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Review Article

MICRO CARRIER AS COLON DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

During the last decade, there are new developments in site-specific formulations for targeting drugs 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 discussed in brief about the introduction to the colon, Micro Carrier as a colon drug delivery system. Microcarrier may include Microspheres, Nanoparticles, and Granules, etc.

Keywords: Colon, Colonic drug delivery, colonic transition, Microcarriers, etc..

INTRODUCTION

Oral administration of drugs was found to be a more suitable route of administration of drugs to the patient. The absorption of drugs given by the oral route from the gastrointestinal tract (GIT) depends upon the various physical and chemical properties of the drugs. Nowadays new approaches have been made of delivering the drugs directly into the colon without exposure in the upper GI tract. These are known as Colon Specific drug delivery system (CDDS) or Targeted drug delivery system. The CDDS has many advantages as compare to other drug delivery system. The targeting of colon is very useful because it has longer retention time so even the absorption of poorly absorbed drug May takes place here. Also, in the targeted drug delivery system higher drug concentration is achieved with lower dose of the drugs so it may minimize the side effects of the drugs. The Various disease of the colon like ulcerative colitis, Colon cancer, Crohn's disease, inflammatory bowel disease can be treated by using CDDS. (Choudhury P.K et al 2012).

There are various approaches by which a drug can be delivering to colon. The approaches for CDDS are given below (Patra B.S et al 2012):

- ☐ pH Sensitive Polymer Coated Drug Delivery to the Colon.
- ☐ Delayed Release Drug Delivery to Colon.
- ☐ Microbially Triggered Drug Delivery to Colon.
- ☐ Pressure Controlled Drug-Delivery Systems.
- ☐ Osmotic Controlled Drug Delivery.

ANATOMY AND PHYSIOLOGY OF COLON

Anatomy of colon

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, Muscularis 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 valve90% of which is absorbed by the colon. The colon contains approxymately 220 gm of wet material which is equivalent to 35 g of dry matter. The majority of which is bacteria.(Reddy R. Vet al 2013).

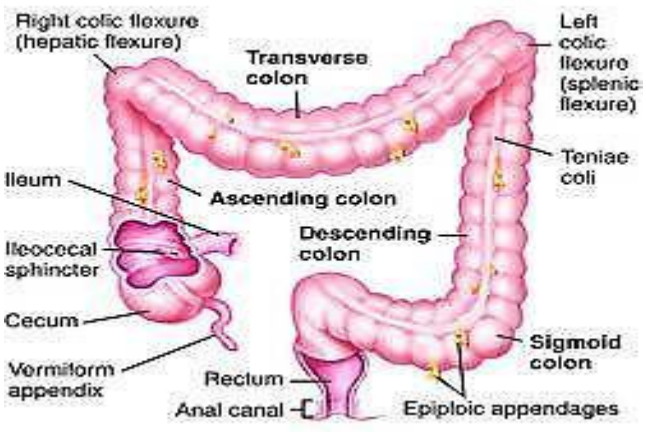

Fig 1: Different parts of Colon

Physiology of colon (Sreelatha D et al 2012)

a. Gastric emptying

Drug delivery to the colon upon oraladministration depends mainly on gastricemptying and bowel transit time. Upon reachingthe colon the transit time of dosage formdepends on the size of the particles. Smallerparticles have more transit time compared tolarger particles. Diarrhoea patients have shortertransit time whereas constipation patients havelonger transit times.

Table 2: 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

b. pH of colon

The pH of GIT varies between differentindividuals.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 isdone to target the drug to the site.

Table 3: pH in different parts of Colon

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

c. Colonic microflora and enzymes

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

Advantages ofCDDS (Philip et al 2012)

☐ Colon is an ideal site for the delivery ofagents to cure the local diseases of thecolon.

☐ Local treatment has the advantage ofrequiringsmaller 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.

Table 4: Different microflora, enzymes released and action.

Microorganism	Enzyme	Metabolic reaction catalysed
E.coli, Bacteroids	Nitroreductase	Reduced aromatic and heterocyclic nitro compounds
Clostridia, Lactobacilli, E.coli	Azoreductase	Reduced cleavage of azo compounds
E.coli	N-oxide reductase, Sulfoxide reductase	Reduced N-oxides and sulfoxides
Clostridia, Lactobacilli	Hydrogenase	Reduced carbonyl groups and aliphatic double bonds
E.coli, P.vulgaris, B.subtilis, B.mycoides	Esterases and amidases	Cleavage of esters or amidases of carboxylic acids
Clostridia, Eubacteria	Glucosidase	Cleavage of b-glycosidases of alcohols and phenols

☐ It has a longer retention time andappears highly responsive to agents that enhance the absorption of poorly absorbed drugs.

Limitations of CDDS

☐ The resident microflora 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 fecal matter.

☐ Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.

☐ Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.

☐ 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.

Criteria for Selection of Drug for CDDS

The criteria for selection of drug candidate for CDDS are summarized in table 5. The selection of carrier for a particular drug candidate depends on the physical and chemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers influences the carrier selection.

Micro Carrier as CDDS

The various micro carrierfor CDDSinclude pellets,microparticles, granules and nanoparticles. Micro carrier systems are preferred oversingle unit dosage forms as the Micro carrier systems enables the drug to reach the colonquickly and retained in colon for long period oftime. These systems pass through the GIT easilydue to their smaller size. Micro carrier systems are dispersed more uniformly in theGIT resulting in more uniform drug absorption. (Asghar L et al 2006).

Table 5: Criteria for selection of drugs for CDDS

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

Table6: Example of various Micro carriers as CDDS

Sr.no	Drug	Method	Polymer	Inference	Reference
1.	Metronidazole	Solvent Evaporation Method	Chitosan, Eudragit S-100	Eudragit coated Chitosan Microsphere Showed drug release rate 90.52 to 95.65 %.	Behin S.R *et al*(2013)
2.	5-Fluorouracil	Emulsion Dehydration method	Pectin, Eudragit S-100	Eudragit Coated pectin Microsphere of showed drug release rate 92.13 to 94.56%.	Jain S.K *et al*(2007)
3.	Glipizide	Solvent Evaporation method	Eudragit S-100, Eudragit R-100	Eudragit S-100 and Eudragt R-100 Coated Microsphere Encapsulaton Efficiencies was found to be 80.45% Showed release profile of 82.34 to 90%.	Behera B.C *et al*(2008)
4.	Mesalamine	Ionic gelation method	Chitosan, Eudragit S-100	Eudragit Coated Chitosan microsphere showed Drug release rate 88.12 to 95.12%.	Graud A. *et al*(2013)
5.	Aspirin	Emulsification Solvent evaporation method	Ethyl Cellulose	Ethyl Cellulose coated Showed Drug Encapsulation Efficiencies 65.23 to 90.12 % and release profile was found to be 89.32 to 95%.	Patel M. *et al*(2012)
6.	Losartan	Emulsification Solvent evaporation method	Ethyl Cellulose, Sodium alginate	Combination of Both polymer Showed Sustained Drug release of losartan.	Rout P. *et al*(2009)
7.	Salbutamol Sulphate, Theophylline	Emulsion Sovent Evaporation method	Ethyl Cellulose	Ethyl Cellulose coated Microsphere Showed drug release rate 82.67 to 92.13%.	Pchaua L. *et al* (2008)
8.	Ciprofloxacin	Emulsion Solvent evaporation method	Ethyl Cellulose	Ethyl Cellulose coated microsphere Showed Drug release rate 84.45 to 95.23%.	Hardenia S.S *et al* (2011)
9.	Ibuprofen	Emulsion Solvent diffusion method	Eudragit L-100	Eudragit L-100 Coated Microsphere showed Drug release rate 78.14 to 84.13%.	Canefe K. *et al* (2006)
10.	Acelofenac	Heat Denaturation Method	Albumin	Albumin Coated Microsphere showed Drug release rate 79.13 to 85.43%.	Deveswaran R. *et al* (2010)
11.	Glimepiride	Emulsification Slovent evaporation	Ethyl Cellulose ,Eudragit L-100	Eudragit L-100 Coated Ethyl Cellulose microsphere of showed Drug release rate 88.13 to 94.65%.	Sriram B. *et al* (2013)
12.	5-Fluorouracil	Ionic Gelation	Chitosan, PEG, Gelatin	Chitosan Nano particle Showed drug release rate 88.21 to 96.23%.	Rajan *et al* (2013)
13.	5-Fluorouracil	Precipitation Polymerization	Carboxy methyl cellulose, sodium dodecyl Sulfate	Nano Sized hydrogels Carboxy methyl Celluose Showed release rate of 84.56% to 91.34%	Moha patra D.K *et al*(2012)
14.	Indomethacin	Wet granulation method	HPMC, Pectin	Indomethacin granules showed Release rate of 81.34 to 94.23%.	Mishra J. *et al* (2012)

Microspheres

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µmto 1000 µm). Microspheres are sometimes referred to as micro particles. Microspheres can bemanufactured from various natural and synthetic materials. Various natural and synthetic polymersused are Agarose, carrageenan, chitosan, starch, albumin, collagen, poly alkyl cyano acrylates,poly anhydrides, poly methyl methacrylate etc. Glass microspheres, polymer microspheres andceramic microspheres are commercially available (Behin S.R et al2013).

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 varioustechniques 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 (Koteshwara K.Bet al 2011).

Granules

Granules are preparations consisting of solid, dry aggregates of powder particles sufficiently resistant to with stand handling. They are intended for oral administration. Some are swallowed as such, some are chewed and some are dissolved or dispersed in water or another suitable liquid before being administered. Granules contain one or more active substances with or without excipients and, if necessary, colouring matter authorised by the competent authority and flavouring substances. Granules are presented as single-dose or multidose preparations. Each dose of a multidose preparation is administered by means of a device suitable for measuring the quantity prescribed. For single-dose granules, each dose is enclosed in an individual container.

Mechanism of drug release from microspheres:

The mechanism of drug release from the microsphere is a complex process and interplay of different mechanisms. The mechanisms involved are:

☐ Dissolution controlled monolithic systems

In dissolution controlled monolithic microsphere systems, the drug is dissolved in the matrix and is distributed uniformly throughout. The drug is strongly bound to the matrix and is released only on degradation of the matrix. The diffusion of the drug is slow compared with the degradation of the matrix. When degradation is by homogeneous bulk mechanism, drug release is slow initially and increases rapidly when rapid bulk degradation starts. Drug release from such type of devices is independent of the geometry of the device.

☐ Diffusion controlled monolithic systems

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Degeneration of the polymer matrix affects the rate of release and has to be taken into account. Rate of release also depends on whether the polymer degrades by homogeneous or heterogeneous mechanism.

☐ Diffusion controlled reservoir systems

Here the active agent is encapsulated by a rare controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix. Polymer that remains as such till the complete, release of drug and then degrades by homogenous mechanism so that the device is removed from the body is better for this type of delivery (Shah N. et al 2012).

CONCLUSION

Microcarriers as colon drug delivery system offer benefits of local and systemic effects. The main advantage of microcarriers as colon drug delivery system is that they have increase biocompatibility, higher stability and fewer side effects. The controlled release or delayed release can also be achieved by using microcarriers as colon drug delivery system. So microcarriers is an useful approach to be used for colon drug delivery.

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