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### Microparticle as Suitable Drug Carriers For Colon Targeting – A Recent Review”

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#### 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 last 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. Micro carriers as colon drug delivery System has 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, Micro Carrier 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.

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## INTRODUCTION

### Colon Targeted Drug Delivery Systems (CTDDS)

Since past 70 years, it has profound insights into the physiology, physical chemistry of organs, biology cells, membranes, compartments, cellular organelles and functional proteins related with the absorption processes of drugs in the gastrointestinal tract (GIT). Oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders. <sup>1</sup> Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel disease such as ulcerative colitis, crohn's disease, amebiasis, colonic cancer and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs. <sup>2</sup> Dosage forms that deliver drug in the colon rather than upper GIT has number of advantages. Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon where by high local concentration can be achieved while minimizing side effects. <sup>3</sup>

#### Need of colon targeted drug delivery: <sup>2,4</sup>

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer side effect.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon specific formulation could also be used to prolong the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel diseases, e.g. ulcerative colitis or Crohn's disease .Such inflammatory conditions are usually treated with glucocorticoids and sulfasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

#### Why colon targeted drug delivery needed? <sup>5,6</sup>

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative

colitis or Crohn's Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

#### **Advantages of colon targeting drug delivery system<sup>4,7</sup>**

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bypass initial first pass metabolism.
- Extended daytime or night-time activity.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route

#### **Limitations of colon targeting drug delivery system<sup>4,7</sup>**

- Multiple manufacturing steps.
- The resident micro flora could also affect colonic performance via metabolic degradation of the drug.
- Incomplete release of drug Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.

- An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis
- Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage

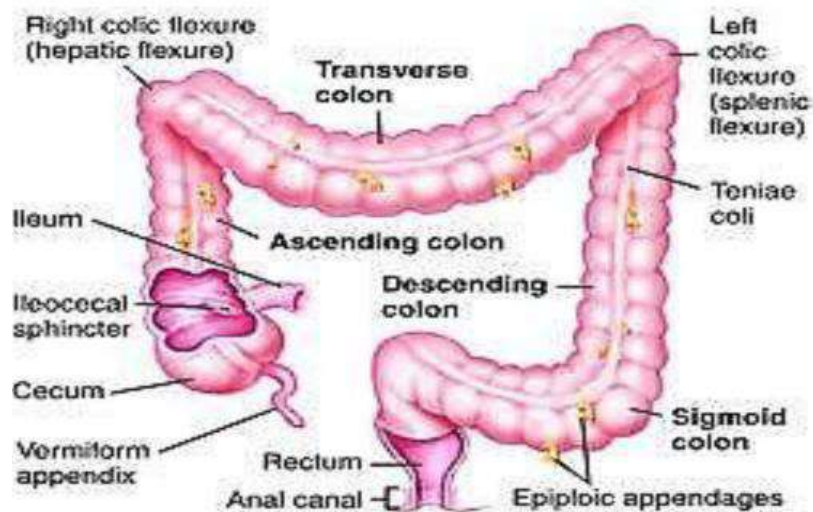
## **ANATOMY AND PHYSIOLOGY OF COLON**

### **Anatomy of colon**<sup>8</sup>

The whole GIT is divided into three parts Stomach, Small intestine and large intestine. The large intestine is 1.5m long and further divided into caecum (6-9 cm), appendix, colon and rectum. The colon is further dividing into the ascending, transverse and descending colon. The colon removes the water, salts and some nutrients from the stools. The ascending colon (20-25cm) runs through the abdominal cavity upwards towards the transverse colon. Its main function is to remove water and nutrients. The waste materials are move upward into the transverse colon by process known as peristalsis.

The transverse colon (40-45cm) is the part of the colon from the hepatic flexure to the splenic flexure. The descending colon (10-15cm) is the part of the colon from the splenic flexure to the beginning of the sigmoid colon (35-40cm). The function of the descending colon is to store the food which emptied into the rectum. The human colon is shown in Figure 1. Colon is comprises of four different layers these are Mucosa, Sub mucosa, Muscular is externa, and Serosa. The Billions of bacteria coat the colon and its contents. The main function of the colon is providing the suitable environment for Colonic microflora growth and also as a storage reservoir of fecal contents and the removal of waste materials from the colon at an appropriate time. The absorption salt water and some nutrients may also take place from the colon.

The absorption capacity of colon was found to be very high nearly about 2000ml. The fluid enters the colon through ileocecal valve 90% of which is absorbed by the colon. The colon contains approximately 220 gms of wet material which is equivalent to 35 g of dry matter. The majority of which is bacteria.



**Figure 1: Different parts of Colon**

### Physiology of colon (Sreelatha D et al 2012)

#### Gastric emptying

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. Diarrhea patients have shorter transit time whereas constipation patients have longer transit times.

**Table 1: 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

#### pH of colon<sup>8</sup>

The pH of GIT varies between different individuals. The food intake, diseased state, etc. Influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

**Table 2: pH in different parts of Colon<sup>8</sup>**

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small intestine	6.6- 7.5
Colon	
Ascending colon	6.4
Transverse colon	6.6
Descending colon	7.0

**Colonic microflora and enzymes**

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. The enzymes released by different microorganisms *E. coli*, *Clostridia*, *Lactobacilli*, *Eubacteria*, *Streptococci* are responsible for the various metabolic reactions that take place in the GIT.

**MICROSPHERES**<sup>12</sup>

Earlier patients have been using conventional dosage forms like Tablet, Capsule to treat the acute and chronic diseases, but these conventional dosage forms have to be taken several times in a day for maintaining the peak plasma level concentration. Hence to overcome these problems controlled release drug delivery system were developed. Controlled drug delivery system (Microspheres) releases the drug in controlled rate and overcome the problems of conventional drug delivery system and enhances the therapeutic efficacy of a given drug. 9 The main purpose of Controlled drug delivery system is to ensure optimum plasma drug concentration, thus enhancing efficacy, safety and bioavailability of drug with improved patient compliances 10.

Microsphere is small spherical particle having the particle size range 0.1-200 $\mu$ m, and made up of biodegradable and non-biodegradable material and can be injected by 18 or 20 number of needles 5-6. Drug absorption and side effects due to the irritating drugs against the gastrointestinal mucosa is improved because of small particle size of microspheres which get widely distributed throughout the gastrointestinal tract .

Oral route is the most convenient and commonly employed route for most of the drugs. Some Drugs that are easily absorbed by the G.I.T. and having short  $t_{1/2}$  are eliminated quickly from the blood circulation. Controlled Drug delivery System can avoid the problems of conventional drug delivery system by releasing the drug slowly into the G.I.T. and maintain a constant drug concentration in the serum for longer period of time .<sup>11</sup>

**Advantages of microspheres**<sup>12</sup>

- Microspheres provide prolonged and constant therapeutic effect.
- Microspheres reduce the dosing frequency and therefore improve the patient compliance.
- Microspheres provide controlled, sustained and targeted delivery of the drug.
- Microspheres produce more reproducible drug absorption.
- Drug discharge in stomach is hindered and that's why local unwanted effects are reduced.
- In case of microspheres, better therapeutic effect for short half-life of drugs can be achieved.

- Microspheres provide freedom from drug and recipients incompatibilities especially with buffer.
- Microspheres reduce dose dumping.
- Microspheres provide the protection of drugs against environment.
- Microspheres also mask the taste and odor.
- Microspheres avoid the first pass metabolism.
- Microspheres can be easily injected in body because of their small and spherical size.
- Microspheres enhance the biological half-life and also improve the bioavailability.
- Microspheres also reduce the chances of G.I. irritation.

#### **LIMITATIONS OF MICROSPHERES:** <sup>13</sup>

- Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may be food, rate of transit through gut, mucin turnover rate etc.
- There are differences in release from one to another dosage form.
- Low drug loading is done in case of parenteral microspheres.
- In case of parenteral application of microspheres it is difficult to remove carrier completely from the body.
- Parental delivery of microspheres may interact or form complex with blood components.
- The release of formulation can be modified.
- Any loss of integrity in release pattern may cause potential toxicity.

#### **Preparation of Microspheres**

Microspheres of azathioprine were prepared by ionotropic gelation method using Sodium alginate, Eudragit S100 and calcium chloride. Weighed quantity of drug and polymer were added to 50 ml of sodium alginate solution with stirring at about 300 rpm. The resultant solution was then added drop wise to 100 ml of calcium chloride solution under continuous stirring. Stirring was continued for 30 minutes. The obtained microspheres were filtered and washed with purified water and then dried for 6 hours at 40°C. <sup>14</sup>

#### **CHARACTERIZATION AND EVALUATION OF MICROSPHERES** <sup>15 16</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 Scanning Electron Microscopy 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 minutes.

The resultant dispersion was diluted and observed for zeta values.

### **Fourier Transform-Infrared Spectroscopy**

FT-IR 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 upon manufacturing procedures and conditions.

### **The microspheres prepared by the above techniques were evaluated for**

1. Percentage yield
2. Drug content
3. Entrapment efficiency
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 by 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 hours then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 279nm.

$$\text{Drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 10$$

### **Entrapment efficiency:**

The prepared formulations were examined for entrapment efficiency. 40mg of the prepared formulation was taken in equivalent quantity of 7.4 phosphate buffer. The suspension is ultra-centrifuged at 17240rpm for 40 minutes.



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

### **In-vitro drug release study of microsphere formulations in phosphate buffer pH 7.4:** <sup>17</sup>

The dissolution rate testing apparatus was employed to study the release of azathioprine using phosphate buffer pH 7.4 as a dissolution medium. 50mg equivalent of azathioprine microspheres was taken and dissolution test was being carried out at 50rpm maintained at 37°C ± 0.50°C. 5ml of sample were withdrawn at specific time interval for 12 hours. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometric ally at 279nm.

**Table 3: Drugs Reported For Colon Targeting**

<b>Drug</b>	<b>Carrier</b>	<b>Methods</b>	<b>Polymer used</b>	<b>Purpose</b>
Mesalamine	Microspheres	Ionic-gelation emulsion method	Chitosan microspheres coated with Eudragit S100	Treatment of Ulcerative colitis <sup>21</sup>
Curcumin	Microspheres	Ionic cross-linking technique	Guar Gum, Xanthan Gum	Treatment of Colon cancer <sup>22</sup>
Satranidazole	Microspheres	Emulsion Solvent Evaporation Method	Eudragit S100	Ulcerative Colitis, Amoebiasis, Chron's Disease, Carcinomas & Infections <sup>23</sup>
Curcumin	Microparticles	Solvent Evaporation Technique	Eudragit S 100	Colorectal Cancer <sup>27</sup>
Flurbiprofen	Microcapsule	Solvent Evaporation Method.	Eudragit L-100, Eudragit S-100	Treatment Of Local Diseases <sup>24</sup>
Capecitabine	Microspheres	O/W Emulsification-Solvent Evaporation Technique	Eudragit L 100, Eudragit S 100	Colorectal Cancer <sup>28</sup>
Zidovudine	Microspheres	Ionic Gelation Techniques	Chitosan	HIV And AIDS Related Conditions <sup>29</sup>
Meloxicam	Microspheres	Ionotropic Gelation Technique	Sodium Alginate Coated With Eudragit S100	Colorectal Cancer <sup>16</sup>
Glipizide	Microspheres	Ionotropic Gelatination Technique	Eudragit S 100	Treatment Of Type II Diabetes <sup>30</sup>
Diclofenac Sodium	Microspheres	Ionotropic Gelation Technique	Eudragit S 100	Treatment Of Arthritis <sup>31</sup>
Piroxicam	Microspheres	Ionotropic Gelation Method	Sodium Alginate Microspheres Coated With Eudragit S 100	Treatment Of Rheumatoid Arthritis <sup>32</sup>
Aceclofenac	Microspheres	Ionic Gelation Method	Sodium Alginate Microspheres Coated With Cellulose Acetate Phthalate	Used In Treatment Rheumatoid Arthritis Diseases <sup>33</sup>

## REVIEW OF LITERATURE

- **Asha Patel *et al.***, reviewed 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. This article gives an overview on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery.<sup>18</sup>
- **Singh A. *et al.***, reviewed that local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS.<sup>19</sup>
- **Laila Fatima Ali Asghar and Sajeev Chandran**, reviewed that Colon specific drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases associated with the colon but also as potential site for the systemic delivery of therapeutic peptide and proteins.<sup>20</sup>
- **Badhana *et al.***., the purpose of the present study was to prepare, characterize and evaluate the colon-targeted microspheres of mesalamine for the treatment and management of ulcerative colitis (UC). Microspheres were prepared by the ionic-gelation emulsification method using tripolyphosphate (TPP) as cross linking agent. The microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach.<sup>21</sup>
- **Vajpyee *et al.***, reported Curcumin loaded microspheres prepared by ionic cross linking technique using calcium chloride. Three formulations with each polymer (Sodium alginate: guar gum/ Sodium alginate: xanthan gum) using different concentrations were formulated by ionic cross linking technique. Their result suggested that Xanthan gum microspheres showed more retarded release than guar gum microspheres. The microspheres are spherical in shape and having rough surface.<sup>22</sup>
- **Dinesh Chandra *et al.***, developed multiparticulate system of Eudragit based Satranidazole microspheres exploiting pH sensitivity property and specific biodegradability for colon targeted delivery of Satranidazole. They reported the release profile of satranidazole from Eudragit microspheres was pH dependent. In acidic medium, the release rate was much slower; however, the drug was released quickly at pH 7.4.<sup>23</sup>

- **Najmuddin *et al.***, reported colon specific drug delivery of Flurbiprofen, non-steroidal anti-inflammatory drug with short half life. They evaluated the microcapsule for various physicochemical parameters such as particle size, percentage yield, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy (SEM).<sup>24</sup>
- **Balasubramaniam J *et al.***, have prepared the sodium alginate microspheres of Metformin hydrochloride by emulsion cross-linking method with sodium alginate alone and in combination with gellan gum. The effect of various formulation variables like polymer concentration, drug loading, cross-linking agent concentration and cross-linking time on the in vitro dissolution of the prepared microsphere were evaluated and reported.<sup>25</sup>
- **Kumar *et al.***, reported on colonic drug delivery system of trimetazidine hydrochloride for angina pectoris. They concluded that the formulated microspheres could be successfully targeted to colon by the design of time dependent and polysaccharides based chronopharmaceutical formulation.<sup>26</sup>

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