

## REVIEW ARTICLE

# Colon Targeting by Novel Drug Delivery Drug System: Microsphere a Review Report

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**Received: 10-05-2021; Revised: 27-06-2021; Accepted: 10-07-2021**

### ABSTRACT

In the recent year, colonic drug delivery has gained importance for delivery of drug for the treatment of local diseases associated with colon and systemic delivery of therapeutic peptides and proteins. Treatment could be more effective if it is possible for drug to be directly delivered to colon. During the past decade, there are new developments in site-specific formulations for targeting drug to the colon. Colon has proved to be a site for the absorption of poorly soluble drugs. Microcarriers as colon drug delivery system have gained importance for the delivery of the drug in the colon because of their increase biocompatibility, controlled release of drug, and higher stability. This review is discusses in brief about introduction to colon, microcarrier as colon drug delivery system. Oral delivery is still the most favorable route of drug administration, especially for chronic therapies where repeated administration of drug is required. Oral administration offers less pain, good patient convenience, and reduced risk of cross infection and needle stick injuries.

**Keywords:** Colon targeted drug delivery system, Microsphere, Preparation and Evaluation of Microsphere, etc.

### INTRODUCTION

The aim of a targeted drug delivery system is to provide a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site. It is suitable and required for the drugs having instability, low solubility, short half-life, a large volume of distribution, poor absorption, low specificity, and therapeutic index. Targeting may provide maximum therapeutic activity (by preventing degradation or inactivation of drug). Meanwhile, it can also minimize adverse effects, the toxicity of potent drugs by reducing dose.<sup>[1]</sup> The oral route is the most convenient and important method for administration of drugs for systemic effect.

In addition, less pain, reduced risk of cross-infection, needlestick injuries, patient acceptance, and ease of administration made it more preferred. Nearly 50% of the drug delivery systems available in the market are oral drug delivery systems. Apart of these advantages, the oral route is not suitable to the administration of the drug for lower gastrointestinal (GI) diseases; this happened due to their release at upper GI tract (GIT) (stomach and small intestine), which further minimizes the accessibility of drugs at the lower GIT.

To overcome this difficulty, colon-specific drug delivery systems have been broadly analyze during the past two decades. By definition, a colonic delivery refers to delivery of drugs accurately into the lower GIT (by avoiding the drug release in upper GIT), which occurs primarily in the large intestine (i.e., colon).<sup>[2-4]</sup> Rectal administration is another route used for colon targeting, but it shows less compliance (uncomfortable) and becomes

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difficult to reach the colon. Conventional dosage forms that are used in the prevention of colon diseases (ulcerative colitis, Crohn's diseases, and amebiasis) are failing as an improper amount of drug reaches site of action. Conventional dosage form affords the drug to be absorbed from the upper part of GIT, that is, stomach. This action of conventional dosage form has a serious drawback for colonic localized delivery. Thus, for efficient and safe therapy, the drug is needed to be preserve from upper hostile environment.<sup>[3-6]</sup>

Site-specific delivery into the colon is not only needed for local treatment of a variety of colon diseases, such as ulcerative colitis, Crohn's diseases, amebiasis, and colon cancer but also systemic delivery of proteins and peptides this is because of less diversity and intensity of digestive enzymes and less proteolytic activity of colon mucosa than that observed in the small intestine. Besides the colon diseases, this system is also helpful in the treatment of asthma, angina, and rheumatoid arthritis for taking advantage of chronotherapeutic drug delivery and for delivery of steroids.<sup>[7]</sup>

Some factors to be considered for successful colonic drug delivery including the properties of the drug, the type of delivery system, and its interaction with healthy or disease gut. The longer residence time, less peptidase activity, natural absorptive characteristics, and high response to absorption enhancers make it most promising site for drug delivery. The absorption enhancers are subcharacterized into categories of chelating agents, nonsteroidal anti-inflammatory agents, surfactants (mostly as mixed micelles), phenothiazines, and a general class of molecules which include fatty acids, acylcarnitine acyl amino acids, and dicarboxylic acid.<sup>[3,8]</sup>

### Advantages<sup>[4,9]</sup>

1. Ideal site for the delivery of active agents to cure the colon diseases (ulcerative colitis, Crohn's diseases, amebiasis, etc.)
2. Smaller drug quantities should be required for local treatment
3. Less side effects and drug interactions occurs
4. Dosage frequency is less so, cost effective

5. The long retention time of colon, improved bioavailability of poorly absorbed drug molecules (up to 5 days)
6. Reduce gastric irritation caused by many drugs by preventing their absorption in upper GIT (e.g., NSAIDS)
7. Bypass initial first pass metabolism
8. Extended daytime or nighttime activity
9. Limitation and challenges<sup>[4,9]</sup>
10. Hard accessibility of the colon because of its location at the distal part of the alimentary canal
11. The drug may bind non-specifically to intestinal contents (dietary residues, intestinal secretions, and fecal matter) cause reduce drugs bioavailability
12. Metabolic degradation of the drug by resident microflora could also affect colonic performance
13. Restrict drug transport across the mucosa and into the systemic circulation due to lower surface area and relative tight junctions in the colon
14. Lack of an appropriate dissolution testing method to evaluate the dosage form *in vitro*
15. The drug in solution form required for successful colon delivery or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs
16. Factors to be considered in the design of colon-specific drug delivery system
17. Anatomy and physiology of colon.

The GIT (alimentary canal) is a muscular, digestive tube that extends from mouth to anus, having functions to digest dietary food, to absorb nutrients, electrolytes, and fluids, and to prevent the absorption of potentially harmful substances, as shown in Figure 1.

The GIT is divided into stomach, small intestine, and large intestine. The longest part of the GIT is small intestine where most enzymatic digestion and absorption occur. The large intestine is the last major portion of the GIT (starts from the distal end of the ileum to the anus) and is about 1.5 m long.<sup>[10]</sup> Colon is upper five feet of the large intestine and mainly situated in the abdomen. Colon is a

cylindrical tube that is lined by a moist, soft pink lining called mucosa, as shown in Figure 2. The cecum is the first part of the colon and leads to the right colon or the ascending colon followed by the transverse colon, the descending colon, sigmoid colon, rectum, and the anal canal. The right colon is made up of the cecum, ascending colon, hepatic flexure, and the right half of the transverse colon and left colon is made up of the left half of the transverse colon, splenic flexure, descending colon, and sigmoid. The colon does not have villi unlike small intestine, but due to the presence of plica semilunaris (crescentic folds), the intestinal

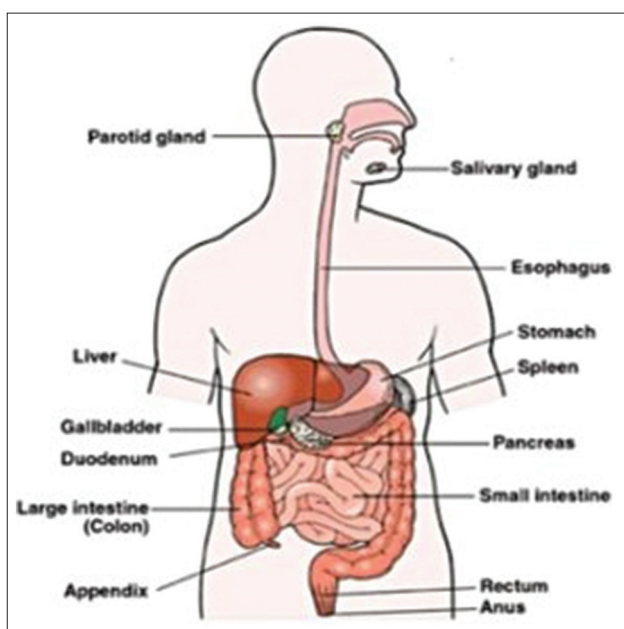


Figure 1: Gastrointestinal tract

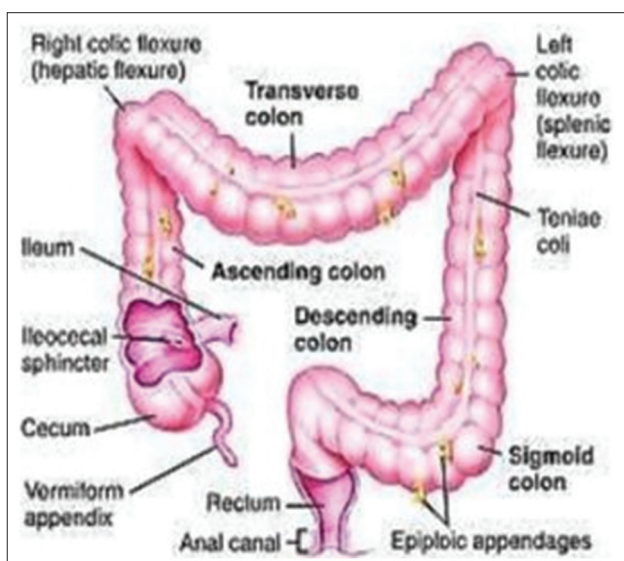


Figure 2: Structure of colon

surface of the colon is increased to approximately  $1300 \text{ cm}^2$ .<sup>[4,9,11]</sup>

Structure of Colon:<sup>[1,2,11]</sup> the colon is made up of different layers and different parts as given in table 1.

Function of Colon:

1. The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and storage of feces until excreted from the body
2. To provide a favorable environment for the growth of colonic microorganisms
3. Absorption of  $\text{H}_2\text{O}$  and  $\text{Na}^+$  from the lumen, and secretion of  $\text{K}^+$  and  $\text{HCO}_3^-$ .

## MICROSPHERES

Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically  $1 \mu\text{m}$ – $1000 \mu\text{m}$ ). Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats, and waxes. The natural polymers include albumin and gelatin, the synthetic polymers include polylactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations.<sup>[1]</sup>

Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate

Table 1: various parts of git and its pH

S No.	Location	pH
1.	Rectum	7.0
2.	Terminal ileum	7.5+0.5
3.	First parts of colon	6.4+0.6
4.	Mid colon	6.6+0.8
5.	Left colon	7.0+0.7
6.	Right colon	6.4

GIT irritation. In addition, multiparticulate delivery systems spread out more uniformly in the GIT. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating and polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided.<sup>[2]</sup>

## TYPES OF MICROSPHERE<sup>[9-11]</sup>

### Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane using the sticking property of the water-soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, and nasal can be termed as bioadhesion. These kinds of microspheres exhibit a prolonged residence time at the site of application and cause intimate contact with the absorption site and produce better therapeutic action.<sup>[12-14]</sup>

### Magnetic microspheres

This kind of delivery system is very much important which localizes the drug to the disease site. In the magnetic microsphere the larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug by this drug targeting can be easily achieved. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran, etc. The different types are therapeutic magnetic microspheres and diagnostic microspheres.<sup>[15]</sup>

1. Therapeutic Magnetic Microspheres: It is used to deliver chemotherapeutic agent to liver tumor. Drugs such as proteins and peptides can also be targeted through this system<sup>[16]</sup>
2. Diagnostic Microspheres: It can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles supermagnetic iron oxides.

### Floating microspheres

In floating types, the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover, it also reduces chances of striking and dose dumping. One another way it produces prolonged therapeutic effect and therefore reduces dosing frequencies.<sup>[17,18]</sup>

### Polymeric microspheres

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and synthetic polymeric microspheres.<sup>[19]</sup>

#### *Biodegradable polymeric microspheres*

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bioadhesive in nature. Biodegradable polymers prolong the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, result gel formation. The rate and extent of drug release are controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.<sup>[20]</sup>

#### *Synthetic polymeric microspheres*

The interest of synthetic polymeric microspheres is widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles drug delivery vehicles, etc., and proved to be safe and biocompatible. However, the main disadvantage of these kinds of microspheres is tended to migrate away from injection site and lead to potential risk, embolism, and further organ damage.<sup>[21,22]</sup>



## METHOD OF PREPERATION

### Ideal characteristics of microspheres<sup>[3,4]</sup>

The ability to incorporate reasonably high concentrations of the drug. Stability of the preparation after synthesis with a clinically acceptable shelf life. Controlled particle size and dispersability in aqueous vehicles for injection. Release of active reagent with a good control over a wide time scale. Biocompatibility with a controllable biodegradability. Susceptibility to chemical modification.

### Advantages of microspheres<sup>[24-26]</sup>

1. Particle size reduction for enhancing solubility of the poorly soluble drug
2. Provide constant and prolonged therapeutic effect
3. Provide constant drug concentration in blood, thereby increasing patient compliance
4. Decrease dose and toxicity
5. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein
6. Reduce the dosing frequency and thereby improve the patient compliance
7. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects
8. Microsphere morphology allows a controllable variability in degradation and drug release
9. Convert liquid to solid form and to mask the bitter taste
10. Protects the GIT from irritant effects of the drug
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal
12. Controlled release delivery biodegradable microspheres are used to control drug release rates, thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections (Mohan *et al.*, 2014).<sup>[4]</sup>

## Limitation

Some of the disadvantages were found to be as follows:

1. The costs of the materials and processing of the controlled release preparation are substantially higher than those of standard formulations
2. The fate of polymer matrix and its effect on the environment
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants, and fillers
4. Reproducibility is less
5. Process conditions such as change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation, or biological agents.<sup>[3,27]</sup>

## Application of microspheres in pharmaceutical industry<sup>[5,6]</sup>

- For taste and odor masking
- To delay the volatilization
- For separation of incompatible substances
- For improvement of flow properties of powders
- To increase the stability of the drug against the external conditions
- For safe handling of toxic substances
- To improve the solubility of water-insoluble substances by incorporating dispersion of such material in aqueous media
- To reduce the dose dumping potential compared to large implantable devices
- For conversion of oils and other liquids to solids for ease of handling.

## CHARACTERIZATION AND EVALUATION OF MICROSPHERES<sup>[28,29]</sup>

The microspheres prepared by the above techniques were characterized for

1. Particle size
2. Zeta potential
3. Drug-polymer interaction scanning electron

### microscopy (SEM)

Suspension was made to obtain photomicrographs of the azathioprine-loaded microspheres using the SEM is used to determine the shape, size, and surface morphology of the microspheres. Zeta potential: The prepared microspheres were dispersed in deionized water and sonicated for 30 min. The resultant dispersion was diluted and observed for zeta values. Fourier-transform infrared (FT-IR) spectroscopy is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microspheres is investigated measuring alternated total reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATR-FTIR provides information about the surface composition of the microspheres depending on manufacturing procedures and conditions. The microspheres prepared by the above techniques were evaluated for (1) percentage yield, (2) drug content, (3) entrapment efficiency, and (4) *in vitro* drug release. Percentage yield: The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Product yield is calculated using the following Equation  $\text{Product yield} = \frac{\text{Weight of the product}}{\text{Weight of raw materials}} \times 100$ . Drug content: The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of ethyl acetate in two necked round bottomed flask. With the help of mechanical stirrer allow it to stir for 3 h then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 279 nm. Drug content =  $\frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 10$  Entrapment efficiency: The prepared formulations were examined for entrapment efficiency. Forty milligrams of the prepared formulation were taken in equivalent quantity of 7.4 phosphate buffer. The suspension is ultracentrifuged at 17240 rpm for 40 min.

$\text{EE} = \frac{\text{Total amount of drug}-\text{Amount of drug in supernatant}}{\text{Total amount of drug}} \times 100$  *In vitro*

drug release study of microsphere formulations in phosphate buffer pH 7.4: 17. The dissolution rate testing apparatus was employed to study the release of azathioprine using phosphate buffer pH 7.4 as a dissolution medium. Fifty milligrams equivalent of azathioprine microspheres was taken and dissolution test was being carried out at 50 rpm maintained at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . Five milliliters of sample were withdrawn at specific time interval for 12 h. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometrically at 279 nm.

### CONCLUSION

From past two decades, considerable amount of research work has been carried out in the area of colon targeting. By considering the advantages of CDDS like providing friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site-specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc., different approaches are designed to develop colonic drug delivery system. The release of drug load in colon region is depended on pH of GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule.

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