REVIEW

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A REVIEW ON COLON-SPECIFIC DRUG DELIVERY IS A PROMISING TOOL FOR COLONIC DISEASES

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ABSTRACT:- Colon-targeted drug delivery is a promising drug delivery approach to target drugs into the colonic environment without premature drug release and provides proper therapeutic efficacy with less adverse effects. Presently several drugs came to the market to treat local treatment of colonic diseases but they have high toxic effects. In recent years global marketers giving importance to macromolecules to provide site-specificity, better patient compliance, and high therapeutic effectiveness with fewer side effects. Targeted drug delivery into the colon is highly desirable for local treatment as well as chronic diseases like inflammatory bowel diseasesuch as Ulcerative colitis, Crohn's disease, Amoebiasis, colonic cancer, local treatment of colonic pathologies. To achieve the more efficient colon targeting drug delivery various approach has been explored include pH-dependent polymer, time-dependent, and bacteria-dependent drug delivery approach. Multiparticulate drug delivery systems provide site-specificity, stability, reduction of dose dumping, and enhancement of bioavailability with high drug-loading capacity. This review, Describes the colon-specific delivery systems for local treatment as well as specific diseases such as inflammatory bowel disease as ulcerative colitis, Crohn's disease, and suitable drugs for useful treatment and future aspects of targeted drug delivery formulation with particular approaches to enhancement of drug stability in the gastric environment have been covered.

KEYWORDS:-New technology,Importance of Colon targeted drug delivery,anatomy of colon,targeting of various regions,Advantages & disadvantages.

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INTRODUCTION : In the present era, New development of colon-specific drug delivery gaining too much importance to targeting the local diseases of the colon associated with Inflammatory bowel disease, Crohn's disease, Amoebiasis, etc. The colon is the terminal part of the gastrointestinal tract, to deliver the drug into a specific area of the colon is very tough to get therapeutic effectivity. Targeting the colonic region has been followed by not premature drug release before reaching the colonic environment with proper efficacy. Presently several drugs came to the market to treat local treatment of colonic diseases but they have high toxic effects. In recent years global marketers giving importance to macromolecules to provide site-specificity, better patient compliance, and high therapeutic effectiveness with fewer side effects. **[1]**

Targeting the colonic region is the biggest challenge to researchers. The main drawback of colonic delivery as, before reaching the colonic environment premature drug release may occur which leads to serious adverse effects and less therapeutic activity. Colon-targeted drug delivery refers to the selective release of a drug in response to the colonic environment without premature drug release in the upper GI tract. To overcome these problems several strategies, help to achieve target specificity to the colonic environment as pH-dependent drug delivery which consists of several polymers which can be degraded and dissolved only in the desiredpH range, Time-dependent drug delivery system as the release of the drugs in a controlled manner in presence of pH-dependent polymers and most important approaches of colon targeted drug delivery as Bacteria dependent drug delivery where microflora in the colonic environment played an important role to degrade the polymers at the colon. **[2][3]**

Some major importance of colonic drug delivery systems as

- Less amount of dose is enough to provide therapeutic efficacy.
- In the treatment of the distal gut, delayed-release drugs to the colonic environment can be improved through colonic drug delivery systems by various polymeric ratios.
- Time-dependent delivery also impacts to release rate of drugs into the colonic environment.
- Some protein-related drugs are premature release at the stomach and intestine which can be overcome through colonic drug delivery systems. **[4],[5]**

The oral route is the most preferred route for conventional drug delivery systems to the colonic environment. Oral administration is most convenient in the treating of colonic diseases such as ulcerative colitis, Crohn's disease, amoebiasis because targeting region concentration can be achieved, reducing side effects because of unnecessary systemic absorption can be overcome. Compare to the parenteral route,the oral route is the best convenient for patients because avoidance of pain and possible contamination through injection and self-administration could not possible in parenteral preparation. In another route of administration to targeting the colon as the Rectal route of administration is not suitable for targeting local diseases. The rectal route may provide the shortest route for targeting the colon but it has difficulty in administration and is very tough to reach the proximal part of the colon. The Rectal route of administration is very uncomfortable for patients and that's the biggest disadvantage of the rectal route.**[6],[7]** The topical application may provide therapeutic efficacy but the time to reach the concentration in the colonic environment is more, that's the drawback of topical formulation to targeting local treatment of colonic diseases.

***Importance of colon targeted drug delivery systems* – [8],[9]**

- Maximum drugs couldn't reach the colonic environment and have a higher toxic effect which can be overcome through colon-targeted drug delivery systems.
- Colon-targeted drug delivery provides site-specificity, safety, and efficacy.
- Protein and peptide drug delivery are more convenient through Colon targeted drug delivery systems because peptide delivery showed premature drug release.
- Colon-targeted drug delivery provided less amount of dose can show therapeutic activity.

- Ability to prevent drugs from the dosage form and provide rigidity.
- Provide direct treatment to the local and chronic diseases of the colon.

Location of Colon –

The colon is mainly situated in the lower part of the gastrointestinal tract and ileocecal junction to the anus and consists of ascending colon, transverse colon, sigmoid colon, rectum, and anus. The colon looks like a cylinder tube lined by mucosa and a pathway called a Lumen and diameter in the range of 2-3inches.**[10]** The proximal and distal colon can be separated based on the absorption at each site and consist of the mucosal lining.

Table 01 – Different parts of the colon[11],[12]

	Anterior	Posterior
Ascending colon	Small intestine Greater omentum Anterior abdominal wall	Iliacus& quadratus lumborum Right Kidney Iliohypogastric& ilioinguinal nerves
Transverse Colon	Greater omentum Anterior abdominal wall	Duodenum Head of the pancreas Jejunam&ilieum
Descending Colon	Small intestine Greater omnetum Anterior abdominal wall	Iliacus &quadratas lumborum Left kidney Iliohypogastric& ilioinguinal nerves
Sigmoid colon	Urinary bladder Uterus & upper vagina(Womans only)	Rectum Sacrum Ilieum

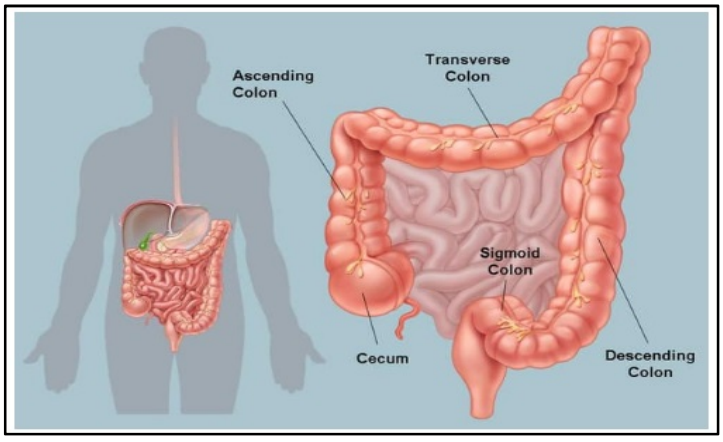

Figure 01 – Schematic diagrammatic representation of Colon

Benefits of Colon targeted drug delivery systems – **[13],[14]**

- Localization of the treatment of local diseases and chronic diseases of the colon as inflammatory bowel disease, amoebiasis, etc.
- Premature drug release at upper gastro-intestinal tract.
- Suitable for conventional drug delivery and protein and peptide delivery systems.
- prominent stability, rigidity, and convenience.
- Enhancement of bioavailability.
- Reduction of adverse effects and adverse events
- Enhancement of therapeutic effectiveness.

***The drawback of Colon targeted drug delivery systems* – [15],[16],[17]**

- Consisting of multiple processes of manufacturing.
- Microflora affects the drug activity which may impact drug stability and efficacy.
- Till now there are no such appropriate dissolution testing methods to evaluate in-vitro drug release studies.
- Due to tight junction in the colon can easily restrict drug particles to transport across the cell membrane and impact on therapeutic efficacy.

***Colon targeted disease with convenient dosage form* –[18],[19],[20]**

Table 02 – Targeting the colonic region with suitable drugs

Target sites	Disease conditions	Drug and active agents
Local action	Pancreatactomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements 5-Flourouracil.
Systemic action	• To avoid stomach irritability • To prevent orally administered drugs from undergoing first-pass metabolism • Oral delivery of peptides • Oral delivery of vaccines	Insulin Typhoid
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine, Balsalazide.

***Table 03- Criteria for selection of drugs for colon targeted drug delivery* [21],[22]**

Criteria	Pharmacological class	Peptide drugs	Non-peptide drugs
Drugs that degrade in stomach and small intestine	Peptides and proteins	Gonadoreline, Insulin, Interferons	Bromophenaramine, 5-Flourouracil, Doxorubicin
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Protirelin, sermorelin, Saloatonin	Bleomycin, Nicotine
Drugs for targeting	Antiarthritic and antiasthamatic drugs	Somatropin, Urotoilitin	Prednisolone, hydrocortisone, 5-Amino-salicylic acid
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Amylin, Antisense oligonucleotide	Oxyprenolol, Metoprolol, Nifedipine
Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Cyclosporine, Desmopressin	Ibuprofen, Isosorbides, Theophylline

Various approaches for colon targeted drug delivery systems –

The colonic targeted drug should not be premature released in the upper GI tract and not be broken down in the strong acid present in the stomach and have to disintegrate in the colonic environment and reaching to the target site.**[23]** Various approaches have been developed to achieve colonic targeting area as follows –

pH-dependent drug delivery approach –

Due to different pH environments (stomach – 1.5-3.5, small intestine – 5.5-6.8, and colon 6.4-7.5), drugs must have to stable in the stomach and small intestine and need to release in the colonic environment. That's why polymer materials are used to coat the drug which helps to stabilize the drug and release it at particular pH.

***Table 04 – pH-dependent polymers*[24]**

Polymer	pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L -30D	5.6
Polyvinyl Acetate phthalate	5.0
Hydroxy-propyl methylcellulose phthalate	4.5-4.8
Polyvinyl acetate phthalate	5.0
Cellulose acetate trimellate	4.8

***Time-dependent drug delivery approach* – [25]**

The time-dependent drug delivery approach is also known as delayed or sustained, the pulsatile release which occurred after the pre-determined lag time (time for transit from mouth to colon). The time-dependent formulation is consisting of pH-dependent polymers because it is influenced by the gastric transit time and it depends upon the size of the particle and gastric motility.

***Bacteria dependent drug delivery approach* –[26]**

GI microflora played an important role in metabolism. Microflora release enzymes that help to metabolize both endogenous and exogenous materials such as carbohydrates, proteins substance by breaking their internal bonds. Microflora secrets such enzymes like glucuronidase, azoreductase, deaminase, and urea dehydroxylase. Bacteria-dependent drug delivery approach consists of a prodrug, coating with biodegradable azo compound, hydrogels,Polysaccharides as carriers.

***Recent and future aspect of colon targeted drug delivery systems-* [27]**

The colon-targeted drug delivery system is very much suitable for targeting local diseases as well as chronic or long-term diseases like inflammatory bowel disease as Ulcerative colitis and Crohn's disease, amoebiasis, etc. Though traditional drug delivery systems targeting the colon region may overcome through colon targeted drug delivery, during application of traditional drug delivery systems are facing several problems as dose dumping, immediate-release after administration, fluctuation of blood plasma level, and inconvenience of patients can be seen. That problem can be overcome through multiparticulate drug delivery systems.

Day by day pharmaceutical invention and research constantly focus on such a delivery system that can provide proper therapeutic efficacy with fewer side effects. Recent trends indicate the multiparticulate drug delivery systems are suitable for achieving controlled or delayed-release oral formulation with low risk of flexibility, dose dumping, and fluctuation of blood plasma level, and shorter residence time. The most important advantage of a multiparticulate drug

delivery system is that enhance of bioavailability of poorly soluble drugs as reduction of particle size leads to an increase of surface area which leads to enhancement of absorption rate.**[28]**

Table05: Difference between Conventional DDS and Targeted DDS**[29],[30]**

Conventional drug delivery system	Targeted polymeric drug delivery system
Affect healthy tissues or organs	Don't
Non-specific	Specific
Low bioavailability	High bioavailability & biocompatibility
Lower efficacy	Efficacy is high
Lower therapeutic effect	Therapeutic effect is high
High toxicity	Low toxicity
High dose is required	Required low dose
Chances of side effect are high	Chances of side effect are low

***The ideal characteristic of multiparticulate drug delivery systems to the colon targeting* – [31],[32]**

- It provides enhancement of bioavailability through enhancement of absorption rate, especially for poorly soluble drugs.
- Drug leakage can be overcome.
- Dose frequency can be reduced.
- Dose dumping issue can be solved.
- Localization of target sites.
- Carrier used in the formulation must be biodegradable, non-toxic, and non-immunogenic.
- Drug release shouldnot impact drug action.
- Drug release must be the controllable and predictable rate of drug release.
- Restriction on the drug distribution to target cells or tissue or organ.

***Advantages of multiparticulate drug delivery systems over conventional drug delivery systems* – [33]**

- Minimum toxicity can be achieved.
- First pass metabolism can be overcome through this process.
- Dose dumping problem can be solved.
- Suitable for protein and peptides drug delivery systems.
- Avoids premature drug release.
- Target specificity.
- Administration process simple.

***Disadvantages of multiparticulate drug delivery systems over conventional drug delivery systems* – [34]**

- Clearance is rapid.
- Insufficient localization during targeting to the tumor cell.
- Required highly sophisticated technology for the manufacturing process.
- Difficult to maintain the stability of the dosage form.
- Drug loading capacity is usually low therefore difficult to predict dose regiment.
- Required skill person for manufacturing, maintaining storage conditions, and administration.
- Some times immune reaction happened leads to hypersensitivity reaction may occur.

***Major disorders of the colon and their characterization* – [35]**

Ulcerative colitis and Crohn's disease have different conditions but they have some common symptoms. Crohn's disease mainly occurred in the last part of the small intestine as the ileum and the first part of the colon and can cause blockage in the intestine, ulceration (sores) in the intestinal tract. The symptoms of Crohn's disease as diarrhea (sometimes bleeding), abdominal pain, cramping, fever, and fatigue. Ulcerative colitis mainly affected the mucosal lining of the large intestine especially all three layers of the bowel wall. The symptoms of abdominal pain, fever, and cramping, loose and bloody stools, fatigue, loss of appetite,

and anemia and can increase the formation of holes in the colon, liver disease, blood clot, and osteoporosis. The cause of inflammatory bowel disease is still unknown and several factors have been noticed such as genetic, environmental, and immunological.

***Table06- Major disorders of the colon and their characterization*[36]**

Diseases	Characterization
Inflammatory bowel diseases (IBD)	Idiopathic chronic multifactorial gastrointestinal inflammatory disorders.It comprises two diseases named • Ulcerative colitis • Crohn's disease
Ulcerative colitis	Ulcers grow in the mucosa of the colon or rectum, the inner lining of the gut, causing diarrhea, blood, and pus.
Crohn's disease	Crohn's disease, also known as regional enteritis, is a chronic intestine inflammation that is usually limited to the ileum, the terminal section of the small intestine.
Colon cancer	Cancerous growths in the colon, rectum, and appendix are all part of large bowel cancer.
Irritable bowel syndrome	Irritable bowel syndrome (IBS), often known as spastic colon, is a condition marked by chronic abdominal pain, discomfort, bloating, and bowel irregularities in the absence of an intrinsic cause. IBS can develop as a result of an infection or a stressful event in one's life.

CONCLUSIONS *:*

Treatment of local and chronic diseases of the colon like inflammatory bowel disease as ulcerative colitis and Crohn's disease has been winded strongly associated with adverse effects and poor bioavailability.Though traditional drug delivery systems targeting the colon region may overcome through colon targeted drug delivery, during application of traditional drug delivery systems are facing several problems as dose dumping, immediate-release after administration, fluctuation of blood plasma level, and inconvenience of patients can be seen.Previously lack of knowledge of pH-dependent, time-dependent, and bacteria-dependent approach maximum drugs premature release in the stomach and intestine before reaching to the colonic environment to show therapeutic efficacy.

In recent years, an Increase no of studies using Multiparticulate or targeted drug delivery systems gained too much interest to the researcher to target colon regions. To overcome the problem of bioavailability, target specificity, and dosing frequency targeted drug deliveryplays an important role. They have higher drug loading capacity, stable at in-vivo as well as in-vitroconditions, controllable and predictable drug release which help to gain much moreinterest to the researcher. pH-dependent polymer, time-dependent polymer, and bacteria-dependent drug delivery approach help to enhance the drug stability and easy to stable at altering gastric pH. For inflammatory bowel disease, the targeted drug delivery systems for oral delivery have been recognized to have the potential to improve delivery to active compound and therapeutics outcomes.

Compare to the parenteral route, the oral route is the best convenient to patients because avoidance of pain and possible contamination through injection and self-administration could not possible in parenteral preparation.

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