Review Article *ISSN: 2277-8713*
Jawalkoti Sunil, IJPRBS, 2013; Volume 2(2): 122-136 *IJPRBS*

COLON TARGETED DRUG DELIVERY SYSTEM: A REVIEW

JAWALKOTI SUNIL P.[1], JADHAV PRAKASH D.[1], MANE SANDEEP V.[1], KHADE MEGHA M.[2]

IJPRBS-QR CODE *PAPER-QR CODE*

1. Arvind Gavali College of Pharmacy, Satara, Jaitapur, Maharashtra, India.
2. Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Maharashtra, India.

Accepted Date:
05/04/2013
Publish Date:
27/04/2013
Keywords
Colon targeted drug delivery,
Amoebiasis,
Novel approaches,
OROS CT.

Corresponding Author
Mr.Jawalkoti Sunil P

Abstract

The colon is the terminal part of the GIT which has gained in recent years as a potential site for delivery of various novel therapeutic drugs,i.e. peptides. However, colon is rich in micro flora which can be used to target the drug release in the colon.colon targeted drug delivery system (CDDS) is an promising tool for local treatment of variety of bowel diseases such as ulcerative colitis, chrohn's disease, amoebiasis, colon cancer and for the systemic delivery of protein and peptide.This review is focused on the potential opportunities & challenges available in novel area of colon targeted drug delivery system.It also includes comparison of primary approaches for CDDS i.e. pH controlled, Time controlled, microbially triggered, prodrug, polysaccharide based approach which have achieved limited success & had limitations as compared with novel CDDS namely pressure controlled, CODESTM, OROS-CT, Nanoparticle for CDDS,TARGIT technology,Gas empowered drug delivery (GEDD), microsphere, COLAL-PRED system.Colon targeting holds a great potential and still need more innovative work.

INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs.[1,2,3]The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.[4]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.[5]And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.[6]

Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal.[7]

Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.[8]Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most

drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides[9].

Advantages of colon targeting drug delivery system: [11, 12, 13]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency Hence lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bypass initial first pass metabolism.
- Extended daytime or night time activity.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones can be given through this route.

Why colon targeted drug delivery is needed?[10]

• 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.

The Colon[10]

The entire colon is divided into five major segments across its 150 cm length. The last anatomic segment before the anus is the rectum. Peritoneal folds called mesentery supports 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 consists of the left half of the transverse colon, splenic flexure, descending colon, and sigmoid (Fig.1).

Physiology of the colon [10, 14]

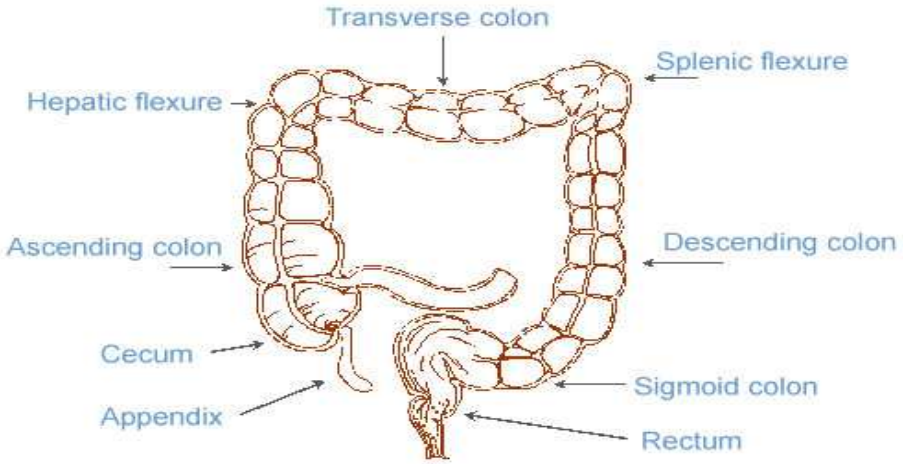

Fig.1: Anatomy of colon

The main functions of the colon are elimination of waste material, storage of feces and Reabsorption of water and electrolytes. The storage function of the colon is the main function of the colon that allows a longer period for absorption of useful material by

preventing rapid elimination of colonic contents. All colonic area are capable of storing function but with different storage capacity. The ascending colon is thought to be the main storage site[15].It was shown that only 150 ml of water is eliminated with feces from each 1000 ml of chyme in the colon. The slower movement in the colon compared with any other area of the G.I.T allows for this absorption. Water reabsorption in the colon occurs as a result of the absorption of sodium and chloride ions and associated excretion of potassium and bicarbonate ions[16]. The first portion, including the cecum, ascending colon, and part of the transverse colon, has a unique pattern of motility compared to the subsequent sections. This area has a motility that was first described by Cannon, (1902) as antiprestaltic. Antiprestalsis causes the chyme to be pushed back towards the ileocecal junction this results in thorough mixing and increased efficiency of absorption of water and electrolytes from the chyme[17]. Antiprestalsis leads to a prolonged residence time in the proximal colon. This effect, together with the fact that the contents are less viscous at this site[18], makes the ascending colon an ideal site for drug release.

COLON TARGETED DRUG DELIVERY APPROACHES:

A. Primary Approaches:[19]

1.pH Controlled release system: In pH controlled release systems, the different pH of human GIT is exploited by coating the dosage form with pH dependent polymers which remains as such in the upper GIT and degrade in the large intestine where the pH is high i.e. 7-8.This approach can be used in any dosage form such as tablets, capsules,pellets etc.[20-21] On coating the dosage forms with pH sensitive polymers, the active drug is protected from gastric fluid and also a delayed release is obtained. Methacrylic acid and methyl methacrylate are the most commonly used polymers for colonic drug delivery. On the in vitro evaluation of Eudragit S100 and Eudragit FS, it was found that the latter proves to be more appropriate for ileocolonic drug delivery.[22] Combination of different polymers, coating level, pH of media are some factors that affect the dissolution rate of Eudragit. The pH controlled systems are commercially available for some drugs like mesalazine (5 ASA),budesonide for the treatment of ulcerative colitis and crohn's disease respectively 2 as mentioned below in table 1 &2 depicting enteric coating polymers &pH.

2.Time Controlled Release System:

The time controlled systems works on the principle of drug release after a predetermined lag time at the desired site of action and time of release [25].A considerable lag time of five hours is considered adequate for colon targeting. The coated polymer or mixture of polymers and their thickness influences the time required for dosage form to release drug in colon. As the gastric emptying time of dosage forms differ from person to person, the colon arrival time of dosage form can't be predicted accurately. However, these systems are useful in the therapy of diseases based on circadian rhythms. [26, 27] A time controlled system in the form of capsules and bilayer tablets is described. Here the balance between the thickness of water insoluble membrane and the amount of swellable excipient controls the release time of drug from dosage form.

The disadvantages of this system are:

1. Gastric emptying time shows intersubject and intrasubject variation leading to unpredictable colon arrival time of drug.[22, 26]

2. The peristaltic movements or contractions in the stomach result in altered gastrointestinal transit of the drug[22].

3. Altered transit is also observed in conditions of IBD, diarrhea, ulcerative colitis.[28]

Thus the integration of pH and time release systems in a dosage form may improve the targeted drug delivery to colon and also the transit time of dosage forms in small intestine is less variable i.e. about 3±1 hr[29]. Different polymers used for developing time dependent systems are Hydroxyl Propyl Methyl Cellulose, Hydroxy Ethyl Cellulose, Ethyl Cellulose, Microcrystaline Cellulose, Hydroxy Propyl Methyl Cellulose Acetate Succinate, Lactose/Behinic acid etc.

3. Microbially Triggered Approach:

The principle involved in this system is the degradation of the polymers coated on the dosage form by the microflora of the colon releasing the drug load there.[30] Colon has a range of complex microflora which fulfills its energy requirements by fermenting the substrate e.g. Polysaccharides present in the intestinal region.[31, 32] These microflora produces wide variety of enzymes which are able to metabolize substrates like carbohydrates and proteins that escape digestion in upper GIT[33]. The majority of polymers are used in pharmaceutical composition and generally regarded as safe

excipients. Polymer pectin was needed in large quantity when used alone to control the release of drug from the dosage form. But when pectin was mixed with chitosan and hydroxyl propyl methyl cellulose in adequate quantity, it proved to be very efficient to prevent the drug release in stomach and releasing it in the colon.[32] The microbially degradable polymers includes Chitosan, Pectins, Guar Gum, Dextrans, Inulin, Lactulose, Amylose, Cyclodextrins, Alginates, Locust bean gum, Chondroitin sulphate, Boswellia gum etc. Microbially triggered approaches include the following three approaches mentioned below.

a. Prodrug approach:

Prodrug is defined as the pharmacologically inactive derivative of a parent drug which requires spontaneous or enzymatic transformation in vivo in order to release the active agent. In this approach there exist a covalent linkage between the drug and its carrier which remains as such in the upper GIT and breakdown in the colon releasing the drug. A number of linkages of drug with hydrophobic moieties like amino acids, glucoronic acid glucose, galactose, cellulose etc. have been prepared which are succeptible to hydrolysis in the colon[34]. The major limitation for prodrug approach is that for its design and development the functional group present on the drug moiety plays a very significant role for chemical linkage. An example of prodrug is 5-ASA, which was conjugated with glycine by amide linkage which was found stable in upper GIT and hydrolysed by ceacal contents to release 5-ASA[35]

b. Azo- Polymeric Prodrugs:

Newer techniques involve the use of different polymers as carrier of drugs for their colonic delivery. Polymeric prodrug with azo linkage between polymer and drug moiety are designed by using sub synthetic polymers[36]. Polymers cross linked with azo aromatic group when coated on drug protected it from degradation in upper GIT and released in the colon where the azo bonds were reduced. An example of azo polymer based drug delivery system is segmented polyurethane was coated over the pellets of budesonide and when evaluated in vivo and in vitro resulted in the colonic delivery of drug[37].

c. Polysaccharide based approach: Naturally occurring polysaccharides are widely in use for drug targeting because of their abundance, easy availability, and also they are inexpensive[38].They are highly stable, safe,

nontoxic, hydrophilic, gel forming and biodegradable importantly as shown in Table3.

A number of natural polysaccharides are investigated which include Chitosan, Pectin, Chondroitin sulphate, Alginates etc. obtained from plants, animals, algae or microbes as depicted below in table 5. Colonic microflora is able to break down these polysaccharides into simpler ones[39]. Chitosan is used mainly in the form of capsule forming material for the colonic delivery.

PolysaccharideCarriers for Colonic DrugDelivery[40]

Since last decade a novel oral colon specific drug delivery system (CDDS) has beendeveloping as one of the site specific drug deliverysystem[41].To overcome the toxicity concerns of synthetic polymers (azo polymers), natural polymers especially glycosidic bond containing materials offer a viable alternative for colonic drug delivery. The glycosidic bond containing polymers includes disaccharides, oligosaccharides and polysaccharides Polysaccharides naturally occurring in theplant (e.g. pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g. alginates) or microbial (e.g., dextran) origins are generally used for colon targeting of various drugs.Although specifically degraded in the colon, many of these polymers are hydrophilic in nature and swell under exposeto upper GIT conditions,which leads to premature drug release. To overcome these problems the natural polysaccharides are chemically modified andmixed with hydrophobic water insoluble polymer,whereas in the case of formulations they areusually covered with pH sensitive polymer. Enteric coating is another formulation approach used to prevent the rapid swelling or disintegration of polysaccharide based formulations in the upper GIT[42]. Successful colonic delivery requires careful consideration of a number of factors including the properties of drug .the type of delivery system and its interaction with the healthy or diseased gut. The polysaccharide which is polymer of monosaccharide retains their integrity, becausethey are resistant to digestive action of GI enzymes, matrices of polysaccharide are assessed to remain intact in physiological

environment of stomach and small intestine, as they reach colon they are acted upon bacterial polysaccharidases and results in degradation of the matrixes. Family of natural polysaccharide has appeal to area of drug delivery as it comprised of polymer with large number of derivitizable groups with wide range of molecular weight, varying chemical composition and form most low toxicity and biodegradability, yet a high stability .A novel colonic drug delivery was investigated and the In-vitro experiments demonstrated that high methoxy pectin, when applied as compression coat, proved capable of coat tablet during condition stimulating gastrointestinal environment and was susceptible to enzymatic attack.

The use of pectinolytic enzymes to stimulate breakdown in colon showed that pectin/chitosan mixture was susceptible to enzymatic break down and releasing its content. A study was carried out to access the potential pectin: chitosan films for colonic delivery and found that pectin alone was able to protect the premature release, but only when a substantially thick coat was provided.Pectin and HPMC compressed core tablets of 5- ASA for colon delivery, Drug dissolution/system erosion/ Degradation studies were carried out in pH 1.2 and 6.4 buffers using pectinolytic enzymes, system was designed that transit time from the GI tract and arrival time for colon is 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the stability of pectin. The optimum concentration of 20% HPMC was preferred for 6h that corresponds to 25-30% erosion and after that the influence of the pectinase system degrade faster and release 5-ASA to the colon.The preparation and demonstration of the efficacy of chitosan microcores entrapped within acrylic microspheres containing diclofenac sodium as model drug[43]. The drug was efficiently entrapped within the chitosan microspheres using spray drying and then microencapsulated into Eudragit L100 and Eudragit S100 using oil in oil solvent evaporation method. Numerous Eudragit coated oral dosage forms for targeting colon are recently in use for treatment of ulcerative colitis.

2. NEWLY DEVELOPED APPROACHES FOR CDDS1

a. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water.In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation.[32, 44] The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid.45Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

b. Novel Colon Targeted Delivery System (CODES^{TM}) 1

CODES^{TM} is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.46,47CODES^{TM} is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon (Fig.2).The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, EudragitL. 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.48Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid

soluble coating and subsequent drug release.49

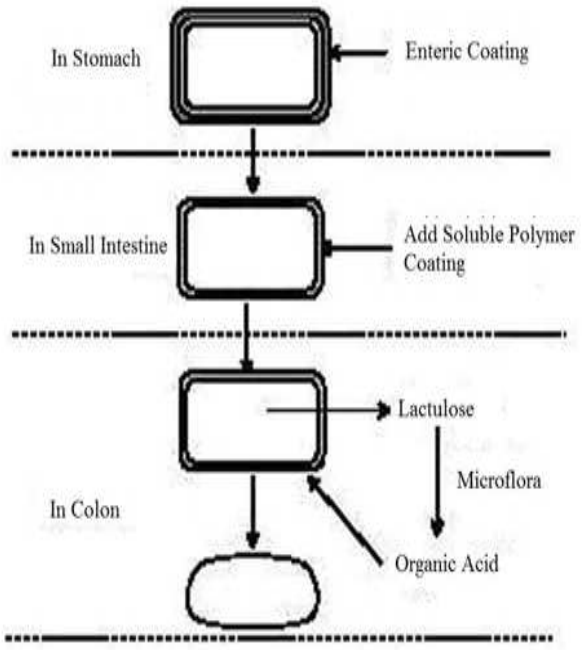

Figure 2: Schematics of the conceptual design of CODES

c.Osmotic Controlled Drug Delivery (OROS-CT)1

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable.50The OROS-CT system can be a 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 (Fig. 3).51Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin 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. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. 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 hour.

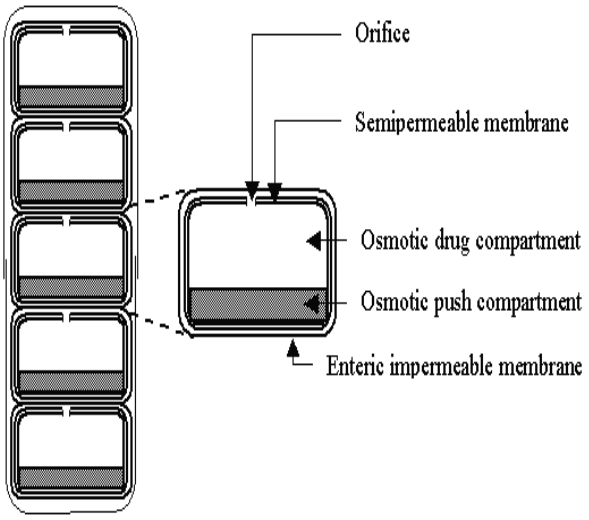

Figure 3: Cross-Section of the OROS-CT colon targeted drug delivery system

d.Nanoparticles for Colon Targeted Drug Delivery19:

Nanoparticles are now days become novel area for colon specific drug delivery as depicted in table7. These are novel approaches used to target drugs. These are small colloidal particles of size about 200 nm made up of biodegradable and non- biodegradable polymers. The drug moiety can be dissolved, entrapped, or encapsulated in the nanoparticle matrix52.They are better than conventional dosage forms in many aspects .They results in more efficacy, reduced toxicity, better biodistributionand improved patient compliance53. They results in controlled release due to biodegradability, pH, ion, temperature sensitivity54.

e.TARGIT Technology19:

This technology is developed for the targeted delivery of drugs in colonic region. It is mainly used in the delivery of therapeutic agents to the lower GIT for local treatment of disorders. In this technique pH sensitive coating is done on the moulded starch capsules. The in vivo studies confirmed that about 90% of the TARGIT Capsules delivered their contents to the target site56.

f. Gas Empowered Drug Delivery System (GEDD)19:

It is also a novel drug delivery system to colon which is designed to target the proteins and peptides to the intestinal region by using mucoadhesive polymer polyethylene oxide and TMC as penetration enhancer using co2. By the presence of mucoadhesive polymer the drug remains adhered to the mucous layer and the permeation enhancer is used to open the tight junctions to promote paracellular pathway for drug absorption. In this system the co2 gas is used as driving force to push the drug substance to the absorbing membrane and also it covers the dosage form completely to

protect it from enzymatic and proteolytic degradation. 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 57.

g. Microspheres:

Microspheres are used now a day for the delivery of proteins and peptides .They provides stability to the compounds which are prone to degradation in vivo. 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.58,59 The mechanisms of drug release from microspheres can be diffusion, degradation, hydrolysis or erosion60. The drug encapsulated in microspheres have shown increased stability, reduced toxicity and also targeted delivery to the site of action. Some of the examples where microspheres are prepared for colon targeting are given below in Table 8.

h. COLAL-PRED system:

This system is designed 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 provides the effective treatment of ulcerative colitis without the side effects of steroids. There is no competitor of this product yet in the market. Its colon targeting is done by coating it with such substances which get degraded by the colonic bacteria 64.

LIMITATIONS AND CHALLENGES IN COLON TARGETED DRUG DELIVERY 65

One challenge in the development of colon-specific drug deliverysystems 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.

As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location in the

distal part of the alimentary canal, the colon is particularly difficult to access.

In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.

Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or, alternatively, it should dissolve in the luminal fluids of the colon, 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.

OPPORTUNITIES IN COLON TARGETED DRUG DELIVERY[66]

In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades.

Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful transcolonic administration of drugs, but also for systemic delivery of drugs like proteins andpeptides, which are otherwise degraded and/or poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon.

This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Moreover, there is an 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 enable reduction of the required 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 isvery low because of instability in the GI tract is one of the greatest challenges for oral peptide delivery.

The bioavailability of protein drugs delivered at the colon site needs to bead dressed.

More research is focused on the specificity of drug uptake at the colon site isnecessary. Such studies would significant in advancing the cause of colon targeted drug delivery in future.

Table 1: Colon targeting diseases, drugs and sites[10]

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	Pancreactomy 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.	NSAIDS, Steroids, Insulin, Typhoid.

Table 2: Threshold pH of most commonly used enteric polymers [19, 23, 24]

ENTERIC POLYMERS	THRESHOLD pH
Polyvinyl acetate phthalate(PVAP)	4.5-5.0
Cellulose acetate phthalate (CAP)	5.0
Shellac	7.0
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L 100-55	5.5
Eudragit L 30 D	5.6
Hydroxypropyl methylcellulose Phthalate (HPMCP)	>5.5
Hydroxypropylethylcellulose phthalate	5.2
Cellulose acetate trimelliate	5.5
Hydroxypropyl methylcellulose acetate succinate	>6.0
Eudragit FS 30 D	6.8

Table 3: Marketed pH dependent systems

DRUG USED IN DISEASE	POLYMER USED	DOSAGE FORM	DISEASE
Tegaserod maleate	Eudragit L 100, Eudragit S 100.	Tablet	IrritableBowel Syndrome
Prednisolone	Eudragit L 100, Eudragit S 100.	Tablet	Ulcerative collitis

Table 4: Marketed Microbially controlled systems[19]

DRUG USED	POLYMER USED	DOSAGE FORM	DISEASE
Valdecoxib	Guar Gum and Sodium Starch Glycholate	Tablet	InflammatoryBowel disease
5- fluorouracil	Pectin	Tablet	Colon cancer
Metronidazole	Sesbania Gum	Matrix Tablet	Intestinal Amoebiasis

Table 5: Novel forms of natural polysaccharides used[19]

DRUG	POLYSACCHARIDE	DOSAGE FORM
Diclofenac Sodium	Chitosan	Microspheres
Insulin	Chitosan	Capsules
Indomethacin	Pectin	Matrix Tablet
Dexomethasone	Guar Gum	Matrix Tablet
Indomethacin	Chondroitin Sulphate	Matrix Tablet
5-ASA	Alginates	Swellable Beads
Theophylline	Locust- Bean Gum	Film
Theophylline	Dextran Fatty Acid Esters	Film

Table 6: Characteristics of Various Biodegradable Polysaccharides for Colon Targeted Delivery

POLYSACCHARIDE	CHEMICAL NAME	GENERAL PROPERTIES	BACTERIAL SPECIES
Amylose	α-1,4 D-glucose	Unbranched constituents of starch used as excipients in tablets formulation.	Bacteriods, Bifidobacterium
Arabinogalactone	β-1,4 and β-1,3 D-galactose, β-1,6 and β-, 3 D-arabinose and D-galactose.	Natural pectin, hemicelluloses used as thickening agents.	Bifidobacterium
Chitosan	Deacetylated β-1,4 N-acetyl D-glycosamine	Deacetylated chitin used as absorption enhancing agents.	Bacteroids
Chondroitinsulfate	B-1,3, D-glucoronic acid and N-acetyl D-glycosamine	Mucosopolysaccharides contains sulphate ester group at 4 or 6 position.	Bacteroids
Cyclodextran	α-1,4 D-glucose	Cyclic structure of 6, 7 or 8 units, high stability against Amylase, used as drug solubilizing agent and absorption enhancer.	Bacteroids
Dextran	α-1,6 D-glucose α-1,3 D-glucose	Plasma expanders	Bacteroids
Guar gum	α-1,4 D-mannose α-1,4 D-galactose	Galactomannan used as thickening agents	Bacteroids Ruminococcus
Pectin	α-1,4 D-galactouronic acid and 1,2 D- rhamnose with D-galactose and D-arabinose side chains	Partial methyl ether commonly used as thickening agents	Bacteriods, Eubacterium Bifidobacterium
Xylan	α-1,4 D-xylose with α-1,3 L-arabinose side chains	Abundant hemicelluloses of plant cell wall.	Bacteriods, Bifidobacterium

Table 7: Novel nanoparticles based systems.[19]

DRUG USED	POLYMERS USED	METHOD OF PREPARATION	DISEASE
5- Fluorouracil	Soyalecithin, Dynasan and Dynasin	Solid-Lipid Nanoparticles	Colon cancer [55]
Tripeptide, Lys-Pro-Val	Alginate and Chitosan	Double-emulsion/solvent evaporation	Inflammatory bowel disease

Table 8: microspheres based colon targeted system

DRUG	POLYMER USED	METHOD OF PREPARATION	DISEASE
Theophylline	Ca-pectinate, Eudragit S100	Ionotropic gelation method	Anti-asthmatic activity[61]
Indomethacine	Eudragit L-100, Eudragit S-100	Solvent evaporation method	Rheumatoid disorders[62]
Aceclofenac	Guar gum	Emulsification method	Rheumatoid arithritis[63]

REFERENCES –

1. Anil k. Philip,BettyPhilip,colon targeted drug delivery system,Oman medical journal,April2010,vol.25,issue 2,1.

2. Philip AK, Dabas S, Pathak K. Optimized prodrug approach: A means for achieving enhanced anti inflammatory potential in experimentally induced colitis, J Drug Target 2009; 17:235-241.

3. Oluwatoyin AO, John TF, In vitro evaluation of khaya and albizia gums as compression coating for drug targeting to the colon, J Pharm Pharmacol 2005; 57: 63-168.

4. Akala EO, Elekwachi O, Chase V, Johnson H, Marjorie L, Scott K., Organic redox initiated polymerization process for the fabrication of hydrogel for colon specific drug delivery, Drug DevInd Pharm 2003; 29:375-386.

5. Chourasia MK, Jain S K. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Sci 2003; 6:33-66.

6. Basit A, Bloor J. Prespectives on colonic drug delivery, Business briefing. Pharmtech 2003; 185-190.

7. Watts P, Illum L. Colonic drug delivery. Drug DevInd Pharm 1997;23:893- 913.

8. Wood E, Wilson CG, Hardy JG. The spreading of foam and solution enemas. Int. J Pharm 1985; 25: 191-197.

9. Chien YW, Oral drug delivery and delivery systems, In: Chien YW, editor, Novel drug delivery systems. New York: Marcel Dekker Inc; 1992; 139-196.

10. S.Pradeep Kumar, D.Pratibha, Novel colon specific Drug delivery system,International journal of Pharmacy & Pharmaceutical sciences,23,2012,22-29.

11. Akhil Gupta, Anuj Mittal, Colon targeted drug delivery system,International Journal of Pharmaceutical & Clinical research , 2010, 112-120.

12. Jain NK: Advances in Controlled and novel Drug Delivery. 1st edition, New Delhi, Cbs publisher and distributors; 2008, 86-90.

13. Kinget R, KalalaW, Vervoort L, van denMooter G: Colonic drug targeting. J Drug Targeting 1998; 6(2): 129-149.

14. 14.Sarasija S, Hota A. Colon-specific drug delivery systems, Indian journal of pharmaceutical sciences 2000; 62(1): 1- 8.

15. Christensen, J., The response of the colon to eating. Am. J. Clin. 1985; Nutr.42: 1025-1032.

16. Dawson, D.C., (1991). Lon channels and colonic salt transport. Annu. Rev. Physiol., 53, 321-329.

17. Cannon, W.B., (). The movements of the intestines studied by means of rontgen rays. Am.J.Physiol. 1902; 6: 251.

18. Christensen, J., (1981). Motility of the colon, in Physiology of the gastro intestinal tract, 1st ed., Vol 1, Jonson-LR, Ed, Raven Press, New York.

19. Surendra Varma,vipin Kumar, D. N. Mishra, S. K. Singh, Colon Targeted Drug Delivery Current and Novel Prospectives, International Journal of Pharmaceutical sciences and Research,2012,3(5),1274-1284.

20. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ and Hardcastle JD: Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988, 29:1035-1041.

21. Rodríguez M, Vila-Jato JL and Torres D: Design of a new multiparticulate system for potential site-specific and controlled drug delivery to the colonic region. Journal of Control Release 1998; 55:67.

22. Bussemer T, Otto I and BodmeierR: Pulsatile drug-delivery systems. Critical Reviews in Therapeutic Drug Carrier Systems 2001; 18:433-458.

23. Ashford M, Fell JT, Attwood D, Sharma H and Woodhead PJ: An in vivo investigation into the suitability of pH-dependent polymers for colonic targeting. International Journal of Pharmaceutics 1993; 95:193.

24. Markus W, Rudolph, Klein S, Beckert TE, Petereit H and Dressman JB: A new 5-aminosalicylic acid multi-unit dosage form for the therapy of ulcerative colitis. Eurupeon Journal of Pharmaceutics and Biopharmaceutics 2001; 51:183.

25. Arora S, J Ali and Ahuja A: Pulsatile drug delivery systems: an approach for controlled drug delivery. Indian Journal of Pharmaceutical Sciences 2006; 68:295-300.

26. Gazzaniga A, Iamartino P, Maffino G and Sangalli ME: Oral delayed release system for colonic specific drug delivery. International Journal of Pharmaceutics 1994; 108:77-83.

27. Vonderohe MR, Camolleri M, Kvols LK and Thomforde GM: Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. The New England Journal of Medicine 1993; 329:1073.

28. Cummings JH and Englyst HN: Fermentation in the human large intestine and available substrates. American Journal of Clinical Nutrition 1987; 45:1243-1255.

29. Hergenrother RW, Wabewr HD and Cooper SL: The effect of chain extenders and stabilizers on the in vivo stability of polyurethanes. Journal of Applied Biomaterials 1992; 3:17-22.

30. Sinha V.R. and Kumaria R: Microbially triggered drug delivery to the colon. European Journal of Pharmaceutical Sciences 2003; 18:3-18.

31. Rubunstein A: Microbially controlled drug delivery to the colon. Biopharmaceutics and drug Disposition 1990; 11:465-475.

32. Takaya T, Ikeda C and ImagawaN : Development of a colon delivery capsule and pharmacological activity of recombinant human granulocyte colony stimulating factor in beagle dogs.Journal of Pharmacy and Pharmacology 1995; 47:474-478.

33. Kaur G, Jain S and Tiwary A.K: Investigations on microbially triggered system for colon delivery of budesonide. Asian Journal of pharmaceutical Sciences 2010; 5:96.

34. Tiwari G, Tiwari R, Wal P, Wal A and Rai A.K: Primary and novel approaches for colon targeted drug delivery – A review. International Journal of Drug Delivery 2010; 2:01-11.

35. Tozaki H, Komoike J, Tada C, Maruyama T, Terabe A, Suzuki T, Yamamoto A and MuranishiS: Chitosan capsules for colon-specific drug delivery: improvement of insulin absorption from the rat colon. Journal of Pharmaceutical Sciences 1997; 86:1016-1021.

36. Mooter GV, Samyn C and Kinget R: In vitro evaluation of a colon specific drug delivery system: An absorption study of

theophylline from capsules coated with azo polymers in rats. Pharmaceutical Research 1995; 12:244-247.

37. Hita V, Singh R and Jain SK: Colonic targeting of metronidazole using azo aromatic polymers, development and characterization. Drug Delivery 1997; 4:19-22.

38. Friend DR, Phillip S and Tozer TN: Colon specific drug delivery from a glucosidic prodrug in the guinea pig efficacy study. Journal of Controlled release 1991; 15:47-54.

39. Fukui E, Miyamura N and Kobayashi M: An in vitro investigation of the suitability of presscoated tablets with hydroxypropyl methylcellulose acetate succinate (HPMCAS) and hydrophobicin additives in the outer shell for colon targeting. Journal of Controlled Release 2001; 70:97-107.

40. 40.Abhishek Bhattacharjee, Oral Micro-Particulate Colon Targeted Drug Delivery System For The Treatment of crohn's disease: a review, International Journal of life sciences and biotechnology and pharmaresearch, vol 2,april 2012,35-37.

41. K S Salunkhe and M V Kulkarni (2008). "Formulation and in vitro evaluation of dextrin matrix tablet of Ibuprofen for colon specific drug delivery", Pak. J. Pharm. Sci, Vol. 21, No. 1, pp. 17-20.

42. J Kopecek, P kopeckova, H Bronsted, T Rathi, B Rihova, P Y Yeh, K Ike Sue (1992), Polymers of Colon Specific Drug Delivery, J. Control. Rel., Vol. 19, pp. 121-130.

43. Lorenzo-Lamosa M L, Remunan-Lopez C, Vila-Jato J L and Alonso M J (1998), "Design of microencapsulated chitin microspheres for colonic drug delivery", J. Control. Rel., Vol. 52, pp. 109-118.

44. Muraoka M, Hu Z, Shimokawa T, Sekino S, Kurogoshi R, Kuboi Y, Yoshikawa Y, Takada K. Evaluation of intestinal pressure-controlled colon delivery capsule containing caffeine as a model drug in human volunteers. J Control Rel 1998; 52(1-2):119-129.

45. Hay DJ, Sharma H, Irving MH. Spread of steroid containing foam after intrarectal administration. Brit Med J 1979; 1:1751-1753.

46. 46 Watanabe S, Kawai H, Katsuma M, Fukui M. Colon specific drug release system. U. S. Patent, 1998, 09/183339.

47. Takemura S, Watanabe S, Katsuma M, Fukui M. Human gastrointestinal treatment study of a novel colon delivery system (CODES) using scintography, Pro Int Sym Control RelBioact Mat 2000, 27.

48. Masataka K, Watanabe S, Takemura S, Sako K, Sawada T, Masuda Y, Nakamura K, Fukui M, Connor AL, Wilding IR. Scintigraphic evaluation of a novel colon-targeted delivery system (CODESTM) in healthy volunteers. J Pharm Sci 2004; 93(5):1287-1299.

49. Yang L, James S, Joseph A. Colon specific drug delivery new approaches and in vitro/ in vivo evaluation. Int J Pharm 2002; 235:1 - 15.

50. Theeuwes F, Guittared G, Wong P. Delivery of drugs to colon by oral dosage forms. U. S. Patent, 4904474

51. Swanson D, Barclay B, Wong P, Theeuwes F. Nifedipine gastrointestinal therapeutics system. Am J Med 1987; 8(6):3.

52. Farokhrad O C, Langer R: Advance drug delivery review 2006; 58:1456-1459.

53. Nayak A K, Dhara A K: Archives of Applied Science Research 2010; 2:284-293.

54. Panyam J. Journal of control Release 2003; 92:173 – 187.

55. Bayat A, Dorkoosh F A, Dehpour A R, Moezi L, Larijani B, Junginger H E, Rafiee T M: Nanoparticles of quarternized chitosan derivatives as carrier for colon delivery of insulin: ex vivo and in vivo studies. International journal of pharmaceutics 2008; 356:259-66.

56. Yassin A E B, Alsarra I A, Alanazi F K, Al-Mohizea AM, Al-Robayan AA and Al-Obeed O A: New Targeted-Colon Delivery System: In vitro in vivo evaluation using x-rays Imaging. Journal of drug targeting 2010; 18:59-66.

57. Shibata N, Ohno T, Shimokawa T, Hu Z, Yoshikawa Y, Koga K, Murakami M and Takada K: Application of pressure controlled colon delivery capsule to oral administration of glycyrrhizin in dogs. Journal of Pharmacy and Pharmacology 2001; 53:441-447.

58. Thanou M, Verhoef J C and Junginger H E: Advanced Drug Delivery Review 2001; 50:91-101.

59. Bochard G, Lueben H L, Verhoef H C, Leher C M, Boer A G and Junginger H E: Journal of control Release 1996; 39:131-138.

60. 60.Johnson O L, Cleland J L, Lee H J, Charnis M, Duenas E and Jaworowicz W: Nat Med 1996; 2:795-799.

61. Maestrelli F, Cirri M, Corti G, Mennini N and Mura P: Development of Enteric Coated Calcium pectinate Microspheres intended for colonic Drug Delivery. European Journal of Pharmaceutics and Biopharmaceutics 2008; 69:508-518.

62. Keshavarao K P, Dixit M, Selvum P and Singh D R: Formulation and evaluation of indomethacine microspheres for colonic drug delivery system. International research journal of pharmacy 2011; 2:181-184.

63. Ravi P, RaoKusumanchi R M, Mallikarjun V, BabuRao B and B R N: Formulation and Evaluation of Guar gum Microsperes of Aceclofenac for Colon Targeted Drug delivery. Journal of Pharmacy Research 2010; 3:1510-1512.

64. Rangasamy M, Colon targeted drug delivery system, International journal of drug formulation and research 2010; 1:30-54.

65. Brahma P. Gupta, Navneet Thakur, Surabhi Jain, Priyanka Patel , Deepak Patel, Nilesh Jain, Nishi P. Jain , A Comprehensive Review On Colon Specific Drug Delivery System (CSDDS), Journal of Pharmacy Research 2010, 3(7),1625-1629

66. Tarak Jayraj Mehta, Mr. A. D. Patel, Dr Mukesh R. Patel, Dr N. M. Patel, Need of colon specific drug delivery system review on primary and novel approaches, International Journal of Pharma Research and Development, 2011, 3(1), 146-14.