Journal of Applied Pharmaceutical Research
Volume 9, Issue 4, Year of Publication 2021, Page 09 – 15
DOI: 10.18231/j.joapr.2021.9.15

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Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | ***JOAPR***

www.japtronline.com ***ISSN: 2348 – 0335***

A BRIEF REVIEW ON COLON-SPECIFIC DRUG DELIVERY SYSTEM FOR TARGETING TO COLONIC REGION

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Article Information
Received: 3rd February 2021
Revised: 8th September 2021
Accepted: 12th October 2021
Published: 31st December 2021

Keywords
Nanoparticles, Amoebiasis, Inflammatory bowel disease, Colorectal cancer, colonic dysmotility, chronic diarrhea

ABSTRACT

Drug delivery to the colonic region refers to the drug that should have to released in the colonic environment instead of released in the upper gastrointestinal tract. To reach the site-specificity of the local treatment of the colon such as amoebiasis, colorectal cancer, and inflammatory bowel disease the target-specific drug delivery played an important role. To the establishment of the target-specific drug delivery to the colon, the various approach that has been explored include pH-dependent polymer, time-dependent, and bacteria-dependent drug delivery approach. Nanotechnology has been gaining much more interest due to target specificity and enhancement of bioavailability and high loading capacity. In this review, oral nanoparticle formulation for colon targeting specifically inflammatory bowel disease and suitable drugs for useful treatment and future aspects of nanoparticle formulation with particular approaches to enhancement of drug stability in the gastric environment have been covered.

INTRODUCTION

A nanoparticle is defined as the solid colloidal particles ranging from 10 nm to 1000 nm in size where the drug can be dissolved, absorbed, entrapped, or encapsulated into a nanoparticle matrix. The hydrophobic drugs suffer precipitation problems at high concentrations and toxicity issues with additives, it can be overcome through nanoparticle drug delivery system. Nanoparticulate drug delivery systems provide target specificity and release therapeutics effectiveness at a particular region. Stability and bioavailability can be enhanced through a nanoparticulate formulation which allows the physicians to give a lower dose to the patient. Nanoparticles have a high preference rather than a single-unit dose to the colon because capable of passing the GI tract easily and have less inter-intra subject variability [1].

The oral administered route is preferentially better in the treating of colonic diseases such as inflammatory bowel disease, colorectal cancer, chronic diarrhoea, colonic dysmotility because targeting region concentration can be achieved,

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reducing side effects because of unnecessary systemic absorption can be overcome [2]. 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.

Orally delivering drugs as conventional drug delivery systems faces several problems before reaching to targeting colon sites as pH of gastrointestinal tract varies site by site (stomach pH - 1.3-3.5, small intestinal pH – 6-8). The drug may not be stable in this different pH range, pancreatic enzymes, bile salt, bicarbonate, and colonic enzymatic activity [3]. Nanoparticles stables at the gastric environment and encapsulated drugs can be stable in the harsh pH and different enzymatic environments. The modified nanoparticle can easy to penetrate mucus layers reach to site and show therapeutic activity. The drug efficacy and retention time can be improved through nanoparticulate formulation, Nanocarriers encapsulated drug can be reached to the inflamed colon by endocytosis process [4], [5].

Colon-specific drug delivery can be defined as the drug should reach the target site and show therapeutic activity without premature drug release in the stomach acid. Untreated ulcerative colitis leads to colorectal cancer. Day by day ulcerative colorectal cancer active cases increasing and the rate of cancerous colonic polyp selectively low and that is why it took a long time [6], [7].

Ulcerative colitis and Crohn's disease have major differences as they have common symptoms with different conditions. Crohn's disease refers to the blockage in the intestine and ulceration in the intestine and it is mainly affected to the lower part of the intestine and the first part of the colon. Several symptoms can be seen in Crohn's disease such as abdominal pain, fatigue, cramping, fever, and diarrhoea. The symptoms of ulcerative colitis such as abdominal pain, fever, cramping, loose and bloody stools, fatigue, loss of appetite, and anemia and can increase the formation of holes in the colon, liver disease, blood clots, and osteoporosis [8], [9].

Advantage of colon targeted drug delivery [10], [11]-

- Target specificity at the desired location.
- Less enzymatic activity.
- Lesser amount of dose is required to produce therapeutic activity
- Local and systemic treatment can be possible
- Suitable for protein and peptides.
- Reduce gastric irritation especially NSAIDs (non-steroidal anti-inflammatory diseases)
- Use to prolong drug therapy.

Disadvantages of colon targeted drug delivery [12], [13]-

- Stability problem of drugs and polymer due to different pH, enzymatic activity.
- Gastric empty time can be varying, depending upon food intake
- Disease condition may be affecting the colonic transit time and drug release profile.

pH of the colon depends upon disease state and food intake capacity.

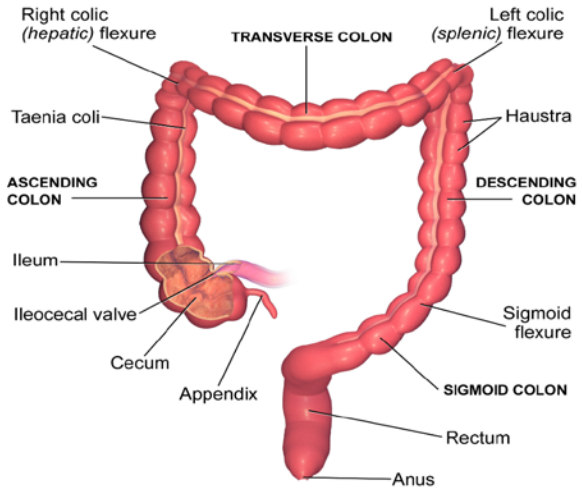

Fig 01 – Figure of Large Intestine

Some important factor affecting colon-specific drug delivery

1. pH of the colon –

The pH of the colon may depend upon inter- intra subject variability which impacts colon-specific drug delivery systems. The gastric environment depended upon food intake capacity, disease condition, and regular diets. The drug must need to stable in the variable pH and release at the particular pH region and show proper therapeutic effectiveness. The pH of the colon varies due to long-chain fatty acid obtained from bacterial fermentation of polysaccharides [14], [15].

2. Gastric-intestinal transit-

Gastric empty primarily depends on the subject is fed or fasted, dietary fiber content, stress, mobility, diet, disease, and drugs content. The transit time depends on the size of the particles as smaller particle sizes have more transit time comparison with larger particle sizes [18], [19]. Disease condition also played a

major role in gastric transit time. A patient who suffers from diarrhea has a shorter transit time compared with constipation patients [20], [21].

3. Colonic microflora and enzymes -

GI tract contains various enzymes released by various microorganisms such as Eubacteria, streptococcus, E. coli, clostridia, lactobacilli, P. Vulgaris, B. subtillis, B. mycoides, A. aerogenes which helps for the metabolism and degrade coating materials as well as breaking bonds between biodegradable and active moiety. The concentration of bacteria present in the human colon is 10^{11} to 10^{12} CFU/ml [22], [23].

Table 01: pH of Gastro-intestinal tract [16], [17]

Gastrointestinal Tract		Length (cm)	pH
Stomach		----------	1.5-3 (Fasted) 2-5 (Fed)
Small intestine	Duodenum	20-30	6.1 (fasted) 5.4 (fed)
	Jejunum	150-200	5.4
	Ileum	200-350	7.4
Large Intestine	Cecum	6-7	5.5-7
	Ascending colon	20	
	Transverse colon	45	
	Descending colon	30	
	Sigmoid colon	40	
	Rectum	12	
	Anal canal	3	

Various approaches of colon-specific drug delivery systems

The drug should be stable at different pH regions and degrade in the colonic microflora when targeting particularly colonic diseases and provide proper therapeutic efficacy and maintaining the therapeutic concentration [27]. The various approach has 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 upper GIT tract 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 [28].

Table 03: Enzymes present in different microorganisms [24], [25], [26]

Enzymes	Microorganism
Esterase and amidase	E. coli, P. vulgaris, B. mycoides
Azoreductase	Lactobacilli, E. coli, Clostridia
Glucuronidase	A. aerogenes, E. coli
Nitroreductase	E. coli, Bacteroides
Glycosidase	Eubacterium, Clostridia

Table 04: Polymers in the different pH range [29], [30] [31]

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

- **Time-Dependent drug delivery approach**

The time-dependent drug delivery approach is also known as delayed or sustained, a pulsatile release that occurred after the pre-determined lag time (time for transit from mouth to colon) [32], [33]. 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**

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 release some enzymes such enzymes as glucuronidase, urea dehydroxylase, and deaminase which help to degrade the drug in the colon region. Bacteria-dependent drug delivery approach consists of the prodrug, coating with biodegradable azo compound, hydrogels, Polysaccharides as carriers [34], [35].

Why nanoparticle suitable for colon targeted drug delivery

A nanoparticle is a most promising application to colon-targeted drug delivery because of increased bioavailability, reduce

administration frequency, and promotes drug targeting. They have small in size increase the surface area which helps to enhance the absorption rate as well as bioavailability and have high drug loading capacity.

Some important properties of nanoparticles are as follows [36], [37], [38]

- Proper efficiency and effectiveness in the target region with biochemical inert, non – immunogenic as well as non-toxic in nature.
- They are stabilized in the in-vitro and in-vivo environments.
- Uniform distribution at the target site.
- The controllable and higher concentration at the target site.
- Simple, reproducible, and cost-effective
- Target specificity.

Advantages of nanoparticle [39], [40]-

- Higher stabilities.
- Higher carrier with drug loading capacity.
- Suitable with both hydrophilic and hydrophobic substances.
- Suitable of the variable route of administration.
- Can be stored longer period without degradation.
- Reduced dosing frequency.

Disadvantages of nanoparticles [41], [42]-

- Very costly formulation.
- Productivity is much more difficult than conventional drug delivery.
- Minimized the ability to adjust the dose frequency.
- Highly sophisticated and expensive technology.
- Requires skilled persons with the proper knowledge to manufacture.
- Stability and safety of dosage form is a big issue owing to its Nano range.

Recovery of dosage form after administration is much more difficult.

Future prospects of colon-specific drug delivery

Nanoparticle drug delivery is suitable to target the colon region with their proper bioavailability, site-specificity, and stability at the variable pH environment and showing higher concentration at the target site [45].

- The safety of the different Nanoparticle delivery systems should have to improve further.
- Structural stability of the nanoparticle formulation in the GI environment should be developed to prevent premature drug release in the upper GI tract and release at the colonic region.
- Nanoparticulate drug delivery design should be optimized properly, efficient, and can be manufactured in large-scale production [46].

Table 05: Drug suitable for colon targeting [43], [44]

Drugs	Polymers	Uses
Mesalamine	Chitosan with Eudragit S-100	Ulcerative colitis
Satranidazole	Eudragit s100	ulcerative colitis, Crohn's disease
Curcumin	Eudragit s100	Ulcerative colitis, amoebiasis, Crohn's disease
Capecitabine	Eudragit L-100, Eudragit s100	Colorectal cancer
Meloxicam	Sodium alginate with Eudragit s-100	Colorectal cancer
Piroxicam	Sodium alginate with Eudragit s 100	Rheumatoid arthritis

CONCLUSION

In recent years, an increased no of studies using targeted drug delivery has been found successfully targeting to colonic region. To overcome the problem of bioavailability, target specificity, and dosing frequency targeted drug delivery systems play an important role. Targeted drug delivery systems have higher drug loading capacity, stable in vivo as well as in-vitro condition, controllable and predictable drug release which help to gain much more interest 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. Targeted drug delivery has been recognized to have the potential to improve delivery to active compound and therapeutics outcomes. The main motto of this review is that colon targeted drug delivery system is successfully targeting to colon region with proper therapeutic activity with fewer adverse effects compared to convention drug delivery systems.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Soumyadip Ghosh, Debgopal Ganguly, and Subhabrota Majumdar design the work and made the required corrections and revisions in the manuscript. Debgopal Ganguly and Soumyadip Ghosh collected that content performs the literature survey and also contributed to designing the manuscript. All the authors design the final manuscript.

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