Review Article CODEN: IJPRNK Impact Factor: 5.567 ISSN: 2277-8713
Upadhye S. S., IJPRBS, 2016; Volume 5(5): 63-80 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A REVIEW ON COLON TARGETED DRUG DELIVERY SYSTEM

MR. UPADHYE S. S.[1], MR. B. K. KOTHALI[2], MRS. A. K. APTE[3], MRS. A. A. KULKARNI[1], MRS. V. S. KHOT[1]

1. Lecturer, Dr. J.J. Magdum Pharmacy College, Jaysingpur, A/P- Jaysingpur, Tal- Shirol, Dist- Kolhapur-416101, Maharashtra, India.
2. Principal, Dr. J.J. Magdum Pharmacy College, Jaysingpur, A/P- Jaysingpur, Tal- Shirol, Dist- Kolhapur-416101, Maharashtra, India.
3. Vice-Principal, Dr. J.J. Magdum Pharmacy College, Jaysingpur, A/P- Jaysingpur, Tal- Shirol, Dist- Kolhapur-416101, Maharashtra, India.

Accepted Date: 18/09/2016; Published Date: 27/10/2016

Abstract: The drug is targeted to the colon in colon targeted drug delivery system. The dosage form is modified to deliver the drug at the target region or at the disease region in the targeted drug delivery system. The CTDDS [Colon targeted drug delivery system] is delivered as both local & systemic delivery of drugs. The Local delivery allows the topical treatment of inflammatory bowel disease. Not only for the treatment of local diseases the colon target drug delivery system has been gained great importance but also for the systemic delivery of the therapeutic peptides, proteins, anti-diabetic agents, anti-asthmatic drugs, antihypertensive drugs. This review article focuses mainly on the various factors to be considered in the design of colon targeted drug delivery system, different factors affecting colon targeted drug delivery, different approaches for colon targeted drug delivery, evaluation tests for colon targeted drug delivery system

Keywords: Colon Targeted Drug Delivery System, Approaches for colon targeted drug delivery system, Evaluation of colon targeted drug delivery system

PAPER-QR CODE

Corresponding Author: MR. UPADHYE S. S.

Access Online On:

www.ijprbs.com

How to Cite This Article:

Upadhye S. S., IJPRBS, 2016; Volume 5(5): 63-80

INTRODUCTION

For local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs, the targeted drug delivery into the colon is highly desirable. The CDDS [colon specific drug delivery system] should be capable of protecting the drug en route to the colon, that is the absorption & drug release should not occur in the small intestine as well as stomach & neither the bioactive agent should be degraded in the either of the dissolution sites but only released & absorbed once the system reaches the colon. For peptides and protein drugs the colon is believed to be the suitable absorption site for the following reasons; [a] The comparative proteolytic activity of the colon mucosa is much less than that observed in the small intestine, [b] the less diversity& intensity of the digestive enzymes, thus the colon specific drug delivery system protects the peptide drugs from hydrolysis & enzymatic degradation in the duodenum & jejunum & the drug is eventually released into ileum or the colon which leads to the greater systemic bioavailability. Finally, because due to the long residence time the colon has which is up to the 5 days & is highly responsive to the absorption enhancers, the oral route is the most preferred & convenient route but other routes for the colon specific drug delivery system may be used. For targeting drugs to the colon the rectal administration offers the shortest route. Reaching the proximal part of the colon via rectal administration is however difficult. The rectal administration can also be uncomfortable for the patients & compliance may be less than the optimal. For intrarectal administration the drug preparation is supplied as foam, suppositories & solutions. Both as a means of systemic dosing and for the delivery of topically active drug to the large intestine the intrarectal route is used. For the treatment of ulcerative colitis the corticosteroids such as Prednisolone & hydrocortisone are administered via the rectum. It is generally believed that their efficacy is due mainly to the topical application although these drugs are absorbed from the large bowel. The concentration of drug reaching the colon depends on the retention time, formulation factors & the extent of retrograde spreading. The suppositories and foam have been shown to be retained mainly in the rectum & sigmoid colon while enema solutions have the great spreading capacity. The colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low, because of the high water absorption capacity of the colon. The human colon has over 400 distinct species of bacteria as resident flora the possible population of up to 1010 bacteria per gram of the colonic contents. Amongst the reactions carried out by these gut flora are azo reduction & enzymatic cleavage that is glycosides. For the metabolism of many drugs these metabolic processes may be responsible and may also be applied to the colon-targeted delivery of the peptide based macromolecules such as insulin by the oral administration. [1-8]

WHY COLON TARGETED DRUG DELIVERY IS NEEDED?

• To the colon the targeted drug delivery would ensure direct treatment at the disease site, fewer systemic side effects, lower dosing.

• In the treatment of colon diseases, the colon-specific drug delivery system is considered to be beneficial.

• For delivery of drugs which are polar &/or susceptible to the chemical & enzymatic degradation in the upper GI tract, highly affected by the hepatic metabolism, in particular the therapeutic proteins & peptides, the formulations for colonic delivery are also suitable.

• The targeted or Site-specific drug delivery system would allow the oral administration of peptide & protein drugs, to prolong the drug delivery, the colon-specific formulation could also be used.

• If drugs were targeted to the colon, the number of others serious diseases of the colon, for e.g. colorectal cancer, might also be capable of being treated more effectively.

• Colon is the site where the both, local or the systemic drug delivery could be achieved, the topical treatment of the inflammatory bowel disease, for e.g. Ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with the glucocorticoids & sulphasalazine [targeted]. [9, 10]

FACTORS TO BE CONSIDERED IN THE DESIGN OF COLON TARGETED DRUG DELIVERY SYSTEM

Anatomy and Physiology of Colon

From the distal end of the ileum to the anus the large intestine extends. The human large intestine is about 1.5 m long [Table 1]. The colon is mainly situated in the abdomen & is upper 5 feet of the large intestine. The colon is the cylindrical tube that is lined by the moist, soft pink lining called as mucosa the pathway is called the lumen & is approximately 2-3 inches in the diameter. The cecum forms the first part of the colon & leads to the right colon or the ascending colon [just under the liver] followed by the transverse colon, the descending colon, sigmoid colon, rectum & the anal canal. In several respects, the physiology of the proximal & distal colon differs that have an effect on the drug absorption at each site. The physical properties of the luminal content of the colon also change from liquid in the cecum to semisolid in the distal colon.

pH in the Colon The pH of the GI tract is subject to both the inter & intra subject variations. The diseased state, diet & food intake influence the pH of the GI fluid. The change in the pH along the GI tract has been used as the means for the targeted colon drug delivery. There is the pH

gradient in the GI tract with value ranging from the 1.2 in the stomach through 6.6 in the proximal small intestine to the peak of about 7.5 in the distal small intestine [Table 1]. The difference in pH between the stomach & small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. Due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides, there is the fall in pH on the entry into the colon.

Table 1: Summary of anatomical and physiological features of small intestine and colon

Region of Gastrointestinal Tract		Length (cm)	pH	Internal diameter (cm)
Stomach		-------		-------
Small intestine	Duodenum	20-30	≈ 6.1(fasted) ≈5.4(fed)	3.4
	Jejunum	150-200	≈5.4	
	Ileum	200-350	≈7-8	
Large intestine	Cecum	6-7	≈5.5-7	6
	Ascending colon	20	≈7.8	
	Transverse colon	45		
	Descending colon	30		
	Sigmoid colon	40		
	Rectum	12		
	Anal canal	3		

Transit of material in the colon

The gastric emptying of the dosage forms is highly variable & depends primarily on whether the subject is in fasted or fed & on the properties of the dosage form such as the size & density. The

arrival of an oral dosage form at the colon is determined by the small intestinal transit time & the rate of gastric emptying. The small oral dosage forms transit times, in GIT are given in Table 2.

The materials movement through the colon is slow & tends to be highly variable & influenced by the number of factors such as dietary fiber content, diet, disease, drugs & mobility, stress. The dosage forms such as capsules and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur, in healthy young & adult males. The diseases affecting the colonic transit have important implications for delivery of drug: diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant

Table 2: The transit time of dosage form in GIT

Organ	Transit time (hr)
Stomach	<1 (Fasting) >3 (Fed)
Small intestine	3-4
Large intestine	20-30

Colonic micro flora and their enzymes

To trigger drug release in various parts of the GIT, the intestinal enzymes are used. Usually these enzymes are derived from the gut micro flora residing in high numbers in the colon. These enzymes are used to degrade the matrices /coatings as well as to break the bonds between an inert carrier & an active agent [i.e., release of the drug from the prodrug]. Bacterial species Over 400 distinct have been found, 20-30% of which are of the genus Bacteroides. The upper region of the gastrointestinal tract has very small number of bacteria & predominantly consists of the Gram-positive facultative bacteria. In the human colon the concentration of bacteria is 1011- 1012 CFU/ml. Bacteroides, Bifidobacterium, Eubacterium, Peptostreptococcus, peptococcus, Ruminococcus and clostridiums are the most important anaerobic bacteria. The summary of the most important metabolic reaction carried out by intestinal bacteria are given in Table .3 [11-17]

Table 3: Drug metabolizing enzymes in the colon that catalyze reactions

Enzymes	Microorganism	Metabolic reaction catalyzed
Nitroreductase	E. coli, Bacteroides	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. coli	Reductive cleavage of azo compounds
Esterase and amidases	E. coli, P. vulgaris, B. subtilis, B. mycoides	Cleavage of esters or amidases of carboxylic acids
Glycosidase	Clostridia, Eubacterium	Cleavage of β-glycosidase of alcohols and phenols
Glucuronidase	E. coli, A. aerogenes	Cleavage of β-glucuronidases of alcohols and phenols

ADVANTAGES OF COLON TARGETED DRUG DELIVERY SYSTEM

- Has the advantage of requiring smaller drug quantities, for local treatment
- It possibly leading to the reduced incidence of the side effects & drug interactions.
- For the delivery of agents to cure the local diseases of the colon, colon is an ideal site
- It Bypass initial first pass metabolism.
- Improve the patient compliance.
- It has the longer retention time & appears highly responsive to the agents that enhance the absorption of the poorly absorbed drugs.
- Colon is an attractive site where the poorly absorbed drug molecules may have an improved bioavailability.
- It reduces dosage frequency, hence, lower cost of expensive drugs.
- It reduces the gastric irritation caused by many drugs [For e.g. NSAIDS].

- Extended daytime or night-time activity.
- It has the low hostile environment, less peptidase activity so the growth hormones, peptides, insulin, oral vaccines, can be given through this route
- It is targeted drug delivery system. [18-20]

ADVANTAGES OF CTDDS OVER CONVENTIONAL DRUG DELIVERY

The chronic colitis namely the ulcerative colitis & crohn's disease are currently treated with glucocorticoids & other anti-inflammatory agents. The administration of the glucocorticoids namely the methyl Prednisolone & dexamethasone by the oral & intravenous routes produce systemic side effects including the immunosuppression, denosuppression, bone resorption & cushinoid symptoms. Hence the selective delivery of the drugs to the colon could not only lower the required dose but also reduces the systemic side effects caused by the higher doses [4]

LIMITATIONS & CHALLENGES IN COLON TARGETED DRUG DELIVERY

1] The stability of the drug is also a concern, while designing the drug delivery system, because it may bind the non specific way to the intestinal secretions, dietary residues, mucous or the faecal matters.

2] In the development of the colon specific drug delivery systems, one challenge is to establish an appropriate dissolution testing method to evaluate the designed system in vitro.

3] Before the drug arrives in the colon, it should be in the solution form for the successful delivery through the site or alternatively, it should dissolve in the luminal fluids of the colon, but this can be the limiting factor for the 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 gastrointestinal tract

4] For drug delivery, as the site the colon offers a near neutral pH, a long transit time, reduced digestive enzymatic activity & increased responsiveness to the absorption enhancers, the targeting of the drugs to the colon is very complicated. The colon is particularly difficult to access, as the colon is situated in the distal part of the alimentary canal. In addition to that, the wide range of the pH values & various enzymes present throughout the gastrointestinal tract through which the dosage form has to travel before reaching to the target site which complicate the delivery efficiency & reliability.

5] Relative tightness of the tight junctions in the colon & lower surface area, can also restrict the drug transport across the mucosa & into the systemic circulation [21, 22]

FACTORS AFFECTING THE COLON TARGETED DRUG DELIVERY

1. Physiological factors

2. Pharmaceutical factors

1. Physiological factors

a. The Gastric emptying

Upon oral administration the drug delivery to the colon depends mainly on the bowel transit time & gastric emptying. The transit time of dosage form depends on the size of the particles, upon reaching the colon. The smaller particles have more transit time as compared to the larger particles. The constipation patients have longer transit times, whereas the diarrhoea patients have shorter transit time whereas

b. The pH of colon

The pH of the gastrointestinal tract varies between the different individuals. The diseased state, food intakes, etc, influences the pH of the gastrointestinal tract. This change in the pH in different parts of gastrointestinal tract is the basis for the development of the

colon targeted drug delivery systems. To target the drug to the site, coating with different polymers is done

c. The colonic micro flora & enzymes

The gastrointestinal tract contains a variety of the microorganisms that produces many enzymes need for the metabolism.

The growth of this micro flora is controlled by the gastrointestinal tract contents & the peristaltic movements. The enzymes

released by the different microorganisms Clostridia, E. coli, Eubacteria, Streptococci Lactobacilli, are responsible for the various metabolic reactions that take place in the gastrointestinal tract.

2. Pharmaceutical factors

a. The Drug candidates

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

b. The Drug carriers

The selection of carrier for the colon drug delivery system depends on the nature of the drug, the disease for which the drug is used. The different physicochemical factors of drug that effect the carrier selection includes the stability, functional groups of drug molecule, chemical nature, partition coefficient, etc. [8]

THE POLYMERS USED IN COLON TARGETING

The polymer contain the large number of structural unit joined by the same type linkage, form into the chain like structure. Nowadays these are used in formulating the various pharmaceutical products. The naturally found polymers, which include the proteins, gummy exudates, polysaccharides, enzymes, muscle fibre. Natural polymers are widely used in pharmacy in olden days but the variety of synthetic polymer are used nowadays for the pharmaceutical & cosmetic development, using these polymer many therapeutic system of body namely the controlled drug delivery systems, are achieved

Natural polymers: Chitosan, Pectin, Guar gum, Inulin, Dextran, Amylase, Locust bean gum. Chondrotin sulphate, Cyclodextrin,

Synthetic polymers: Cellulose acetate phthalate, Shellac, Eudragit, Poly vinyl acetate phthalate Ethyl Cellulose, HPMC [Hydroxy propyl methyl cellulose]. [23, 24]

APPROACHES FOR COLON TARGETED DRUG DELIVERY

a) The pH sensitive polymer coated drug delivery system

The pH varies in the different parts of the GI tract. In stomach the pH ranges between 1 & 2 during the fasting. In the proximal part of small intestine the pH is 6.5 & in distal part of small intestine the pH is 7.5. In caecum the pH is 6.4, in ascending colon it is 5.7, in transverse colon it is 6.6 & in descending colon it is 7.0. Depending on the solubility of different polymers at different pH ranges, the pH dependent drug delivery system is based. At lower pH values the polymers are insoluble & as the pH increases it gets solubilized. The polymer can protect a formulation in stomach and to some extent in small intestine, as the polymers are insoluble at lower pH values. By this way by altering the polymers used the release of the drug from the formulation can be controlled.

b) The Delayed or time controlled release drug delivery system

The time controlled drug delivery system includes the sustained or the delayed release systems. The delayed release or colon targeted drug delivery is attained by prolonging the lag time, in this system. The transit time varies in different parts of the GI Tract. For the delayed release of drug, this transit time is responsible. The transit time varies from one person to other and also the amount of food intake is the main drawback of this delivery system. It also varies with the peristalsis or contraction in the gastrointestinal tract.

c) Microbial triggered drug delivery system

The different microfloras of the colon are Bifidobacteria, Bacteroides, Clostridia, Eubacteria, Enterococci, Ruminococcus & Enterobacteria etc. This microflora of gut depends on the fermentation of the undigested materials in the small intestine for their energy requirements. By producing a large number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, and deaminase and urea dehydroxylase, the microflora performs fermentation. These biodegradable enzymes have capability of degrading the polymers used for the targeting the delivery of drug to colon. For preventing the release of drug in the stomach & small intestine, the different polymers are used. The biodegradable polymers get degraded by the enzymes produced by the microbial flora and the drug gets released in the targeted region, when the coated formulations reach the intestine. The Prodrug is the main approach of the microbial triggered drug delivery system in which the drug release from a formulation is triggered by the microflora present in the gut. The Prodrug is the inactive form of an active parent drug that undergoes the enzymatic transformation to release the active drug. By linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc, the prodrugs are prepared. In the presence of the enzymes released by the microflora, these prodrug molecules get hydrolysed

Drug	Carrier	Linkage hydrolysed
Dexamethasone	Saccharide carriers	Glycosidic linkage
Salicylic acid	Amino acid conjugates, glycine	Amide linkage
5-ASA	Azo conjugates	Azo linkage

Prednisolone, hydrocortisone, fludrocortisone	Glucose, galactose	Glycosidic linkage

The formulation depends on the functional groups available on drug moiety for chemical linkage, is the main drawback of this approach. Upon linkage the prodrugs formed results in the formation of the new chemical entities that need the lot of evaluation before using them as the carriers. The metabolism of azo compounds by intestinal bacteria is the most widely used prodrug approach is. The polysaccharide based delivery system is the other form of the microbial triggered drug delivery system. The naturally occurring polysaccharides like gum, chitosan, guar gum, alginates, xanthan etc. are used in targeting the drug delivery. By the colonic microflora these are broken down to simple saccharides.

d) Pulsatile colon targeted drug delivery

i) The Pulsincap system

In this system, in the capsule form the formulation is developed. In the capsule the plug placed controls the release of the drug. To seal the drug contents the swellable hydrogels are used. When the capsule comes in contact with the dissolution fluid it gets swelled & after the lag time the plug gets pushed off from the capsule & the drug will be released. The polymers such as the different grades of HPMC [hydroxy propyl methyl cellulose], polyvinyl acetate & poly methyl methacrylate are used as the hydrogel plugs. By the length & point of intersection of the plug in the capsule body the lag time is controlled.

ii) The Port system

The capsule body is enclosed in the semipermeable membrane in this system. The capsule body consists of drug formulation & an insoluble plug consisting of the osmotically active agent. The semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug when the capsule comes in the contact with the dissolution fluid. With time gap between the successive intervals the drug is released at regular intervals.

e) The Pressure controlled drug delivery system

Due to the contractility of the stomach and peristaltic movement of the intestine the digestion mainly occurs. The contractility movement of the stomach leads to the digestion or the breakdown of the larger particles to the smaller ones which are then transferred to the intestine. For the passage of the bolus from one part of GIT to the next part the peristaltic

movement of the intestine is responsible. The peristaltic movement of the ascending colon transfers the bolus to the transverse colon is called as the mass peristalsis. In limited numbers i.e. three to four times a day these peristaltic movements occur. This peristaltic movement of the intestine results in an increase in the luminal pressure. In the development of pressure controlled drug delivery system this increase in luminal pressure is the key point. A pressure controlled drug delivery system consists of the capsule in which the drug is present. These gelatin capsules are coated on their inner side with water insoluble polymer like ethyl cellulose. Along with suppository base the drug is introduced into the capsule. The disintegration capacity of the capsule determines the thickness of the ethyl cellulose coating. The suppository base dissolves at body temperature after administration. From the intestinal contents the water is absorbed which results in increased viscosity which leads to the increase in the pressure in the capsule. The drug is expelled into the colon due to the pressure in the capsule. The intestinal pressure developed varies with the state of body, food administration, circadian rhythms, etc.

f) CODES technology

To minimize the problems associated with the pH and time dependent drug delivery systems this method is developed. The pH sensitive polymers are used in this system along with the polysaccharides that are degraded only by the specific bacteria present in the intestine. This system consists of the core tablet coated with the polymer coatings having 3 layers. The outer coating is composed of the Eudragit L polymer. Once the tablet passes through the pyloric & duodenum this coating gets dissolved & exposes the next coating. The next coating is composed of Eudragit E polymer. The release of lactulose is allowed by this layer which is present in the inner core. This released lactulose gets metabolized into the short chain fatty acids that lower the surrounding pH where the Eudragit E polymer layer dissolves. The dissolving of the Eudragit E polymer layer results in the exposure of the drug. Other polysaccharides that are used along with the drug in a core tablet are the maltose, mannitol, etc. For the degradation of polysaccharides the bacteria present in the colon are responsible which are released from the core tablet. The polysaccharides degradation results in organic acids formation that lowers the pH of the contents that are surrounding the tablet

g) The Osmotically controlled colon targeted drug delivery system

This system consists of the osmotic units. These units are used either singly or as many as five-six push pull units that are encapsulated in the hard gelatin capsule. These push pull units are bilayered with the outer enteric impermeable membrane & inner semi permeable membrane. The central part or internal part of the push pull consists of the drug layer & the push payer. Next to the drug layer the semipermeable membrane is present which consists of an orifice

through which the drug contents are expelled during the course of time. The capsule body which encloses the push pull units gets dissolved immediately after administration. The enteric impermeable membrane prevents the water absorption into the unit during the passage of the push pull units through the gastrointestinal tract. Once it reaches the small intestine the coating gets dissolved due to the higher pH [>7]. Through the semi permeable membrane the water enters the unit causing the push layer to swell. Swelling of the push compartment forces the drug into the surrounding environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at the constant rate for up to 24hours.

h) The Multi particulate system based drug delivery

Reduced risk of systemic toxicity, increased bioavailability, reduced risk of local irritation, are the various advantages of the multiparticulate systems. Microparticles, pellets, nanoparticles & granules are the different multiparticulate approaches. As the multiparticulate systems enables the drug to reach the colon quickly & retained in colon for the long period of time the Multiparticulate systems are preferred over the single unit dosage forms. These systems pass through the gastrointestinal tract easily due to their smaller size. The multiparticulate systems are more uniformly dispersed in the gastrointestinal tract resulting in the more uniform drug absorption.

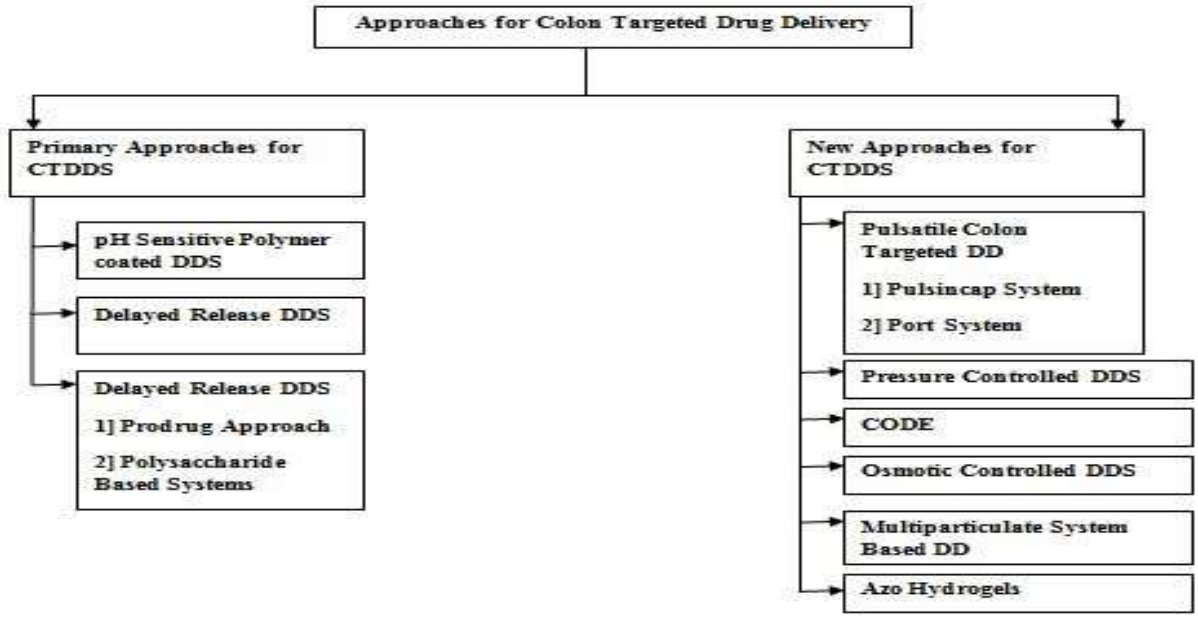
Nanoparticles

Nanoparticles are capable of protecting the protein & peptide drugs from the chemical & enzymatic degradation in gastrointestinal tract resulting in an increase in their stability & absorption of through the intestinal epithelium & the preparation of the nanoparticles is simple. The polymeric nanoparticles are prepared by the different techniques like inverse microemulsion, polymerization and nanoprecipitation. The methods involve the use of the organic solvents, heat & agitation. The heat, agitation is harmful to proteins and peptide drugs which is the drawback of these methods. The most widely used method for proteins and peptide drugs is the Ionic gelation technique.

i) Azo hydrogels

pH sensitive monomers & the azo cross linking agents in the hydrogel produce the colon specificity. During their passage through the gastrointestinal tract, as the pH increases these hydrogels swell. This swelling of hydrogels cleaves the cross links in the hydrogel network thus causing the release of the drug entrapped in the hydrogels. By cross linking polymerization of N- substituted [meth] acrylamides, N- tert- butyl acrylamide & the acrylic acid with the 4, 4-di [methacryloylamino] azobenzene as the cross linking agents these hydrogels are prepared. Also by polymer- polymer reaction, crosslinking polymeric precursors, the hydrogels are prepared

using same polymeric precursor with the corresponding copolymer containing side chains terminating in the NH2 groups. With the degree of swelling the degradation rate of hydrogel is associated & is inversely proportional to the cross linking density. [21, 25-34]



IN-VITRO EVALUATION

For evaluation of colon drug delivery system no standardized evaluation technique is available. As an ideal in vitro model should possess the in-vivo conditions of the gastrointestinal tract such as the volume, pH, stirring, enzymes, the bacteria, components of food & enzyme activity. By diet & physical stress these conditions are influenced. The invitro evaluation of the Colon Targeted DDS includes the in-vitro dissolution study & in-vitro enzymatic test

1. In-vitro dissolution test

Using the conventional basket method the dissolution testing is done. To characterize the behaviour of formulations at different pH levels the dissolution testing is done in different buffers. To simulate small intestine pH 6.8, To simulate large intestine pH 7.4, To simulate gastric fluid pH 1.2, are the different media that are used for the dissolution testing of colon targeted drug delivery. The colon targeted DDS are tested for 2hours in 0.1N HCl, 3hours in pH 6.8 phosphate buffer & finally at pH 7.4 phosphate buffer. The buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems.

2. In-vitro enzymatic test:

For the in-vitro enzymatic test there are 2 tests.

 In fermenter containing suitable medium for bacteria the carrier drug system is incubated. At different time intervals the amount of drug released is determined.

 The drug release study is performed in the buffer medium containing the enzymes dextranase, pectinase, or guinea pig or rat or rabbit cecal contents. The amount of the drug released in the particular time is directly proportional to the rate of the degradation of polymer carrier.

IN- VIVO EVALUATION

The in-vivo evaluation of the Colon Drug Delivery System is done in guinea pigs, pigs, dogs & rats as they resemble the microflora, anatomical & physiological conditions of the human Gastrointestinal tract. The distribution of the various enzymes in the gastrointestinal tract of the rabbit & rat is comparable to that in the human.

OPPORTUNITIES IN COLON TARGETED DRUG DELIVERY

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

• In the targeted delivery area the colonic region of the gastrointestinal tract is the one that has been embraced by the scientists & is being investigated extensively over the past 2 decades.

• At the colon site the bioavailability of the protein drugs delivered needs to be addressed. More research is focused on the specificity of the drug uptake at the colon site is necessary. Such studies would be significant in advancing the cause of the colon targeted DD in future.

• For the treatment of diseases sensitive to circadian rhythms such as angina, asthma & arthritis this is also the potential site. Also, there is an urgent need for the delivery of drugs to the colon that are reported to be absorbable in the colon, such as the steroids, which would enable reduction of the required effective dose & increase efficiency.

• The treatment of disorders of the large intestine, such as colitis, Crohn's disease, IBS [irritable bowel syndrome] other colon diseases where it is necessary to attain the high concentration of the active agent may be efficiently achieved by the colon-specific delivery. One of the greatest challenges for the oral peptide delivery is the development of the dosage form that improves the oral absorption of the peptide & protein drugs whose bioavailability is very low because of the instability in the gastrointestinal tract. [32]

CONCLUSION

The main advantage of colon targeted drug delivery system is that the colon offers long transit time, near neutral pH, increased responsiveness to absorption enhancers, a reduced enzymatic activity. The benefits of local & systemic effects are offered by the colon targeted drug delivery system. Different approaches are being researched in attempts to understand & achieve the desired goal of targeting the delivery to the specific organ, i.e. the colon. For the delivery of drugs the colon targeted drug delivery has also gained increased importance for the treatment of local diseases associated with the colon such as inflammatory bowel diseases [Crohn's disease, ulcerative colitis,], gastrointestinal infection & some carcinomas to maximize the effectiveness of these drugs. The colon is also the potential site for the systemic delivery of the therapeutic peptide & proteins. The natural polymers such as guar gum, chitosan, pectin etc are more favorable carriers for these systems. For new delivery systems, there is the constant need that can provide increased therapeutic benefits to the patients. By delivering the drug at the right time, right place & in right amounts, the colon targeted drug delivery is one such system that holds good promises of benefits to the patients

REFERENCES

1. 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.
2. 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.
3. 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 Dev Ind Pharm 2003; 29:375-386.
4. Chourasia MK, Jain S K: Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Sci 2003; 6:33-66.
5. Basit A, Bloor J: Prespectives on colonic drug delivery, Business briefing. Pharmtech 2003; 185-190.
6. Watts P, Illum L: Colonic drug delivery, Drug Dev Ind Pharm 1997; 23:893- 913.
7. Wood E, Wilson CG, Hardy JG: The spreading of foam and solution enemas; Int J Pharm 1985; 25: 191-197.
8. Chien YW: Oral drug delivery and delivery systems. In: Chien YW, editor, Novel drug delivery systems. New York: Marcel Dekker Inc; 1992; 139-196.
9. Christensen, J: The response of the colon to eating. Am. J. Clin. 1985; Nutr.42: 1025-1032.

10. Dawson, D.C: Lon channels and colonic salt transport. Annu. Rev. Physiol., (1991) 53, 321-329.
11. Vandamme Th F and Chaumeil J C: The Use of Polysaccharides to Target drugs to the Colon, CarboPoly, 48, 2002:219-31.
12. Sarasija S and Hota A: Colon Specific Drug Delivery Systems, Ind J Pharm Sci., 2002; 62(1):1-8.
13. Macfarlane GT and Cummings JH: The Colonic Flora, Fermentation and Large Bowel Digestive Function.In Phillips SF, Pemberton JH, Shorter RG. The Large Intenstine: Physiology, Pathophysiology and Disease. New York: Raven press, 1991: 51.
14. Thomas P and Rhodes J: Absorption of Delayed-release Prednisolone in Ulcerative Colitis and Crohn's Disease, Int J Pharm, 37, 1985: 757-61.
15. Tomlin J and Read NW: The Relation between Bacterial Degradation of Viscous Polysaccharides and Stool Output in Human Beings, Brit J Nutr, 60, 1988, 476.
16. Philip Anil, Betty Philip: Colon Drug Delivery System: A Review on Primary and Novel Approch, Oman Medical Journal, 2010; 25(2).
17. Krishnaiah YSR, Styanarayana S: Colon- Specific Drug Delivery Systems, In Jain NK, Advances in Controlled and Novel Drug Delivery, CBS Publishers and Distributors, New Delhi. 2000: 89-119.
18. Jain NK: "Advances in Controlled and novel Drug Delivery" 1st edition, New Delhi Cbs Publisher and distributors; 2008: 86-90.
19. Halsas M, Penttinen T, Veski P, Jurjenson H, Marvola M: "Time controlled release Pseudoephedrine tablets: bioavailability and in vitro/in vivo correlations" Pharmazie 2001;56: 718-723.
20. Kinget R, KalalaW, Vervoort L, van den Mooter G: "Colonic drug targeting J Drug Targeting" 1998; 6(2): 129- 149.
21. Vishal V. Rajguru, Preeti D. Gaikwad, Vidyadhar H. Bankar, Sunil P. Pawar: An overview on colonic drug delivery system, Int. Journal of Pharmaceutical Sciences Review & Research. 2011; 6(2): 197-204.
22. Bisht S, Bajaj H: Colon targeting approaches; Past Present & Future Indian drugs 2012:49
23. Sinha .V.R, Rachna K: A Review on Polysaccharides in colon specific drug delivery. International Journal of Pharmaceutics; 2001; 224: 19-38.
24. Kumar Ravi, Patil M.P, and Sachin: A review on polysaccharides based colon specific drug delivery. International journal of pharm tech research 2009; (1):334-346.
25. Vinay K Gupta, G. Gnanarajan, Preeti Kothiyal: A Review Article on Colonic Targeted Drug Delivery System. 2012; 1(7): 14-24.
26. Surender Verma, Vipin Kumar, D. N. Mishra: Colon targeted drug delivery: Current and Novel approaches, Int Journal of Pharmaceutical Sciences and Research. 2012; 3(5): 1274-1284.

27. Anil K. Philip: Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches.OMJ.2012; 70- 78.
28. Ankita Patel, Dhruvita Patel, Trupti Solanki, Dr. P. D. Bharadia, Mr. V. M. Pandya and Mr. D.A. Modi: Novel Approaches for Colon Targeted Drug Delivery System, IJPI's Journal of Pharmaceutics and Cosmetology. 2011; 1(5): 86-97.
29. Mundhe Vinayak S, Dodiya Shamsundar S: Novel Approach for Colon Targeted Drug Delivery, Indo American Journal of Pharmaceutical Research.2011; 3:158-173.
30. Tarak Jayraj Mehta, A. D. Patel, Mukesh R. Patel, N. M. Patel: Need of colon specific drug delivery: Review on primary and novel approaches., Int .Journal of Pharma.Research & Development. March 2011; 3(1): 134-153.
31. Baviskar P A, Morankar PG, Bedse A P: Colon targeted drug delivery system. 2012; 1(2): 230-235.
32. S. Pradeep Kumar, D. Prathibha, R. Parthibarajan, C. Rubina Reichal: Novel colon specific drug delivery system: A Review, Int. Journal of Pharmacy & Pharmaceutical Sciences. 2012; 4(1): 22- 29.
33. Kothawade P. D, et.al: Conventional and novel approaches for colon specific drug delivery. E- Journal of Science and Technology, 2011; 2: 33-56.
34. Koteshwara K.B: Primary and novel approaches for colon targeted drug delivery – A review. Int. Journal of Research in Ayurvedic & Pharmacy.2011; 2 (1): 60-65.