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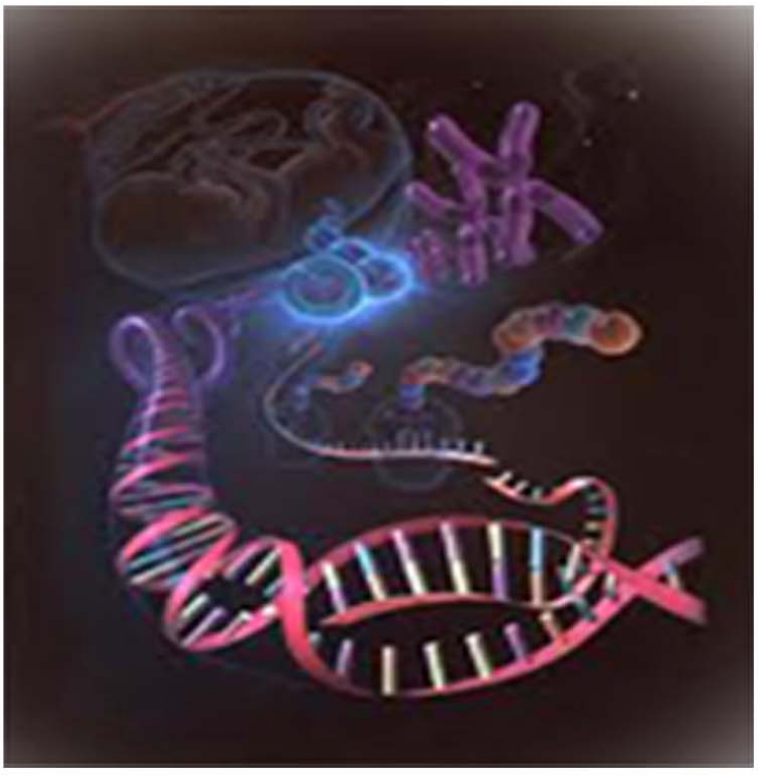

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Review Article

ORAL MICRO-PARTICULATE COLON TARGETED DRUG DELIVERY SYSTEM FOR THE TREATMENT OF CROHN'S DISEASE: A REVIEW

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Crohn's disease is thought to be an autoimmune disease, in which the body's immune system attacks the gastrointestinal tract, causing inflammation, it is classified as a type of inflammatory bowel disease. The microspheres carrier for the delivery of the dosage form to the colon is composed of physiological and biodegradable natural polysaccharides and which in turn cause low systemic toxicity, low cytotoxicity and lesser side effects. Most of the polysaccharides used in the processing of pharmaceutical formulations have an approved status of generally accepted as safe which includes accepted food additives for human use or as excipients in various dosage forms. Their natural behaviour to release the entrapped drug moiety at neutral or slightly alkaline pH can enhance the absorption of the drug from the colon which has made them popular as a drug carrier to the colon. Furthermore, they provide the possibility to supply the active drug over a prolonged period of time and the microbial flora present in the colon can initiate the drug release from the delivery system containing polysaccharides. The colonic bacteria are predominantly anaerobic in nature and secrete enzymes that are capable of metabolizing both endogenous and exogenous substrates that escape digestion in the upper gastro intestinal tract. The microspheres when formulated into tablets and coated with pH sensitive enteric coated polymers avoid the problem of degradation of the drug by the gastric pH. Thus when the tablet enters into the small intestine the pH sensitive enteric coating does not dissolve completely at the pH of the small intestine (5.5-6.4). However, when the tablets reach the colonic region of the gastro intestinal tract the pH sensitive enteric coating dissolves at the pH of the colon (6.4-7.0) releasing the microspheres compressed tablets at the colon.

Keywords: Crohn's disease, Microspheres, Polysaccharides, Colonic microbial flora, Enteric polymers

INTRODUCTION

Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs which are degraded by digestive enzymes of stomach and small intestine but also for the delivery of low molecular weight compounds used

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to treat diseases associated with the colon or large intestine such as crohn's disease, ulcerative colitis, diarrhoea, and colon cancer. In addition, the colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. Drugs, which are destroyed by the stomach acid and / or metabolized by pancreatic enzymes, are slightly affected in the colon, and sustained colonic release of drugs can be achieved. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of drugs and colonic diagnostic agents require smaller doses.

CROHN'S DISEASE

Crohn's disease, also known as inflammatory bowel disease (IBD), or Granulomatous ileocolitis disease is an inflammatory disease of the intestines, causing a wide variety of symptoms. It primarily causes abdominal pain, diarrhea which may be bloody if inflammation is at its worst, vomiting, or weight loss (Baumgart *et al*., 2007), but may also cause complications outside of the gastrointestinal tract such as skin rashes, arthritis, inflammation of the eye, tiredness, and lack of concentration. There has been evidence of a genetic link to Crohn's disease, putting individuals with siblings afflicted with the disease at higher risk (Barrett, JC *et al*., 2008) males and females are equally affected. Smokers are two times more likely to develop Crohn's disease (Cosnes et. al., 2004). Crohn's disease affects between 4 lakhs to 6 lakhs peoples in North America. It tends to present initially in the teens and twenties, with another peak incidence in the fifties to seventies, although the disease can occur at any age.

CLASSIFICATION

Crohn's disease typically manifests in the gastrointestinal tract and can be categorized by the specific tract region affected. A disease of both the ileum (the last part of the small intestine, which connects to the large intestine) and the large intestine, Ileocolic Crohn's accounts for fifty percent of cases. Crohn's ileitis, manifest in the ileum only, accounts for thirty percent of cases, while Crohn's colitis, of the large intestine, accounts for the remaining twenty percent of cases and may be particularly difficult to distinguish from ulcerative colitis. Gastroduodenal Crohn's disease causes inflammation in the stomach and first part of the small intestine, called the duodenum. Jejunoileitis causes spotty patches of inflammation in the top half of the small intestine, called the jejunum.

Crohn's disease may also be categorized by the behavior of disease as it progresses. There are three categories of disease presentation in Crohn's disease: stricturing, penetrating, and inflammatory. Stricturing disease causes narrowing of the bowel that may lead to bowel obstruction or changes in the caliber of the feces. Penetrating disease creates abnormal passageways (fistulae) between the bowel and other structures, such as the skin. Inflammatory disease (or nonstricturing, nonpenetrating disease) causes inflammation without causing strictures or fistulae.

CAUSE

Although the exact cause of Crohn's disease is still unknown, a combination of environmental factors and genetic predisposition seems to cause the disease (Braat *et al*., 2006). The genetic risk factors have now more or less been comprehensively elucidated, making Crohn's

disease the first genetically complex disease of which the genetic background has been resolved. Broadly speaking, the genetic data indicate that innate immune systems in patients with Crohn's disease malfunction, and direct assessment of patient immunity confirms this notion (Henckaerts *et al*., 2008). This had led to the notion that Crohn's disease should be viewed as innate immune deficiency, chronic inflammation being caused by adaptive immunity trying to compensate for the reduced function of the innate immune system.

PATHOPHYSIOLOGY

During a colonoscopy, biopsies of the colon are often taken in order to confirm the diagnosis. Crohn's disease shows a transmural pattern of inflammation, meaning that the inflammation may span the entire depth of the intestinal wall. Grossly, ulceration is an outcome seen in highly active disease. There is usually an abrupt transition between unaffected tissue and the ulcer. Under a microscope, biopsies of the affected colon may show mucosal inflammation. This inflammation is characterized by focal infiltration of neutrophils, a type of inflammatory cell, into the epithelium. This typically occurs in the area overlying lymphoid aggregates. These neutrophils, along with mononuclear cells, may infiltrate into the crypts leading to inflammation known as crypititis or abscess known as crypt abscess. Granulomas, aggregates of macrophage derivatives known as giant cells, are found in 50% of cases and are most specific for Crohn's disease. The granulomas of Crohn's disease do not show "caseation", a cheese-like appearance on microscopic examination that is characteristic of granulomas associated with infections such as tuberculosis. Biopsies may also show chronic mucosal damage as evidenced by blunting of the intestinal villi, atypical branching of the crypts, and change in the tissue type known as metaplasia. One example of such metaplasia, Paneth cell metaplasia, involves development of Paneth cells typically found in the small intestine in other parts of the gastrointestinal system (Crawford *et al*., 1994).

MICROSPHERES AS DRUG CARRIERS

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. It has a particle size of (1-1000nm). Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.

DRUG DELIVERY TO COLON

The challenge of targeting drugs specifically to the colonic region of the GIT (gastrointestinal tract) is one that has been embraced by scientists over the last two decades. The colon has recently

become accepted as an increasingly important site for drug delivery (Ibekwe *et al*., 2004). Colonic drug delivery is required to protect a drug during its transit through the upper GIT and allow its release in colon (Marianne *et al*., 1994).

Research interest in the area of colonic drug delivery has been fuelled by the need to better treat the pathologies of the colon that range in seriousness from constipation and diarrhoea to inflammatory bowel disease (ulcerative colitis and crohn's disease) through to colon carcinoma, the third most relevant form of cancer in both man and women. Most of the approaches (Table 1) developed for targeted colonic drug delivery utilize the physiological properties of the GIT and colon such as pH of the GIT, transit time of the small intestine, luminal pressure of the colon.

The coating with pH-sensitive polymers systems exploit the generally accepted view that the pH of the human GIT increases progressively from stomach (pH 1.5-3.5 which increases to 4 during digestion), small intestine (5.5-6.8) at the site of digestion, and in colon (6.8-7.0). The coating of pH sensitive polymers applied to the tablets, capsules, pellets or microspheres provide a delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems.

Colon targeted drug delivery systems based on methacrylic resins has been described for insulin, prednisolone, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate, and naproxen (Touitou et at., 1986), (Kim *et al*., 2001).

Formulation developement of multiunit dosage form containing 5-ASA for the treatment of ulcerative colitis. Pellets were prepared by granulation and spheronization process and then coated with a new pH sensitive copolymer Eudragit FS 30D to achieve site specific drug release to the ileocaecal valve. From the dissolution studies it was concluded that pellets released rapidly at pH value above 7.5. Between 6.8 and 7.2 drug releases was found to be zero

Table 1: Approaches for Colonic Drug Targeting

Colon Targeting Approach	Features
pH sensitive polymers coating	Formulation coated with enteric polymers (methylmethaacrylate copolymers) release the drug when formulation reaches down towards the alkaline pH range in the intestine
Biodegradable polymers coating	Degradation of the polymer due to the action of the colonic bacteria releases the drug
Biodegradable matrices and Hydrogels	Drug is released by the swelling and/or erosion of the polymer and by the biodegradable action of the polysaccharide
pH sensitive matrices	Drug released by the degradation of the pH sensitive polymer in the GIT
Bioadhesive systems	Formulation coated with bioadhesive polymers that selectively provides adhesion to the colonic mucosa release the drug in the colon
Osmotic controlled drug delivery	Drug releases through semi-permeable membrane after a lag time due to osmotic pressure build up
Timed released systems	Formulation is designed such that the drug releases after a lag time of 3-5 h that is equivalent to small intestinal transit time

order, while at pH 6.5 and below no release occurred.

The formulation of lactose based placebo tablets and coated using various combinations of two methacrylic acid copolymers, Eudragit L100-55 and Eudragit S100 by spraying from aqueous systems (Khan et. al., 1999). The Eudragit L100-55 and Eudragit S100 combinations were 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5 and 0:1. The coated tablets were tested in vitro for their suitability as pH dependent colon targeted oral drug delivery. The same coating formulations were then applied to tablets containing mesalazine as a model drug and evaluated for in vitro dissolution rates under various conditions. Dissolution data further confirmed that the release profiles of the drug could be manipulated by changing the Eudragit L100-55 and Eudragit S100 ratios within the pH range of 5.5 to 7.0 in which the individual polymers were soluble respectively, and a coating formulation consisting of a combination of two polymers can overcome the issue of high GI pH variability among individuals for successful development of colon targeted drug delivery systems.

The comparison of insulin delivery of two formulation containing Eudragit L100 and Eudragit LS respectively (Morishita *et al*., 1993). Formulation containing Eudragit S showed optimal delivery of insulin in the ileum at pH 7.

The GI residence time of the dosage form is another important parameter for pH dependent colon targeted drug delivery systems which is influenced by many physiological and other factors (Khan *et al*., 1996) nevertheless there are some generally accepted GI residence values for different parts of GIT (Ashford *et al*., 1993). Most commonly used pH dependent coating polymers are methacrylic acid copolymers commonly known as Eudragit L and Eudragit S.

Polysaccharide Carriers for Colonic Drug Delivery

Since last decade a novel oral colon specific drug delivery system (CDDS) has been developing as one of the site specific drug delivery system (Salunkhe *et al*., 2008).

To overcome the toxicity concerns of synthetic polymers (azo polymers), natural polymers especially glycosidic bond containing materials offer a viable alternative for colonic drug delivery. The glycosidic bond containing polymers includes diasaccharides, oligosaccharides and polysaccharides.

Polysaccharides naturally occurring in the plant (e.g. pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g. alginates) or microbial (e.g., dextran) origins are generally used for colon targeting of various drugs.

Although specifically degraded in the colon, many of these polymers are hydrophilic in nature and swell under exposer to upper GIT conditions, which leads to premature drug release. To overcome these problems the natural polysaccharides are chemically modified and mixed with hydrophobic water insoluble polymer, whereas in the case of formulations they are usually covered with pH sensitive polymer. Enteric coating is another formulation approach used to prevent the rapid swelling or disintegration of polysaccharide based formulations in the upper GIT (Kopecek *et al*., 1992). Successful colonic delivery requires careful consideration of a number of factors including the properties of drug, the type of delivery system and its interaction with the healthy or diseased gut.

The polysaccharide which is polymer of monosaccharide retains their integrity, because they are resistant to digestive action of GI enzymes, matririces of polysachharide are assessed to remain intact in physiological environment of stomach and small intestine, as they reach colon they are acted upon bacterial polysaccharidases and results in degradation of the matrixes. Family of natural polysaccharide has appeal to area of drug delivery as it comprised of polymer with large number of derivitizable groups, with wide range of molecular weight, varying chemical composition and form most low toxicity and biodegradability, yet a high stability (Table 2).

Pectin is a polysaccharide which contain α-1,4 D-galactouronic acid and 1,2 D-rhamnose with D-galactose and D-arabinose side chains. A novel colonic drug delivery was investigated and the *In-vitro* experiments demonstrated that high methoxy pectin, when applied as compression coat, proved capable of coat tablet during condition stimulating gastrointestinal environment and was susceptible to enzymatic attack. *In-vivo* gamma scintigraphic studies confirmed the in-vitro findings the pectin coating tablets indicate that disintegrating in the colonic region, and illustrated that degradation by microflora, thus necessities in the development of such derivatives of pectin which is less water soluble, Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of Indomethacin (Rubeinstein *et al*., 1993).

Table 2: Characteristics of Various Biodegradable Polysaccharides for Colon Targeted Delivery

Polysaccharide	Chemical name	General properties	Bacterial species
Amylose	α-1,4 D-glucose	Unbranched constituents of starch used as excipients in tablets formulation	Bacteriods, Bifidobacterium
Arabinogalactone	β-1,4 and β-1,3 D-galactose, β-1,6 and β-, 3 D-arabinose and D-galactose	Natural pectin, hemicelluloses used as thickening agents	Bifidobacterium
Chitosan	Deacetylated β-1,4 N-acetyl D-glycosamine	Deacetylated chitin used as absorption enhancing agents	Bacteroids
Chondroitinsulfate	B-1,3, D-glucoronic acid and N-acetyl D-glycosamine	Mucosopolysaccharides contains sulphate ester group at 4 or 6 position	Bacteroids
Cyclodextran	α-1,4 D-glucose	Cyclic structure of 6, 7 or 8 units, high stability against Amylase, used as drug solubilising agent and absorption enhancer	Bacteroids
Dextran	α-1,6 D-glucose α-1,3 D-glucose	Plasma expanders	Bacteroids
Guar gum	α-1,4 D-mannose α-1,4 D-galactose	Galactomannan used as thickening agents	BacteroidsRuminococcus
Pectin	α-1,4 D-galactouronic acid and 1,2 D- rhamnose with D-galactose and D-arabinose side chains	Partial methyl ether commonly used as thickening agents	Bacteriods, Eubacterium Bifidobacterium
Xylan	α-1,4 D-xylose with α-1,3 L-arabinose side chains	Abundant hemicelluloses of plant cell wall	Bacteriods, Bifidobacterium

The use of pectinolytic enzymes to stimulate breakdown in colon showed that pectin/chitosan mixture was susceptible to enzymatic breakdown and releasing its content. A study was carried out to access the potential pectin: chitosan films for colonic delivery and found that pectin alone was able to protect the premature release, but only when a substantially thick coat was provided.

Pectin and HPMC compressed core tablets of 5- ASA for colon delivery, Drug dissolution/ system erosion/ Degradation studies were carried out in pH 1.2 and 6.4 buffers using pectinolytic enzymes, system was designed that transit time from the GI tract and arrival time for colon is 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the stability of pectin. The optimum concentration of 20% HPMC was preferred for 6h that corresponds to 25-30% erosion and after that the influence of the pectinase system degrade faster and release 5-ASA to the colon.

The preparation and demonstration of the efficacy of chitosan microcores entrapped within acrylic microspheres containing diclofenac sodium as model drug (Lorenzo *et al*., 1998). The drug was efficiently entrapped within the chitosan microspheres using spray drying and then microencapsulated into Eudragit L100 and Eudragit S100 using oil in oil solvent evaporation method. Numerous Eudragit coated oral dosage forms for targeting colon are recently in use for treatment of ulcerative colitis.

The microparticulate system consisted of Budesonide containing hydrophobic cores, microencapsulated within an enteric polymer was prepared (Rodringuez *et al*., 1998) which solubilizes at above pH 7, thus providing pH sensitive and controlled release properties.

CONCLUSION

The development of oral micro-particulate colon targeted drug delivery system for delivering the drug at the targeted site i.e. colon for treatment of Crohn's disease will help to improve the bioavailability and reduce the frequency of doses of the drug which would be a very worthy approach considering the prevalence of the disease in India and around the world.

As an oral drug delivery system, micro-particulate carriers possess many obvious advantages. It is assumed that these carriers when administered in small quantities would cause fewer side effects, if any, than the conventional formulations. The high specific area of the micro-particles facilitates better absorption of encapsulated drugs into the body.

Thus such latest developments of innovative micro-structured carriers for oral delivery of the drug to the colon for treatment of inflammatory bowel disease (crohn's disease) can be achieved. The advantages in terms of overall cost reduction, convenience and improved quality of treatment are evident. It is certainly a unique and industry feasible approach to overcome the problem of low oral bioavailability associated with many drugs for colon targeting. Development of such formulation technology will have tremendous commercial potential and significant contribution to the field of novel drug delivery systems.

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REFERENCES

1. Ashford M, Fell J T, Attwood D, Sharma H and Woodhead P J (1993), "An in vitro

investigation into the suitability of pH-dependent polymers for colonic targeting", *Int. J. Pharm*, Vol. 94, pp. 193-199.

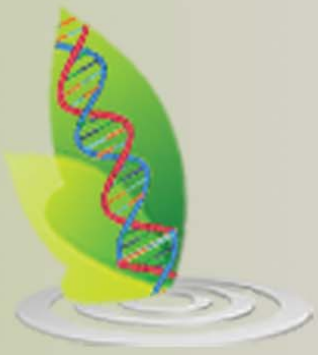
2. Barrett J C, Hansoul S, Nicolae D L Cho J H *et al*., (2008), "Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease", *Nature Genetics*, Vol. 40, No. 8, pp. 955-962.
3. Baumgart D C and Sandborn W J (2007), "Inflammatory bowel disease: clinical aspects and established and evolving therapies", *The Lancet*, pp. 1641–1657.
4. Braat H Peppelenbosch M P and Hommes D W (2006), "Immunology of Crohn's disease". *Ann. N. Y. Acad. Sci*, pp. 135–54.
5. Cosnes J (2004), "Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice", *Best Pract Res Clin Gastroenterol*, Vol. 18, No. 3, pp. 481–96.
6. Crawford J M (1994), "The Gastrointestinal tract, Chapter 17", In Cotran RS, Kumar V, Robbins SL. Robbins Pathologic Basis of Disease: 5th Edition. W.B. Saunders and Company, Philadelphia.
7. Henckaerts L, Figueroa C, Vermeire S and Sans M (2008), "The role of genetics in inflammatory bowel disease", *Curr Drug Targets,* Vol. 9, No. 5, pp. 361-368.
8. Ibekwe C Valentine, Kendail A Richard and Basit W Abdil (2004), "Drug delivery to colon, The drug delivery companies report spring/ summer", *Pharma Ventures Ltd*.
9. J Kopecek, P kopeckova, H Bronsted, T Rathi, B Rihova, P Y Yeh, K Ike Sue (1992), Polymers of Colon Specific Drug Delivery, *J. Control. Rel*., Vol. 19, pp. 121-130.
10. Kim C K, Shin H J, Yung S G, Kim J H and Oh Y (2001), "Once a day oral dosage regimen of cyclosporine. A combined therapy of cyclosporine a premicroemulsion concentrates and enteric coated solid state premicroemulsion concentrates", *Pharm Res,* Vol. 18, pp. 454-459.
11. Khan M Z I (1996), "Dissolution testing for sustained or controlled release dosage forms and correlation with in vivo data; challenges and opportunities", *Int. J. Pharm*, pp. 141-143.
12. Khan M Z, Prebeg Z and Kurjakovic N (1999), "A pH dependent oral drug delivery system using methacrylic acid copolymers. Manipulation of drug release using Eudragit L100-55 and Eudragit S100 combinations", *J. Contol. Rel.,* Vol. 58, pp. 215-222.
13. K S Salunkhe and M V Kulkarni (2008). "Formulation and in vitro evaluation of dextrin matrix tablet of Ibuprofen for colon specific drug delivery", *Pak. J. Pharm. Sci*, Vol. 21, No. 1, pp. 17-20.
14. Lorenzo-Lamosa M L, Remunan-Lopez C, Vila-Jato J L and Alonso M J (1998), "Design of microencapsulated chitin microspheres for colonic drug delivery", *J. Control. Rel.,* Vol. 52, pp. 109-118.
15. Marianne Ashford, John Fell, David Attwood and Harbans Sharma (1994), "Studies on pectin formulations for colonic drug delivery", *J. Control Rel.,* Vol. 30, pp. 225-232.
16. Morishita I, Morishita M, Takayama K, Machida Y and Nagai T (1993), "Enteral insulin delivery by microspheres in three

different formulations using Eudragit L100 and S100", *Int. J. Pharm,* Vol. 91, pp. 29-37.

17. Rodriguez M, Vila-Jato J L and Torres D (1998), "Design of a new multi particulate system for potential site-specific and controlled release drug delivery to colon region", *J. Control. Rel.,* Vol. 55, pp. 67-77.

18. Rubinstein A, Radai R, Ezra M, Pathak S, Rokem J M (1993), "In vitro evaluation of calcium pectinate: A potential colon-specific drug delivery carrier", *Pharm Res*, Vol. 10, pp. 258.

19. Touitou E and rubinsstein A (1986), "Targeted eternal delivery of insulin to rats", *Int. J. Pharm*, Vol. 30, pp. 95-99.



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