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A REVIEW ON MICROPARTICULATE DRUG DELIVERY SYSTEM FOR COLON TARGETING

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ABSTRACT

Colon-specific drug delivery systems are desirable for the treatment of a range of local diseases such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, and colonic cancer. In addition, the colon can be a potential site for the systemic absorption of several drugs to treat non-colonic conditions. Drugs such as proteins and peptides that are known to degrade in the extreme gastric pH, if delivered to the colon intact, can be systemically absorbed by colonic mucosa. In order to achieve effective therapeutic outcomes, it is imperative that the designed delivery system specifically targets the drugs into the colon. Several formulation approaches have been explored in the development colon-targeted drug delivery systems. Microparticles 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 discussing in brief about introduction to colon targeted drug delivery, Microparticle as colon drug delivery system. Oral delivery is still the most favourable 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, microparticles, approaches, preparation of microparticles etc.

INTRODUCTION

In recent years, more attention has been paid on oral colon specific drug delivery system due to the advantages in improving local drug concentration, reducing dosage and side effects. Oral colon specific drug delivery system could enhance the systemic bio-availability of poor absorbed drugs as the long retention time in colon. The influencing factor of drugs for transiting through the colon mainly was the eating habits and gastric emptying rate, but the most important was associated with the size of dosage form in consideration of these advantages, various strategies and biomaterials have been investigated for oral colon specific delivery system, especially the natural biomaterials such as polysaccharides, alginates, which could be degraded by specific enzymes only present in the colon.[1] 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. 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.[2]

Need of Colon Targeted Drug Delivery[2]

- 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.

Drawbacks of Colon Targeted Drug Delivery[3]

The development of a colon-specific drug delivery system is associated with specific limitations and challenges. A predominant and an obvious challenge is the fact that the colon is located in the distal part of the gastrointestinal tract (GIT). An orally administered dosage form has to traverse the entire alimentary canal in order to reach the target site. The GIT physiology is complex and has a wide range of pH values, fluid volumes, and transit times. Moreover, the presence of food and metabolic enzymes also increases the physiological complexity. These factors are an obstacle to the reliable and efficient delivery of drugs to the colon. Another factor is the drug solubility. Due to a low colonic luminal fluid volume, higher viscosity, and a neutral pH, the solubilization of the drug could be a rate-limiting factor for colonic absorption. Finally, maintaining the stability of the drug in the colon can be a matter of concern. The non-specific interactions of the drug with the colonic content e.g., dietary residues, intestinal secretions, mucus, or fecal matter can have a negative influence on the stability of the drug. In addition, the colonic bacterial enzymes may also degrade the drug, rendering it ineffective.

Novel Approaches for Colon Targeting

Approaches used for colon targeting are

1) Primary approaches for CDDS
- pH sensitive polymer coated drug delivery to colon.
- Delayed (Time controlled release system) release drug delivery to colon.
- Microbially triggered drug delivery to colon.

2) Newly developed approaches for CDDS
- Pressure controlled drug delivery system (PCDCS).
- Osmotic controlled drug delivery to colon (OROS-CT).
- Novel colon targeted delivery system (CODESTM).

1. Primary approaches for CTDDS[4,5,6]

A. pH sensitive polymer coated drug delivery to colon[4]

In the stomach pH ranges between 1 and 2, during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6, in the descending colon 7.0. Use of pH-dependent polymers is based on these differences in pH levels. The polymers described as pH-dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH-dependent polymer can protect a formulation in the stomach and proximal small intestine.

B. Delayed (Time controlled release system) release drug delivery to colon[4]

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising. However due to potentially large variation of gastric emptying time of dosage forms in humans, in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonial availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 h (range 5 to 6 h).

C. Microbially triggered drug delivery to colon[5]

The various microflora of the colon are Bacteroides, Bifidobacterium, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcin, etc. This microflora of gut depends on fermentation of undigested materials in the small intestine for their energy requirements. The microflora performs fermentation by producing a large number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitro reductase, and deaminase and urea dehydroxylase. These biodegradable enzymes are capable of degrading the polymers used for targeting the drug delivery to colon. Different polymers are used for preventing the release of drug in the stomach and small intestine. When the coated formulations reach the intestine, the biodegradable polymers get degraded by the enzymes produced by the microbial flora and the drug gets released in the targeted region.

a. Prodrug approach for delivery to colon.
b. Polysaccharide based delivery system.

2. Newly developed approaches for CTDDS

A. Pressure controlled drug delivery system (PCDCS)[5]

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. (1995) have developed pressure-controlled colon-delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

B. Novel colon targeted delivery system (CODESTM)[6]

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilising a unique mechanism involving lactulose, which act as a

trigger for a site-specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble materials, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid soluble coating and subsequent drug release.

C. Osmotic controlled drug delivery (ORDS-CT)[4]

The OROS-CT can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach and hence no drug is delivered. As the unit enter the small intestine, the coating dissolve in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon.

Microparticulate Drug Delivery for Colon Targeting

Microparticles have turned out to be a promising approach as a targeted drug delivery system for the treatment of ulcerative colitis. The main aim for the targeted drug strategy is to target the maximum concentration of active agents in inflamed intestinal tissues by using selective delivery to achieve therapeutic efficacy while simultaneously reducing adverse effects. In addition to this, such targeted delivery system must meet the conditions for complete biodegradation and high biocompatibility without pro-inflammatory properties. Controlled release drug delivery system is one of the most efficient methods to overcome most of the difficulties associated with other methods of administration. Controlled release drug delivery includes carriers such as polymer-based disks, microparticles, nanoparticles, pellets in which drug gets encapsulated and release at controlled rates for relatively long periods of time. Such kind of systems often shows several advantages over other methods of administration.[7] The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulations and yet devoid of the danger of alteration in drug release profile and formulation behaviour due to unit to unit variation, change in gastro luminal pH and enzyme population. In the treatment of IBD, sustained release devices like pellets, capsules or tablets have less efficiency due to diarrhoea, a symptom of IBD that enhances their elimination and reduces the total time available for drug release. It has been shown that drug carrier systems with a size larger than 200μm would be subjected to speedy bowel evacuation due to diarrhoea, resulting in a decreased GI transit time and decreased efficiency. Therefore, a multiparticulate system in the micron size range could be a useful option in the design of a suitable dosage form for IBD.[8]

METHODS OF PREPARATION

1. Single emulsion technique
2. Double emulsion technique
3. Polymerization

a) Normal polymerization
b) Inter-facial polymerization

4. Phase separation coacervation technique
5. Spray drying
6. Solvent extraction
7. Solvent-diffusion method
8. Hot-melt method

1. Single emulsion Technique[9]

The microparticulate carriers of natural polymers, i.e. proteins and carbohydrates are prepared by single emulsion technique. In the 1st step, natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium. Ex: chloroform/oil. In the 2nd step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. The chemical cross-linking agents used are formaldehyde, butanol, glutaraldehyde, diacid chloride, terephthalate chloride, etc. Crosslinking by heat is affected by adding the dispersion to previously heated oil. However, cross linking by heat is not suitable for the thermo labile drugs. The chemical cross-linking method has an inherent disadvantage of excessive exposure of active ingredient to chemicals, if added at the time of preparation.

2. Double emulsion technique[10]

It is formation of multiple emulsions i.e. W/O/W is preparing by pouring the primary w/o emulsion into aqueous solution of poly vinyl alcohol. This w/o/w emulsion put a t constant stirring for 30 min. Slowly add some water to the emulsion over a period of 30 min. collect Microcapsules by filtration and dry under vacuum. It is best suited to water soluble drugs, peptides, proteins and the vaccines. Natural as well as synthetic polymer can use for this method. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. Disperse in oil/organic phase

homogenization /vigorous i.e. formation of first emulsion then addition to aqueous solution of PVA (Poly Vinyl Alcohol) i.e. multiple emulsion formed now by addition to large aqueous phase denaturation/hardening after this separation, washings' and drying and collection of microspheres genistein chitosan microsphere were prepared by the o/w/o multiple emulsion method.

3. Polymerization technique[10]

a. Normal polymerization
b. Interfacial polymerization

Normal polymerization. In bulk polymerization, a monomer or a mixture of number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to dissipate the heat of reaction which affects the thermo labile active ingredients. Suspension polymerization is carried out of lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with active drug as droplets dispersion in continuous aqueous phase. Microsphere size obtained by suspension techniques is less than the 100µm. Emulsion polymerization is differed from the suspension as due presence of initiator in aqueous phase but is also carried out at low temperature as suspension external phase normally water in last two techniques so through which heat can easily dissipate. formation of higher polymer at faster rate is possible by these techniques but association of polymer with the un reacted monomer and other additives can occur.

Interfacial polymerization. It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolved in continuous phase while other is disperse in continuous phase (aqueous in nature) throughout which the second monomer is emulsified. Two conditions arise because of solubility of formed polymer in the emulsion droplet. That is formation is monolithic type of carrier if the polymer is soluble in droplet. Capsular type formed if the polymer is insoluble in droplet.

4. Phase separation coacervation technique[9]

It is the simple separation of a micromolecular solution into two immiscible liquid phases. In this process, the polymer is solubilized into a solution. This process is designed for preparing the reservoir type system e.g. encapsulation of water-soluble drugs i.e. peptides and proteins etc. Microparticles can be prepared using the following steps with continuous agitation. The 1st step consists of formation of three immiscible chemical phases. In this method, the core material is dispersed in solution of coating polymer and further step involves deposition of coating polymer on core material, which takes place at interphase between core material and liquid vehicle phase. The final step comprises of rigidising the coating by thermal, desolvation (or) cross linking techniques to form microparticles.

5. Spray drying[11]

This was used to prepare polymeric blended microparticle loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly and cellulose acetate butyrate, in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may lose crystallinity due to fast drying process.

6. Solvent extraction[10]

In this method preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. Isopropanol can be use as water miscible organic solvents. By extraction with water, Organic phase is removed. Hardening time of microsphere can be decrease by this method. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

7. Solvent diffusion method[11]

In order to improve the residence time in colon floating microparticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus, the formed floating microspheres were washed and dried in a desiccator at room temperature. The following microparticles were sieved and collected.

8. Hot melt method[10]

In this technique polymer is disperse in suitable dispersion medium and slowly cooled to form the microspheres. The polymers which having low melting point fabricated into microspheres by this technique easily. For coating and coring of particle wax is use mostly. In which encapsulate the drug by dispersion in the melted wax. The wax suspension is dispersed by high speed mixing into cold solution for example liquid paraffin. Agitate the mixture for one hour. Then decanted the external phase and suspended microspheres collect from solvent. And allow drying it in air. It is inexpensive method as comparison to others and drug release is more rapid. Mostly Carnauba wax and beeswax can be used as the coating materials and these can be mixed in order to achieve desired characteristics.

Recently Reported Drugs for Colon Targeting

AUTHOR	DRUG	METHODS	REMARKS
Garud A *et al* (2013)	Mesalamine	Ionic gelation method	Encapsulation efficiency of micro-spheres was good for all formulations.[13]
Pandya HV *et al* (2012)	trihexyphenidyl hydrochloride	Solvent evaporation method	The solvent-evaporation method using Eudragit polymers at optimum levels was effective for the formation of Trihexyphenidyl microcapsules.[14]
Deore KL *et al* (2013)	tinidazole	emulsification solvent evaporation method	Eudragit based tinidazole microspheres are a potential system for colon delivery of tinidazole for chemotherapy of amoebic infection.[15]
Ramteke KH *et al* (2014)	Pectin-bora rice	Ionotropic gelation technique	Bora rice is potential polysaccharide for colon targeted drug delivery system.[16]
Kshirsagar SJ *et al* (2012)	prednisolone	Nanoprecipitation method	PD is the targeted drug to the colon and may provide effective way of treatment of colonic disease.[17]
Dangi AA *et al* (2013)	Levetiracetam	wet granulation technique	the designed formulation could be used potentially for colon delivery by controlling drug release in stomach and the small intestine.[18]
Swapna A *et al* (2011)	Mesalamine	Emulsion solvent evaporation method	Mesalamine microspheres are promising controlled release carriers for colon-targeted drug delivery.[19]
Verma S *et al* (2011)	Prednisolone	Kneading method	The formulations containing PEG was found to be a promising drug delivery system better release kinetics.[20]
Kumar M *et al* (2015)	metronidazole	emulsification-solvent evaporation method	the developed microspheres could enhance drug entrapment, and inflect the drug release.[21]
Rangari Nt *et al* (2017)	Ciprofloxacin	extrusion-spheronization method	animals treated with this formulation had an improvement in pathology and may be useful for the treatment of inflammatory bowel disease and colon cancer.[22]
Karnakar N *et al* (2017)	Metronidazole	Wet granulation	The formulation reached ascending colon within 6 hour and it was disintegrated after 10 hours.[23]
Chandra s *et al* (2020)	prednisolone	Wet granulation	The prednisolone showed good bioavailability of drug release for F6 at 8.5 hrs.[24]
Suthar D *et al* (2016)	Mesalamine	Spray drying	The system was able to release the drug specifically in the colon over a specific period of time in the variable conditions IBD.[25]
Elkhodairy KA *et al* (2013)	Indomethacin	solid dispersion	the drug release in the colon will be increased in the presence of the rat cecal content.[26]
Pasupathi A *et al* (2013)	Budesonide	Enteric coating method	Prepared formulation of Budesonide capsule was found to be stable.[27]

Application of Microparticles[12]

- **Treatment of cancer:** Many types of treatment exist for cancer, including surgery, standard chemotherapy, radiation therapy, immunotherapy, and targeted therapy. The treatment to be given depends on the specific type of cancer and how advanced it is. Very rarely, one can find monotherapy to be the mainstay for cancer because combinational treatments have advantages. However, the side effects of anticancer drugs limit the use of several standard chemotherapeutics. For example, cardiotoxicity and nephrotoxicity are associated with conventional chemotherapeutics such as doxorubicin and cisplatin respectively**.**
- **Treatment of diabetes:** Diabetes is a chronic disease of major global concern. It is forecasted that, in the future, developing countries will lead the world in diabetic prevalence and India hosts numerous diabetics. Despite several treatment strategies existing for diabetes, the last chance for saving lives if other treatments fail is pancreatic or islet transplantation. MDDS, particularly in diabetes, has gained huge attention because repeated dose administration is avoided, thus preventing the trauma, pain, and injury associated with insult; this method also sustains drug release and enhances therapeutic efficacy.
- **To treat cardiovascular diseases:** Heart-related disorders, including ischemia, myocardial infarction, atherosclerosis, and hypertension, are life-threatening conditions occurring mostly in developed and developing countries and novel therapies are always welcome. For the myocardial infarction, growth factors in a preclinical state of research were found to promising, but their

efficacy was not consistent in clinical trials. The failure of growth factors in clinical trials can be ascribed to their instability and short life span. To prevent this, stable, highly concentrated growth factors must be administered and this can be feasible using a controlled drug delivery system.

- **To treat neurological disorders:** Achieving efficacy of a drug in the central nervous system is a challenging prospect for neurologists because of the lack of efficient permeability properties that makes it incapable of crossing the BBB. However, new strategies have emerged to deliver drugs directly into the central nervous system. For the first time in the 1960s, it was reported by Folkman and Long that digoxin was delivered in to the myocardium via an implant formulation of a silicone rubber device using a polymeric carrier. Then, several studies were performed using different formulation approaches in treating neurologic disorders in which implants of the desired drug were administered surgically.
- **Vaccine delivery:** Multiple strategies to boost immunological responses include reducing organ rejection reactions, encouraging potent vaccine delivery systems, and targeting specific antigens using gene delivery without any alterations in the native protein structure. Repetitive immunization is essential to produce safe and effective protection from infectious diseases. To address these issues, polymeric microparticles loaded with adjuvants and antigens against pathogens are gaining significance with enhanced immune response achieved with controlled release pattern.
- **Ocular delivery:** Ocular drug delivery is an exciting approach to treat eye-related disorders. Limitations pertaining to ocular delivery of drugs include lachrymal drainage and irritation that cause damage to the eye and sometimes may result in loss of vision. Due to lachrymal drainage, the residence time of drug in the eye is short and penetration into the cornea is low, at about 1–3% of the dose administered. For this reason, drug to corneal contact should be prolonged for therapeutic efficacy and, to fulfil this criterion, polymers can be used. Polymers should be bio adhesive, no irritating, and nontoxic.
- **Pulmonary delivery:** The delivery of drugs via the pulmonary route is associated with promising benefits compared with other conventional administration routes because of its large surface area, high permeability and vascularization, and the negligible thickness of the blood–alveolar barrier. Pulmonary delivery is mostly preferred and considered as effective in delivering potent drugs to treat respiratory diseases, including chronic obstructive pulmonary disease, pneumonia, tuberculosis, and cystic fibrosis. In addition to targeting respiratory disorders, the pulmonary route is also used to deliver drugs with poor oral bioavailability and to enhance systemic effects of drugs.

CONCLUSION

Several formulation approaches have been explored in the development colon-targeted drug delivery systems. Microparticles 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.

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