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A COMPREHENSIVE REVIEW ON COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT The colon is believed to be a suitable site where both local and systemic delivery of drugs could be achieved. Colonic drug delivery has gained increased importance not only for localized treatment of several colonic diseases, mainly inflammatory bowel disease (crohn's disease, ulcerative colitis) and colon cancer, but also as a potential site for the systemic delivery of therapeutic proteins and peptides. The site specific delivery of drugs (Drug targeting) to lower parts of GIT improve the efficacy of drugs by concentrating the drug molecules at the site of action and minimize systemic side effects and drug instability issues. Consequently, various strategies have been developed for CTDDS (Colon targeted Drug Delivery System), which includes prodrugs, pH and time dependent systems, Bacterial enzyme dependent colonic DDS, pressure controlled colonic delivery and osmotic controlled drug delivery.

KEYWORDS : CTDDS, inflammatory bowel disease, drug targeting.

INTRODUCTION

Colonic delivery refers to targeted delivery of drugs into the lower gastrointestinal tract, which occurs primarily in the large intestine (i.e. colon).

CTDDS is designed for oral than parenteral route because-
1. Patient acceptance for the oral administration of the drug is quite high.

2. It is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is minimal.[1]

Colonic delivery is beneficial for treating the colonic disorder such as inflammatory bowel diseases i.e. ulcerative colitis, Cohn's diseases, Colon cancer and Amoebiasis.

Anatomy and Physiology of Colon:

The GI tract is divided into upper GI tract and lower GI tract. Upper GI tract includes mouth, pharynx, esophagus and stomach whereas lower GI tract includes small intestine and large intestine.

Colon or large intestine is the last part of digestive system. The entire colon is about 1.5 meters long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. [2]

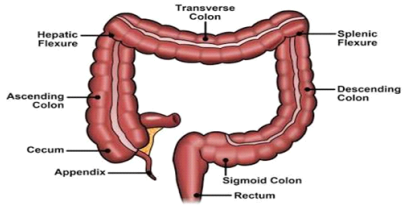

Figure 1: Anatomy of Colon

Ascending Colon[12]

The ascending colon is approximately 15 cm long and joins the cecum at the ileocecal junction. The ascending colon is covered with peritoneum anteriorly and on both sides, however, its posterior surface is devoid of peritoneum. It ascends on the right side of the abdomen to the level of the liver where it bends acutely to the left. At this point it forms the right colic or hepatic flexure and then continues as the transverse colon.

Transverse Colon[13]

This is a loop of colon approximately 45cm long that continues from the left hepatic flexure across to the left side of the abdomen to the left colic flexure. It passes in front of the stomach and duodenum and then curves beneath the lower part of the spleen on the left side as the left colic or splenic flexure and then passes acutely downward as the descending colon.

Descending Colon

This section of colon passes downward on the left side of the abdomen to the level of the iliac crest. It is approximately 25cm in length. The descending colon is narrower and more dorsally situated than the ascending colon.

Sigmoid Colon

The sigmoid colon begins near the iliac crest and is approximately 36cm long. It ends at the centre of the mid-sacrum, where it becomes the rectum at about the level of the third sacral vertebra. It is mobile and is completely covered by peritoneum and attached to the pelvic walls in an inverted V shape.

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, absorb water and ions from food and convert it into feacal content, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen.

Advantages[6][9][10]

Colon is an ideal site for the delivery of agents to cure the local diseases of the colon. Drug targeting to lower parts of GIT is beneficial for

I) Treatment of several local colonic diseases, mainly inflammatory bowel disease (crohn's disease and ulcerative colitis) and colon cancer.

ii) Reduced the incidence of adverse side effects.

iii) Improve the efficacy of drugs by concentrating the drug

molecules at the site of action and bypass initial first pass metabolism.

iv) Minimize drug instability issues associated with premature release of drug in the upper parts of GIT (i.e. stomach and small intestine).

v) Colon is believed to be a suitable site for the delivery of protein and peptides due to less peptidase activity and longer residence time, natural absorptive characteristics make the colon as promising site for the delivery of protein and peptide drug for systemic absorption.

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.

vi) Local treatment has the advantage of requiring smaller drug quantities and possibly leading to a reduced incidence of side effects and drug interactions.
vii) The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
viii) Reduce gastric irritation caused by many drugs (e.g. NSAIDS).

Limitations[11]
I) Overall, there is less fluid in the colon than small intestine and hence, dissolution could be problematic for poorly water-soluble drugs.

ii) Multiple manufacturing steps.
iii) The resident micro flora can affect colonic performance via metabolic degradation of the drug.
iv) Bioavailability of drug may be low due to incomplete release of drug which is trigger through interaction of drug with dietary residues, intestinal secretions, mucus or faecal matter.

Criteria for Selection of Drug for CDDS:[3]
- Drugs which show poor absorption from the stomach or intestine including peptides.
- Drugs used for local effects in colon against GIT diseases
- Drugs poorly absorbed from upper GIT
- Drugs for colon cancer
- Drugs that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs for colon targeting

General Considerations for Design of Colonic Formulations:
In general, Colonic formulations (Delayed-release dosage forms) are designed to provide-
i) A 'burst release'
ii) A sustained/prolonged release

Factors Affecting Colon Targeted Drug Delivery:[3][4][7]
There are various factors, which are considered for designing of numerous colonic formulations, are listed below.

1. Physiological factors

2. Pharmaceutical factors

3. Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and

4. The desired release profile of the active ingredient.

1. Physiological factors
a. Anatomy and Physiology of Colon[7]
The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus.

b. Gastric emptying: Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diseases affecting colonic transit have important implications for drug delivery, diarrhea increases colonic transit and constipation decreases it.

c. pH of colon: The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GI tract. Each individual has a range of pH in GIT which is influenced by various factors such as food intakes, diseased state (inflammatory bowel disease), type of food, fed and fasted state etc. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH = 6.6 + 0.5) to the terminal ileum (pH = 7.5 + 0.4), a decrease in the cecum (pH = 6.4 + 0.4), and then a slow rise from the right to the left colon with a final value of 7.0 + 0.7. pH variation in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is used to develop pH dependent colon drug delivery system.

d. Colonic micro flora and enzymes: In GIT a variety of microorganisms (E. coli, Clostridia, Lactobacilli, Eubacteria, and Streptococci) were found that produces many enzymes, these enzymes are responsible for various metabolic reactions that take place in the GIT.

The growth of colonic micro flora is controlled by the contents of GIT and peristaltic movements. The metabolic activity of micro flora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues.

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract. Intestinal enzymes are used to trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut micro flora residing in high numbers in the colon. These enzymes are used to degrade coatings or matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug).

e. Drug absorption in the colon
Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes.

The colon may not be the best site for drug absorption since the colonic mucosa lacks well defined villi as found in the small intestine. The slower rate if transit in colon lets the drug stay in contact mucosa for a longer period than in small intestine which compensates much lower surface area.

The colon contents become more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced dissolution rate, slow diffusion of drug through the mucosa.

Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. Recent studies have shown that some drugs (e.g. Theophyline and Metoprolol) continue to be absorbed in the colon.

2. Pharmaceutical factors

a. Drug candidates: colon has longer retention time that enhance the absorption of poorly absorbed agents like peptides, etc. Drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.[11]

b. Drug carriers: The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. Selection of drug carriers depends on various physicochemical factors of drug that includes chemical nature, stability, partition coefficient, functional groups of drug molecule etc. [11]

c. Polymers Used in Colon Drug Delivery: [14][15][19]

A polymer is a large molecule, or macromolecule, composed of many repeated subunits. These are nowadays used in formulating various pharmaceutical products. There are various synthetic polymers which are used for colon targeted drug delivery. These can also be called as pH dependent polymers. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fiber, polysaccharides.

Approaches of Colonic Drug Delivery System: [5][14]

[A] Primary approaches for colon drug delivery system: In general, three primary approaches have been proposed for targeted colon delivery, namely,

a) pH Dependent colonic DDS
b) time-dependent colonic DDS (Delayed release drug delivery to colon)
c) Microbially triggered drug delivery to colon

i) Prodrug based system
ii) Azo Polymeric approach
iii) Polysaccharide based approach
a) pH sensitive polymer coated drug delivery to colon [24][25]

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 ceacum. 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, in the descending colon 7.0. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems.

b) Delayed (Time controlled release system) release drug delivery to colon

Transit time dependent colonic DDS such as sustained or delayed release dosage forms are one of important drug release systems. However due to potentially large variation of gastric emptying time of dosage forms in humans, in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonical availability.[26] The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours (range 5 to 6 hours).

Disadvantages of this system are-

(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 time of the drug.[27]

(iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis. [28]

Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. The time-release function should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side and drug release will begin at a predetermined time point after gastric emptying. On the other hand in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time [27].

c) Microbial triggered drug delivery system[28]

The various microflora of the colon are Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus, etc. This microflora of gut depends on fermentation of undigested materials in the small intestine for their energy requirements. The microflora performs fermentation by producing a large number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, and deaminase and urea dehydroxylase. These biodegradable enzymes are capable of degrading the polymers used for targeting the drug delivery to colon. Different polymers are used for preventing the release of drug in the stomach and small intestine. When the coated formulations reach the intestine the biodegradable polymers gets degraded by the enzymes produced by the microbial flora and the drug gets released in the targeted region.

(I) Prodrug approach for drug delivery to colon

A Prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation in vivo to release the active drug at the target site.

This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon. This biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreducatase-galactosidase, β- xylosidase, nitroreductase, glycosidase deaminase, etc.

The produrgs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc. These prodrug molecules get hydrolysed in the presence of the enzymes released by the microflora.

The main drawback of this approach is that the formulation depends on the functional groups available on drug moiety for chemical linkage. The prodrugs formed upon linkage results in the formation of new chemical entities that need a lot of evaluation before using them as carriers. The most widely used prodrug approach is the metabolism of azo compounds by intestinal bacteria.

Azo Prodrug approach

The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The azo

compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic components and extracellular reduction. The use of these azo compounds for colon targeting has been in the form of hydrogels as a coating material for coating the drug cores, and as prodrugs.

Example-Sulphasalazine, which was used for the treatment of rheumatoid arthritis, was later known to have potential in the treatment of inflammatory bowel disease (IBD). This compound has an azo bond between 5-ASA and sulphapyridine.

Amino acid Prodrug

Hydrophilic nature of polar groups like -NH2 and -COOH, which is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins.

Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. By increasing the hydrophilicity and chain length of the carrier amino acid and decreasing the membrane permeability of conjugate (salicylic glutamic acid conjugates).

(ii) Polysaccharide based delivery systems

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting drug delivery. These are broken down by the colonic microflora to simple saccharides [14]. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable.[32]

[B] Newly developed approaches for CDDS

a) Pressure-controlled drug-delivery systems
b) Pulsatile colon targeted drug delivery
i) Pulsincap system
ii) Port system
c) Osmotically controlled colon targeted drug delivery system
1-Osmet Pump
2-OROS CT
d) CODES technology
e) Multi particulate system based drug delivery
f) Nanoparticles

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. (1995) have developed pressure controlled colon-delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation [25]. 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 ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human [17].

b) Pulsatile colon targeted drug delivery

I) Pulsincap system

In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body [18].

ii) Port system

In this system the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid 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. The drug is released at regular intervals with time gap between the successive intervals [29].

c) Osmotically controlled colon targeted drug delivery system

This system consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push layer. The semipermeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time The capsule body enclosing the push pull units gets dissolved immediately after administration [29,30].

1-Osmet Pump (ALZET)

ALZET® Osmotic Pumps are miniature, infusion pumps for the continuous dosing of unrestrained laboratory animals as small as mice and young rats.

These minipumps provide researchers with a convenient, reliable, and cost-effective method for controlled delivery of agents. These dependable drug delivery systems ensure that constant levels of compounds be maintained at therapeutic levels, thus avoiding potentially toxic or misleading side effects. A single ALZET pump provides up to 6 weeks of continuous infusion.

2-OROS CT

The OROS-CT 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. The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer.

d) CODES technology

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine.
This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E.

e) Multi particulate system based drug delivery

The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, microparticles, granules and nanoparticles. Multiparticulate systems are preferred over single unit dosage forms as the multiparticulate systems enables the drug to reach the colon

quickly and retained in colon for long period of time.
These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption.

f) Nanoparticles

The preparation of nanoparticles is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, nanoprecipitation, inverse microemulsion. The methods involve the use of organic solvents, heat and agitation. The drawback of these methods is that the heat, agitation is harmful to proteins and peptide drugs. Ionic gelation technique is the most widely used method for proteins and peptide drugs [31].

Evaluation test of Colon Drug Delivery System

***In vitro* evaluation:** No standardized evaluation technique is available for evaluation of CDDS as an ideal in-*vitro* model should possess in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and components of food. These conditions are influenced by diet and physical stress.
The in-*vitro* evaluation of colon targeted drug delivery systems includes the in-*vitro* dissolution study and in-*vitro* enzymatic test.[20]

1. *In-vitro* dissolution test

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behavior of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 to simulate large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems.[16][21]

2. *In-vitro* enzymatic test

There are 2 tests for the in-*vitro* enzymatic test.
The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.

Drug release study is performed in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier.[17][22]

***In-vivo* evaluation**

The in-vivo evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, micro flora of human GIT. The distribution of various enzymes in GIT of rat and rabbit is comparable to that in human.[18][23]

Applications of CDDS:

1) Chronotherapy.
2) Prophylaxis of colon cancer.
3) Treatment of nicotine addiction.
4) Treatment of local diseases of lower GIT.
5) Potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections.

Table 1: Marketed drug products for the treatment of various diseases of colon [8]

S.No.	MARKETED NAME	COMPANY NAME	DISEASE	DRUG
1.	Mesacol tablet	Sun Pharma, India	Ulcerative colitis	Mesalamine
2.	Mesacol enema	Sun Pharma, India	Ulcerative colitis	Mesalamine
3.	Asacol	Win-Medicare, India	Ulcerative colitis, crohn's disease	Mesalamine
4.	SAZO	Wallace, India	Ulcerative colitis, crohn's disease	Sulphasalazine
5.	5 Intazide	Intas, India	Ulcerative colitis	Balsalazide
6.	Lomotil	RPG Life, India	Mild ulcerative colitis	Diphenoxylate HCl, Atropine sulphate
7.	BUSCOPAN	German Remedies, India	Colonic motility disorder	Hyoscine butyl bromide
8.	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
9.	CYCLOMINOL	Neol, India	Irritable colon syndrome	Diclomine
10.	Eldicet	Solvay, India	Irritable colon syndrome, Spastic colon	Pinaverium bromide
11.	Equirex	Jagsonpal Pharmaceutical , India	Irritable colon syndrome	Clordiazepoxide
12.	Normaxin	Systopic labs, India	Irritable colon syndrome	Clidinium bromide
13.	Pro-banthine	RPG Life, India	Irritable colon syndrome	Propenthline bromide
14.	Entofoam	Cipla, India	Ulcerative colitis	Hydrocortisone acetate

CONCLUSION

Colon specific drug delivery systems are gaining the importance for systemic as well as local effect. Colon specific drug delivery system is popular for treatment of inflammatory bowel diseases (IBD), delivery of protein and peptide drugs, for circadian diseases and also for improving the systemic absorption of the some drugs.

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 and peptides, 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.

REFERENCES

1. Gupta Vinay K, Gnanarajan G., Kothiyal Preeti, 2012, A Review Article on Colonic Targeted Drug Delivery System, The pharma Innovation, Vol. 1 No. 7,14-23.
2. Chourasia M.K.; Jain S.K., 2003. Pharmaceutical approaches to colon targeted drug delivery systems. J.Pharm Sci. 6 (1) : 33-66.
3. Obot Solomon Sunday. Colon-targeted drug delivery systems: design, trends and approaches. Universal Journal of Pharmaceutical Research. 2017; 2(4): 53-57.
4. George Zhu. Treatment of patients with advanced cancer following chemotherapy and traditional medicine -long term follow up of 75 cases. Universal Journal of Pharmaceutical Research. 2018; 3(3): 10-18.
5. Brahamankar BM, Jaiswal SB; 1995.Biopharmaceutics and pharmacokinetics to controlled release medication of oral site specific / colon DDS, 457.
6. Jain NK "Advances in Controlled and Novel Drug Delivery" 1st edition, New Delhi Cbs Publisher and Distributors, 2008, 86-90.
7. Prathap M., Gulshan MD. Rao Rama N., International Journal of Research in Pharmaceutical and Nano Sciences. 3 (5), 2014, 429-437.
8. Gulhati CM: Monthly index of medical specialties 2010; 30(2): 22-24.
9. 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.
10. Kinget R, KalalaW, Vervoort L, van denMooter G: Colonic drug targeting. J Drug Targeting 1998;6(2): 129149.
11. Ratnaparkhi Mukesh P., Somvanshi Fattesingh U., Pawar Sham A., Chaudhari Shilpa P., Gupta Jyoti P., Budhavant Kalyani A., Colon Targeted Drug Delivery System,

International Journal of Pharma Research and Review, August 2013; 2(8):33-42.
12. Thibodeau, G. and Patton, K.T. (2002) Anatomy and Physiology, 5th edition C. V. Mosby, New York.
13. Watson, R. (2000) Anatomy and Physiology for Nurses, 11th edition Baillere Tindall, Royal College of Nursing, Edinburgh.
14. Singh A., Sharma A., Pooja, Anju., A review on "Novel approaches for colon targeted drug delivery system", Int. J. Res. Dev. Pharm. L. Sci., 2014, 3(2), pp. 877-886.
15. Sinha V. R., Rachna K., A Review on Polysaccharides in colon specific drug delivery, International Journal of Pharmaceutics, 2001, 224, 19-38.
16. Mundhe Vinayak S, Dodiya Shamsundar S. Review Article: Novel Approach for Colon Targeted Drug Delivery, Indo American Journal of Pharmaceutical Research, 3, 2011, 158-173.
17. S.Pradeep Kumar, Prathibha D, Parthibarajan R, Rubina Reichal C. Novel colon specific drug delivery system: A Review, Int. Journal of Pharmacy and Pharmaceutical Sciences, 4(1), 2012, 22-29.
18. 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 and Research, 6(2), 2011, 197-204.
19. Kumar Ravi, Patil M.P., Sachin, A Review on polysaccharides based colon specific drug delivery, International Journal of pharm tech research, 2009, vol. 1, 334-346.
20. Threveen Challa, et. Al., Colon specific drug delivery system- a review on primary and novel approaches, International journal of Pharmaceutical Sciences review and research, april2011, 7(2), 171-181.
21. R.B. Desi Reddy, K. Malleswari, G. Prasad and G. Pavani, Colon Targeted drug Delivery system: A Review , International Journal of pharmaceutical Sciences and Research, 2013, 4(1), 42-54.
22. Peter OI, Ifeoma UC. Development and evaluation of Albendazole microcapsule for colonic drug delivery system. Universal Journal of Pharmaceutical Research. 2017; 2(2): 26-29.
23. Kasture V. S., Musmade D.S., Vakte M.B., Sonawane S.B., Patil P.P., A Review on "Metabolomics: Current Technologies and future tends," International Journal of Research and Development in Pharmacy and Life Sciences, 2012, 2(1), page no.: 01-11.
24. Ankita Patel, Dhruvita Patel, TruptiSolanki, 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.
25. Mundhe Vinayak S, Dodiya Shamsundar S. Review Article: Novel Approach for Colon Targeted Drug Delivery. Indo American Journal of Pharmaceutical Research. 2011; 3:158-173.
26. 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 and Research. 2011; 6(2):197-204.
27. Sharma Anuj, Jain K Amit. Colon targeted drug delivery using different approaches. Int. Journal of Pharmaceutical Studies and Research. 2010; 1(1): 60-66.
28. Sachin D. Bhalersao, Paresh R. Mahaparale. Different approaches for colon drug delivery systems: A Review. International Journal of Research and Reviews in Pharmacy and Applied science. 2(3): 529-549.
29. Koteshwara K.B. Primary and novel approaches for colon targeted drug delivery – A review. Int. Journal of Research in Ayurvedic and Pharmacy.2011; 2 (1): 60-65.
30. Bhushan Prabhakar Kolte, et.al. Colon Targeted Drug Delivery System – A Novel Perspective. Asian journal of biomedical and pharmaceutical sciences. 2012; 2 (14): 21-28.
31. Ashwini Sopan Bansode, Avinash Bhausaheb Athare, Veena Sanjay Kasture, P. N. Kendre. Colon targeted drug delivery system: An Overview. Int. Imperial Journal of Pharmaceutics and Cosmetology. 2012; 2(2): 1-7.
32. 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 and Development. March 2011; 3(1): 134-153.