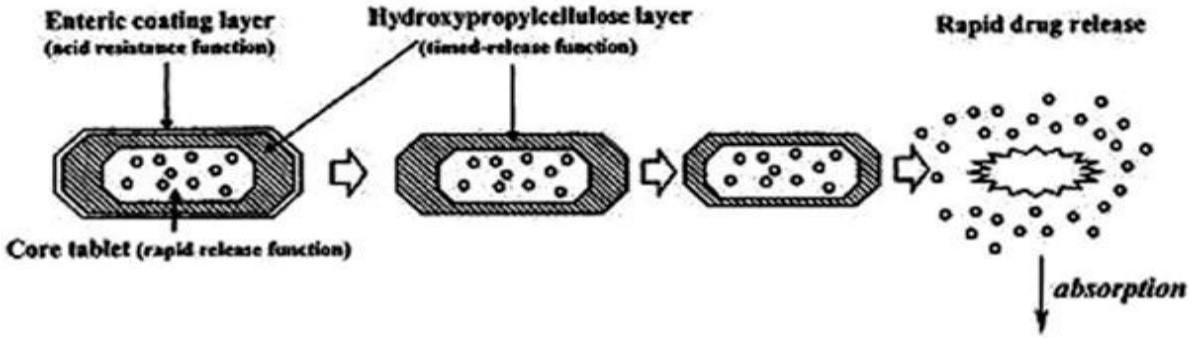

Figure 2: Design of enteric coated timed-release press coated tablet[2]

i. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

ii. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

iii. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea, and the ulcerative colitis.[5.6]

***3.* Pressure controlled drug delivery system**

The digestive processes within the GIT involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis.[8] The muscular contraction of the gut wall generates this pressure which is responsible for the grinding and propulsion of the intestinal contents. The pressure generated varies in the intensity and duration throughout the GI tract while the colon is considered to have higher luminal pressure due to the process that occurs during stool formation. Capsule shells fabricated from a water insoluble polymer such as ethyl cellulose have been used for this purpose**.**[10] In such system drug release occurs following the disintegration of a water insoluble polymer capsule as a result of the pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for the disintegration of the formulation. The system also appears to depend on capsule size and density. Because of the reabsorption of water from the colon, the viscosity of intestinal content is higher in the colon than in the small intestine.[11] It has therefore been concluded that the drug dissolution in the colon would present a problem in relation to colon specific oral drug delivery systems. In pressure controlled ethyl cellulose single-unit capsules, the drug is in a liquid. When pressure controlled capsules are administered to human, Lag times of three to five hours in relation to drug absorption are noted**.**[5]

***4.* Microbially triggered drug delivery to colon**

The micro flora of the colon is in the range of 1011 -1012 CFU/ml, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc.[2] This vast micro flora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. For this fermentation, the micro flora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminase, and urea dehydroxylase.[12] The enzymes present in the colon are:

- Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.,
- Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc.[8]

Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches.[4] These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.[2, 11]

a) Prodrug Approach for Drug Delivery to Colon

There are at least three factors should be optimized for the site specific delivery of drugs by using the prodrug approach.[8, 10]

1. The prodrug must reach to the targeted site of action as early as possible and uptake from the site must be fast and essentially perfusion rate limited.

2. Once the drug reached to the site, prodrug must selectively liberate the active drug relative to its conversion at other sites.

3. Once selectively liberated at the site of action, the active drug must be somewhat retained by the tissue. The classical prodrug design often represents a non-specific chemical approach to mask unwanted drug properties such as low bioavailability, less site specificity and chemical instability. On the other hand, targeted prodrug design represents a new strategy for directed and efficient drug delivery. Particularly, prodrugs targeting to a specific enzyme or a specific membrane transporter or both, have potential drug delivery system especially for cancer chemotherapy.[8] 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.[2] Two classes of the prodrugs are generally used. The first type of the prodrug is broken inside cells to form active substance or substances. The second type of prodrug usually is the combination of two or more substances. Under specific intracellular conditions, these substances react and forms active drug.

Targeted DDS usually includes three components:

- A drug,
- A targeting moiety,
- A carrier.

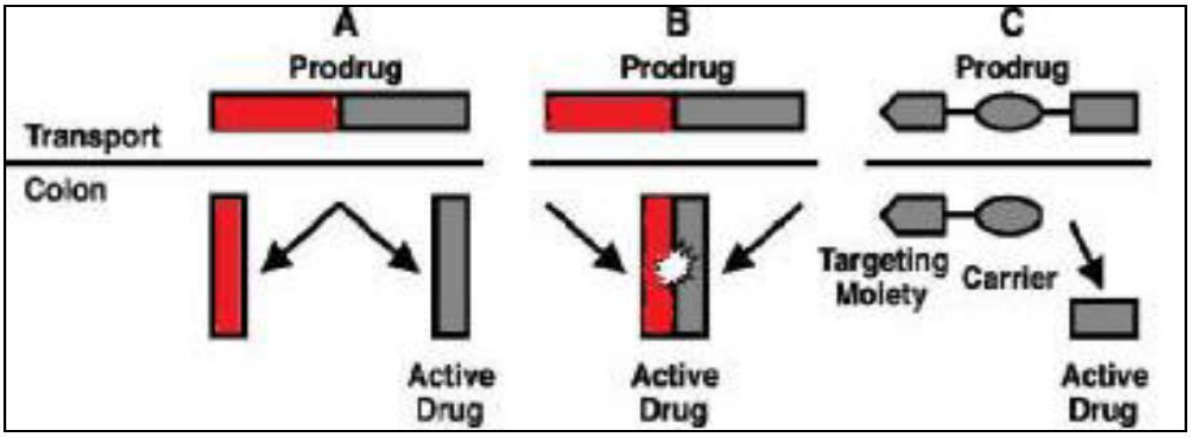

Figure 3: Schematic representation of prodrug approach[5]

The carrier binds the components of DDS together and facilitates the solubility of the whole complex. The drug (active component) is for treatment purpose. The targeting moiety/penetration enhancer increases the internalization of the active component specifically into the targeted cells enhancing specific activity of the whole DDS and reducing adverse effects on healthy tissues. Such targeted DDS should fulfil two major requirements:

- It should prevent the active component(s) from the degradation or decrease in activity during the passage to the site of action
- It should release drug(s) from DDS inside the targeted cells.[5]

i) Azo-Polymeric Prodrugs

Newer approaches are aimed to use the polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. These have been evaluated for CDDS. Various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreductase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group has been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced, and the drug is released.[5]

Sulphasalazine was introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazosulphapyridine (SASP), where sulfapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact. There it splits at the azo bond by the colonic bacteria with the liberation of sulpha pyridine

(SP) and 5- aminosalicylic acid (5 ASA).[6]

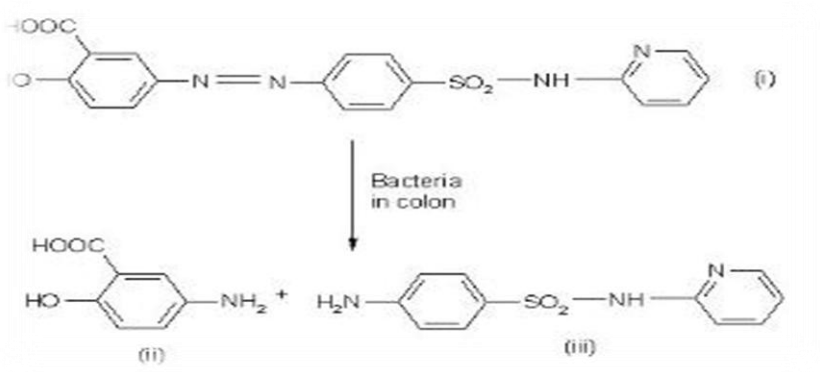

Figure 4: Hydrolysis of sulphasalazine (i) into 5-aminosalicylic acid (ii) and sulfapyridine[4]

ii) **Glycoside Conjugates**

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Drug glycosides are hydrophilic and thus poorly absorbed from the small intestine. Once such a glycoside reaches the colon it can be cleared by bacterial glycosidases, releasing the free drug to be absorbed by the colonic mucosa.

The major glycosidases identified in human faeces are:

1) D-galactosidase,

2) D-glucosidase,

3) L-arabinofuranosidase,

4) D-xylopyranosidase

Due to the bulky and hydrophilic nature of these glycosides, they do not penetrate the biological membrane upon ingestion.[13]

iii) Glucuronide Conjugates

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower GIT, however, secrete glucuronidase and can deglucuronidate a variety of drugs in the intestine. Since the deglucuronidation process results in the release of active drug and enables its re-absorption, Glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.[2, 6]

iv) Cyclodextrin Conjugates

Cyclodextrins (CyDs) are cyclic oligosaccharides consisted of six to eight glucose units through 1, 4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug

molecules. However, they are fermented by colonic micro flora into small saccharides and thus absorbed in the large intestine.[6, 14]

Because of their bio adaptability and multi functional characteristics, CyDs are capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. In an oral drug delivery system, the hydrophilic and ionisable CyDs can serve as potent drug carriers in the immediate release and delayed release formulations, respectively, while hydrophobic CyDs can retard the release rate of water-soluble drugs. Since, CyDs are able to extend the function of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable tool in the improvement of drug formulation. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site; conjugates of a drug with CyDs can be a versatile means of constructing a new class of colon targeting prodrugs.

The 5-ASA concentration in the rat's stomach and small intestine after the oral administration of CyDs- 5-ASA conjugate was much lower than that after the oral administration of 5-ASA alone. The lower concentration was attributable to the passage of the conjugate through the stomach and small intestine without significant degradation or absorption, followed by the degradation of the conjugate site-specific in the cecum and colon. The oral administration of CyD-5-ASA resulted in lower plasma and urine concentration of 5-ASA than that of 5-ASA alone.[15]

b) Polysaccharide Based Delivery Systems

Use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting to colon since these polymers of monosaccharide are found in abundance, have frequent availability, are available in a variety of structures with varied properties and are inexpensive. They are easily modified chemically and biochemically and are safe, highly stable, nontoxic, gel forming, hydrophilic and biodegradable. These include naturally occurring polysaccharides obtained from plant (insulin, guar gum), animal (chitosan, chondrotin sulphate), microbial (dextran) or algal (alginates) origin. These are broken down by the colonic micro flora to simple saccharides. So this fall into the category of "generally regarded as safe" (GRAS). Chitosan is a high molecular weight cationic polysaccharide, poly (N-glucosamine), obtained from chitin in shrimp and crab shells by deacetylation. It is degraded by the rich colonic micro flora. Chitosan have been evaluated for the colon specific drug delivery in the form of a capsule forming material. Pectin is another linear polysaccharide with mainly a-(1-4)-linked D-galacturonic acid residues interrupted by 1, 2-linked L-rhamnose residue**.**[2, 5, 6]

B) Newly developed approaches for CDDS

***1.* Novel colon targeted delivery system (codestm)**

CODESTM is a newly developed CDDS technology that was designed to avoid the problems associated with the pH or time dependent systems. CODESTM is a combination of pH dependent and microbially triggered CDDS. It has been developed by using a unique mechanism that involves lactulose, which acts as a trigger for the site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with an acid soluble material, Eudragit E and then subsequently over coated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.[5] The polysaccharides degradable by enterobacteria to generate organic acid include mannitol, maltose, stachyose, lactulose, fructooligosaccharide etc.[16]

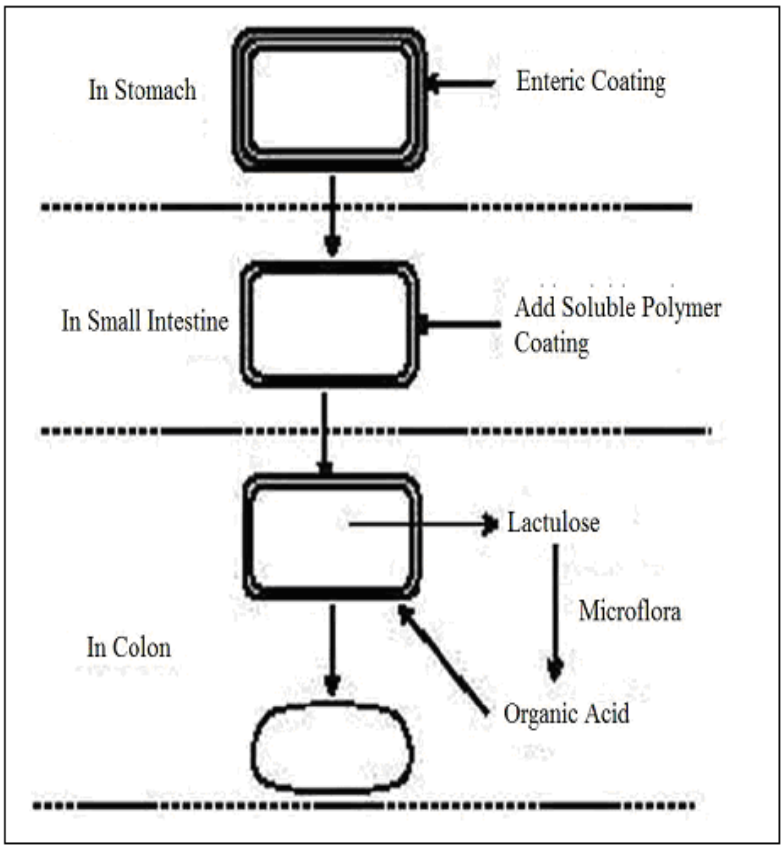

Figure 5: Schematics of the conceptual design of CODES™ [2]

***2.* Osmotic controlled drug delivery (ords-ct)**

The OROS-CT (Alza Corporation) is used to target the drug locally to the colon for the treatment of diseases or to achieve systemic absorption that is otherwise unachievable. The OROS-CT system is a single osmotic unit or it may incorporate as many as 5-6 push-pull units, each 4 mm in diameter and encapsulated within a hard gelatine capsule. Each bilayer push pull unit contains the osmotic push layer and the drug layer, both are surrounded by a semipermeable membrane. An orifice is drilled through a membrane next to the drug layer. As the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves immediately. Because of the drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of stomach, and hence no drug is delivered. The coating dissolves in the higher pH environment (pH >7), as the unit enters small intestine. Water enters the unit and the osmotic push compartment swells, and concomitantly creates a flowable gel in the drug compartment. Swelling of osmotic push compartment forces the drug gel out of the orifice at a rate precisely controlled by rate of water transport through the semipermeable membrane. For the treatment of ulcerative colitis, each push pull unit is designed with a 3-4 hr post gastric delay to prevent the drug delivery in small intestine. Drug releases when the unit reaches the colon. OROS-CT unit maintains a constant release rate for up to 24 hours in the colon.[16] OROS-CT units can 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.[2]

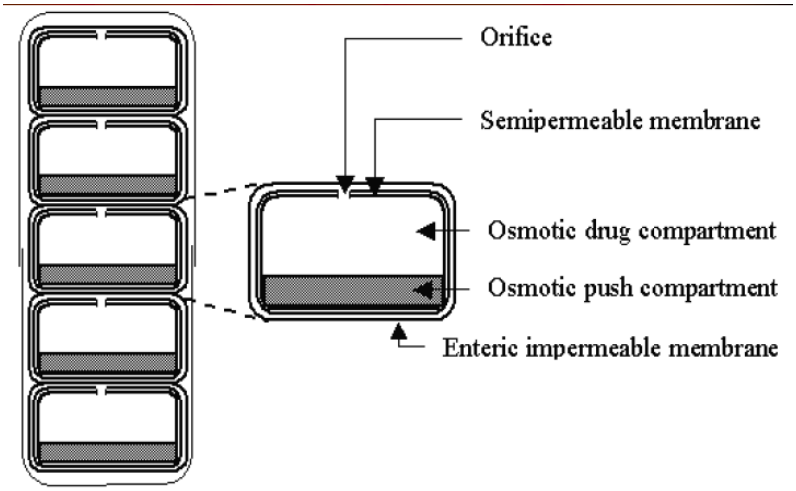

Figure 6: schematic representation of osmotic CDDS

3. Pulsatile drug delivery system

a) Pulsincap System

b) Port System

a) Pulsincap® system

Single-unit systems are mostly developed in a capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion and the drug is released as a "Pulse" from the insoluble capsule body. One such system comprises of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule comes in contact with the dissolution fluid, it swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Polymers used for the hydrogel plug are different viscosity grades of hydroxypropyl methyl cellulose (HPMC), poly methyl methacrylate, polyvinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controls the lag time.[6, 16]

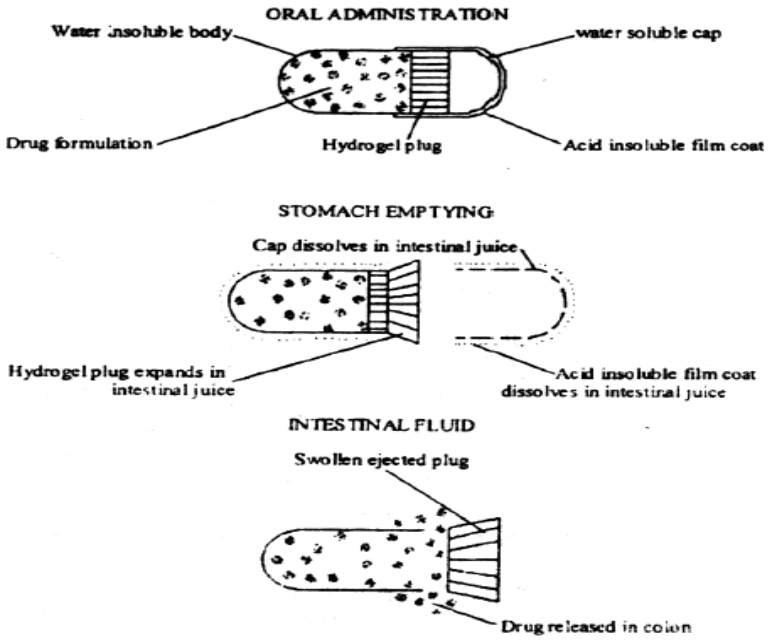

Figure 7: Schematic representation of Pulsincap system

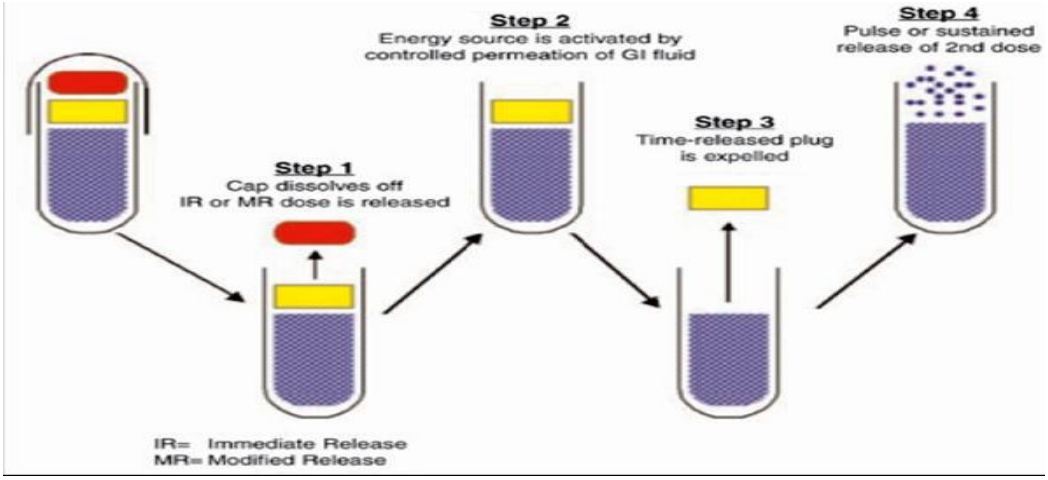

Figure 8: The drug release pattern of port system[6]

b) The Port® System

The Port® System consists of a gelatin capsule coated with a semipermeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation .When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness.[6] This system avoids the second time dosing.[16]

The approach of pulsatile drug delivery system is based on the principle of delaying the time of drug release until the system transits from mouth to colon. The transit time of small intestine is about 3-4 hours so lag-time of 5 hours is usually considered, which is relatively constant.

***4*. Hydrogels**

The presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure produces colon specificity to the formulation. As these hydrogel travels through the GIT, their swelling capacity increases as the pH increases, being highest around pH 7.4. The drug entrapped in the hydrogel is released by the progressive degradation of hydrogel network via the cleavage of the cross-links. They can be obtained by cross-linking polymerization of N-substituted (meth) acryl amides, N-tert-butylacrylamide and acrylic acid with 4,4'-di (methacryloylamino) azobenzene, 4,4'-di (N-methacryloyl-6- aminohexanoylamino) or 3,3',5,5'-tetrabromo-4,4, 4',4'-tetrakis (methacryloylamino) azobenzene as the cross linking agents. The hydrogels were also prepared by polymer–polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH_2 groups. The degradation rate of hydrogel was associated with the equilibrium degree of swelling and being inversely proportional to the cross linking density.[4, 16]

***5*. Microspheres of anti-cancer drugs**

Cross-linked guar gum microspheres containing methotrexate were prepared and characterized for local release of drug in the colon for efficient treatment of colorectal cancer. In this method glutaraldehyde was used as a cross-linking agent and guar gum microspheres were prepared by emulsification method. From the results of in vitro and in vivo studies, the methotrexate loaded cross-linked guar gum microspheres delivered most of the drug load (79%) to the colon, where as plain drug suspensions could deliver only 23% of their total dose to the target tissue. Colon specific microspheres of 5-fluorouracil were prepared and evaluated for the treatment of colon 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.[13]

***6.* Nanoparticles**

Nanoparticles are expected to become drug carriers for achieving oral peptide delivery. Because of polymeric nanoparticles have the advantages of protecting the protein and peptide drugs from chemical and enzymatic degradation in the GIT, thus increasing their stability and absorption across the intestinal epithelium as well as controlling the drug release. A number of techniques such as polymerization, nanoprecipitation, inverse microemulsion can be used to prepare polymeric nanoparticles, however most of these methods involve the use of organic solvents, heat and vigorous agitation which may be harmful to the peptide and protein drugs. More recently the ionic gelation technique is used as the most favourable.[16]

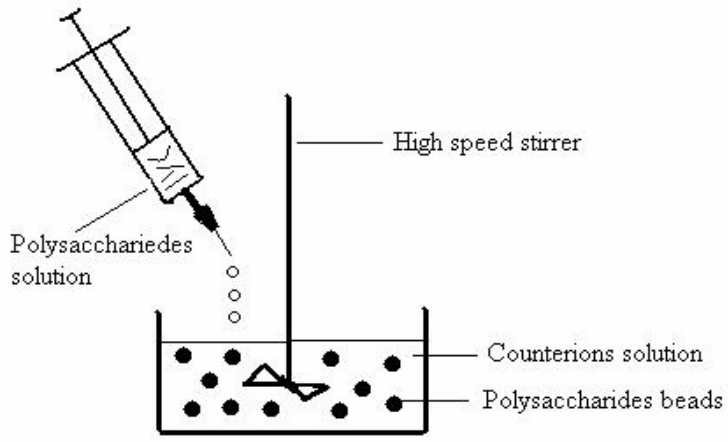

Figure 9: Representation of preparation of polysaccharides particles by ionic gelation method.[17]

In the ionotropic gelation method, polysaccharides (alginate, gallant and pectin) are dissolved in water or in weak acidic medium (chitosan). These solutions are then added drop wise under constant stirring to the solutions containing other counter ions. Due to the complexation between oppositely charged species, polysaccharides undergo ionic gelation and precipitate to form spherical particles. The beads are removed by filtration, washed with distilled water and dried. The counter ions used for ionotropic gelation can be divided into two major categories: Low molecular weight counter ions e.g. CaCl2, BaCl2, MgCl2, CuCl2, ZnCl2, CoCl2, pyrophosphate, tripolyphosphate, tetrapolyphosphate, octapolyphosphate, hexametaphosphate and [Fe (CN)6]-4 /[Fe(CN)6]; High molecular weight ions *e.g.* octyl sulphate, lauryl sulphate, hexadecyl sulphate, cetylstearyl sulphate.[18]

7. Multiparticulate system based drug delivery

Multiparticulate dosage forms are pharmaceutical formulations in which the active ingredient is present as a number of minute independent subunits. To deliver the recommended total dose, these subunits are filled into a capsule or compressed with additional excipients to form a tablet. Multiparticulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, micro particles, nanoparticles and beads. Because of their smaller particle size as compared to single unit dosage form these systems are capable of passing through the GIT easily. Multiparticulate drug delivery system for colon targeting is developed by time controlled explosion system (TES) in which drug release is caused by explosion of a membrane after a definite time period (i.e. lag times), which is precisely programmed. It contains a core drug plus an inert osmotic agent and suitable disintegrants. Individual units can be coated by a protective layer and then by a semipermeable layer, which is the rate controlling membrane for the influx of water into osmotic core. The osmotic pressure build-up by water ingress causes the core to explode, with an immediate release of the drug. The explosion of formulation can also be achieved through use of swelling agents. There are many reasons for designing and delivering drug as a multiparticulate system.[18, 19]

1. Shows better reproducible pharmacokinetic behaviour than conventional (monolithic) formulations.
2. Drug safety may also increased by using multiparticulate dosage forms.

LIMITATIONS AND CHALLENGES IN COLON TARGETED DRUG DELIVERY

- The resident micro flora affects the colonic performance via metabolic degradation of the drug. Lower surface area and relative tightness of the tight junctions in colon can restrict the drug transport across the mucosa and into the systemic circulation.
- As a site for the drug delivery, the colon offers a near neutral pH, a long transit time, reduced digestive enzymatic activity and increased responsiveness to the absorption enhancers; however, targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is difficult to access
- In addition, the stability of drug must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, mucus and intestinal secretions or faecal matter.[5]

OPPORTUNITIES IN COLON TARGETED DRUG DELIVERY

- Targeted delivery to the colon is being explored not only for local colonic pathologies, thus

avoiding systemic effects of drugs, but also for systemic delivery of drugs like proteins and peptides, which are degraded and/or poorly absorbed in the stomach and small intestine.

- This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Urgent need for delivery of drugs to the colon that reported to be absorbable in the colon, such as steroids, which would increase efficiency and reduces effective dose.
- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and other colon diseases, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery.
- The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low (due to instability in the GI tract).[4]

CONCLUSION

The colon is the terminal part of the GIT. In recent years CDDS has gained its importance as a site for delivery of various drugs including novel therapeutic drugs, i.e. peptides. Successful colon specificity is more likely to be achieved by protecting the drug from absorption and /or the environment of the upper GIT and then be abruptly released into the proximal colon, which is considered the optimum site for colon targeted delivery of drugs. The various strategies for targeting orally administered drugs to the colon includes, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bio adhesive systems etc. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs through colon.

REFERENCES

1. Amin AF et al. A synchronous colon-specific drug delivery system for orally administered mesalamine. Acta Pharmaceutica Sciencia, 2009; 51: 251- 260.
2. Philip AK, Philip B. Colon targeted drug delivery system: A review on primary and novel approaches. Oman Medical Journal, 2010; 25(2): 70-78.
3. Vyas SP, Khar RK, Gastroretentive systems. In: Vyas SP, Khar RK, editors. Controlled drug delivery: concepts and advances. New Delhi: Vallabh Prakashan, 2005: 218-253.
4. Mehta TJ et al. Need of colon specific drug delivery system: review on primary and novel approaches. Int J Pharma Res Devel 2011; 3(1): 134- 153.
5. Patel A et al. Novel Approaches for Colon Targeted Drug Delivery System. J Pharma

Cosmetology 2011; 1(5): 85- 97.

6. Singh KI et al. Colon Specific Drug Delivery System: Review On Novel Approaches. Int J Pharma Sci Res 2012; 3(3): 637- 647.
7. Muthumanikandar RV et al. Design and Evaluation of Mesalamine Tablet for Colon Specific Drug Delivery. Int J Drug Deve Res 2011; 3(3): 197- 212.
8. Prasanth VV, Jayaprakash R, Mathew ST. Colon Specific Drug Delivery Systems: A Review on Various Pharmaceutical Approaches. J Applied Pharma Sci 2012; 2(1): 163-169.
9. Chawla G, Gupta P, Koradia V, Bansal AK. Gastro retention a means to address regional variability in intestinal drug absorption. Pharma Techno 2003; 7: 50-68.
10. Saini S et al, Colon: diseases and approaches- an overview. Int J Pharma Techno 2011; 3(3): 1197-1213.
11. Sinha VR, Kumria R. Polysaccharides in colon-specific drug delivery. International journal of pharmaceutics, 2001; 224: 19- 38.
12. Sharma A, Jain KA. Colon targeted drug delivery using different approaches. Int J Pharma Studies Res 2010; 1(1): 60-66
13. Choudhury PK, Panigrahi TK, Murthy PN, Tripathy NK, Behera S, Panigrahi R. Novel Approaches and Developments in Colon Specific Drug Delivery Systems- A Review, Webmed Central Pharmaceutical sciences 2012; 3(2): 1-20.
14. G Kishore et al, Development and Evaluation of Colon targeted tablets of Praziquantel and its β-Cyclodextrin complex to treat Schistosomiasis. J Pharma Sci Techno 2010; 2(8): 269-275.
15. Zou MJ, Cheng G, Okamoto H, Hao XH, An F, Cui FD, Danjo K. Colon-specific drug delivery systems based on Cyclodextrin prodrugs: In vivo evaluation of 5-aminosalicylic acid from its cyclodextrin conjugates. World Journal of Gastroenterol 2005; 11(47): 7457.
16. Kothawade PD et al. Conventional and novel approaches for colon specific drug delivery: a review. e -Journal of Science & Technology, 2011; 2(6): 33-56.
17. Racovita S, et al. polysaccharides based on micro- and nanoparticles obtained by ionic gelation and their applications as drug delivery systems. Revue Roumaine de Chimie, 2009; *54*(9): 709-718.
18. Patel PB, Dhake AS. Multiparticulate approach: an emerging trend in colon specific drug delivery for Chronotherapy. J Pharma sci 2011; 1(5): 59-63.
19. Asghar LFA, Chandran S. Multiparticulate Formulation Approach to Colon Specific Drug Delivery: Current Perspectives. J Pharm Pharma Sci 2006; 9(3): 327-338.