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A REVIEW ON COLON TARGETED DRUG DELIVERY: AN INNOVATIVE APPROACH

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ABSTRACT

Day by day there are new developments in the field of colon specific drug delivery system. Lot of research is undergoing in colon specific drug delivery as this route is not only useful for targeting the drugs required in the treatment of diseases associated with colon like Crohn's disease, ulcerative colitis, etc., but also as a potential site for the local and systemic delivery of peptide and proteins and other therapeutic drugs anti-asthmatic drugs, antihypertensive drugs (Isosorbide, Cyclosporine, Desmopressin) and anti-diabetic agents. The colon is the terminal part of the GIT which has gained increased importance not just for the delivery of the drugs for both local and systemic administration. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon and that system refers to delivery of drug in to lower part of the GI tract, mainly large intestine. When this is the most important delivery of those drug which are normally inactivated in the upper parts of the gastrointestinal tract (GIT). To achieve the maximum site specific and time dependent delivery of drugs to colon, combinations of two or more approaches are preferred over individual approaches. Because of limited success of primary approaches newly developed approaches are preferred.

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INTRODUCTION

The major goal of any drug delivery system is to supply a therapeutic amount of drug to a target site in a body so that highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs[1,2]. Targeted drug delivery may provide maximum therapeutic activity by preventing degradation or inactivation of drug during transit to the target site. Meanwhile, it can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. An ideal targeted delivery system should be nontoxic, biocompatible, and biodegradable and physic chemically stable in vivo and in vitro. The preparation of the delivery system must be reasonably simple, reproducible and cost-effective. The targeted drug delivery is dependent on the identification and exploitation of a attribute that is specific to the target organ[3]. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes,
(ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability[4].

CDDS has been employ to achieve following objectives[5]

1. It should be sustained delivery to reduce dosing frequency.
2. It should be Delay delivery of drug to achieve high Concentration in treatment of disease of distal gut.
3. It should be to delay than in upper GIT, which is the limiting factor for poorly soluble drugs.
4. It should be deliver drug to that region that is less hostile metabolically, drug.
5. This is acid and enzyme labile such as proteins.

Benefit of CSDD [6]

1.Target drug delivery
2.Decrease in dose to be administered
3.Decreased side effects
4.Improved drug utilization
5.It is a promising site for a drug which is unstable or poorly absorbed from upper GI tract.

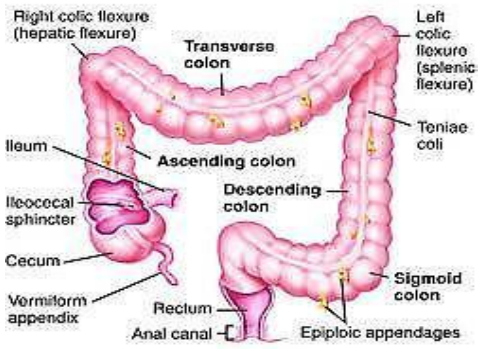

FIG 1: ANATOMY OF COLON.

Advantages[7]

1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.
2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration. Hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs.

Disadvantages of Colonic Drug Delivery [8,9]

1. There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired CSDDS site. The pattern of drug release may differ from person to person which may cause ineffective therapy.
2. The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.
3. The major disadvantage of colonic delivery of drug is poor site specificity.
4. Diet and diseases can affect colonic microflora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In disease conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
5. Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.
6. Substantial variation in gastric retention time may cause drug release at the undesired site in case of time dependent colonic drug delivery system.
7. Lack of manufacturing Reproducibility and efficacy
8. Need of advanced technology.
9. Low dose loading and Higher need of excipients.

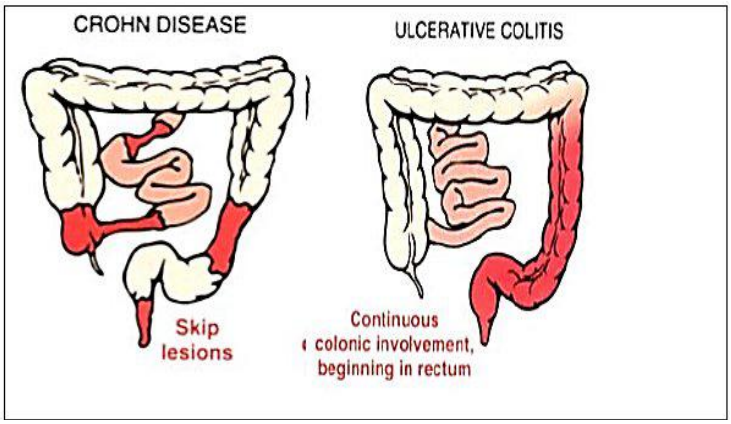

FIG2: LOCATION OF INFLAMMATORY BOWEL DISEASE.

Criteria for Selection of Drug for CDDS

The best candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhea and colon cancer is ideal candidates for local colon delivery. Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drug depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems[10].

Need of Colon Targeted Drug Delivery [11]

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
2. 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.
3. 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 (targeted).
4. 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.
5. 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.

APPROACHES FOR COLON TARGETED DRUG DELIVERY[12]

1. Primary approaches for colon targeted drug delivery

a. pH sensitive polymer coated drug delivery system
b. Delayed release drug delivery system
c. Microbially triggered drug delivery
i. Prodrug approach
ii. Polysaccharide based system

2. New approaches for colon targeted drug delivery
a. Pressure controlled drug delivery system (PCDDDS)
b. Pulsatile
i. Pulsincap system
ii. Port system
c. Azo hydrogels
d. Multiparticulate system based drug delivery
e. CODE
f. Osmotic controlled drug delivery system (OROS-CT)

I. PRIMARY APPROACHES FOR CDDS

a. pH Sensitive Polymer Coated Drug Delivery to the Colon

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 [13].

From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers[14].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, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations[15].

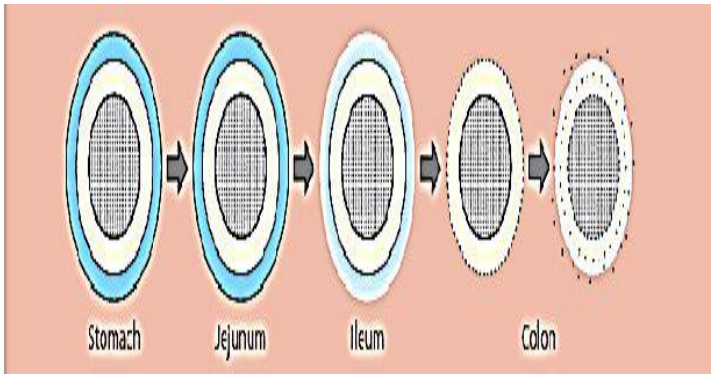

Fig 3: Drug release pattern of a multilayer coated system at different pH conditions in GIT.

b) Delayed or time controlled release drug delivery system

Time controlled drug delivery system includes sustained or delayed release systems. In this system the delayed release or colon targeted drug delivery is attained by prolonging the lag time. The transit time varies in different parts of gastrointestinal tract. This transit time is responsible for the delayed release of drug. The main drawbacks of this delivery system are that the transit time varies from one person to other and amount of food intake. It also varies with the peristalsis or contraction in the gastrointestinal tract[16].

C) Microbially triggered drug delivery to colon

The micro flora of the colon is in the range of 1011 -1012 CFU/ml, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc[15].This vast micro flora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. For this fermentation, the micro flora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminase, and urea dehydroxylase[17].

The enzymes present in the colon are:

1. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.
2. Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, sulfatase etc[18].

Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer [15,19].

A) Prodrug Approach for Drug Delivery to Colon

There are at least three factors should be optimized for the site specific delivery of drugs by using the prodrug approach.

1. The prodrug must reach to the targeted site of action as early as possible and uptake from the site must be fast and essentially perfusion rate limited.
2. Once the drug reached to the site, prodrug must selectively liberate the active drug relative to its conversion at other sites.
3. Once selectively liberated at the site of action, the active drug must be somewhat retained by the tissue. The classical prodrug design often represents a non-specific chemical approach to mask unwanted drug properties such as low bioavailability, less site specificity and chemical instability. On the other hand, targeted prodrug design represents a new strategy for directed and efficient drug delivery. Particularly, prodrugs targeting to a specific enzyme or a specific membrane transporter or both, have potential drug delivery system especially for cancer chemotherapy[20]. Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier.2 Two classes of the prodrugs are generally used. The first type of the prodrug is broken inside cells to form active substance or substances. The second type of prodrug usually is the combination of two or more substances. Under specific intracellular conditions, these substances react and forms active drug. Targeted DDS usually includes three components[21]:

1. A drug,
2. A targeting moiety,
3. A carrier.

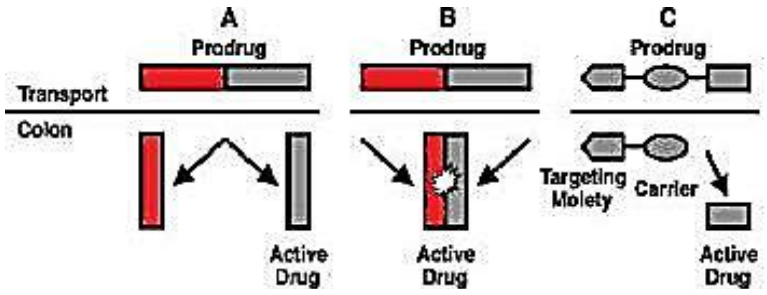

FIG 4 : SCHEMATIC REPRESENTATION OF PRODRUG APPROACH [21].

B) Polysaccharide Based Delivery Systems

Use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting to colon since these polymers of monosaccharide are found in abundance, have frequent availability, are available in a variety of structures with varied properties and are inexpensive. They are easily modified chemically and biochemically and are safe, highly stable, nontoxic, gels forming, hydrophilic and biodegradable. These include naturally occurring polysaccharides obtained from plant (insulin, guar gum), animal (chitosan, chondrotin sulphate), microbial (dextran) or algal (alginates) origin. These are broken down by the colonic micro flora to simple saccharides. So this fall into the category of "generally regarded as safe" (GRAS). Chitosan is a high molecular weight cationic polysaccharide, poly (N-glucosamine), obtained from chitin in shrimp and crab shells by deacetylation. It is degraded by the rich colonic micro flora. Chitosan have been evaluated for the colon specific drug delivery in the form of a capsule forming material. Pectin is another linear polysaccharide with mainly a-(1-4)-linked D-galacturonic acid residues interrupted by 1, 2-linked L-rhamnose residue[15,22,23].

II. NEWLY DEVELOPED APPROACHES FOR CDDS

a) Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine, have developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water[24]. 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[25]. 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[12]. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human [26].

b) Pulsatile colon targeted drug delivery

i) Pulsincap system

In this system (Figure No.5) the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled length and point of intersection of the plug in the capsule body[16].

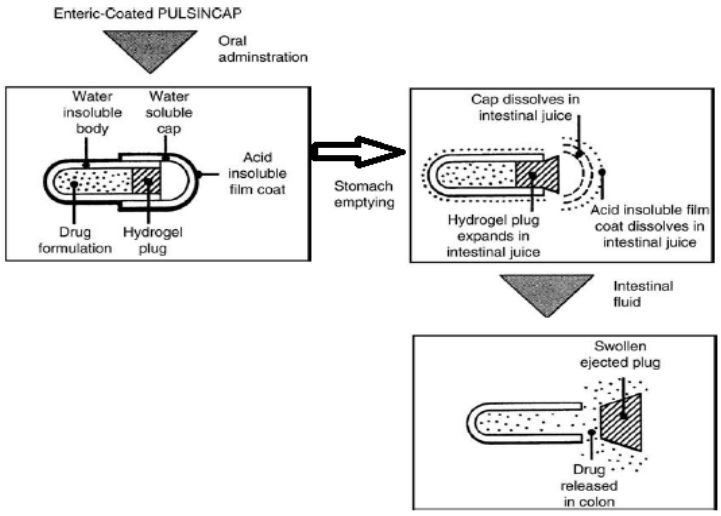

Fig 5: Drug release mechanism of Pulsincap system [27].

ii) Port system

In this system (Figure No.6) the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals[28,29].

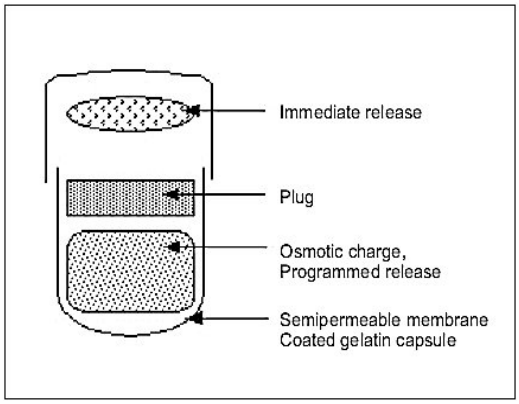

FIG 6 : PORT SYSTEM [30].

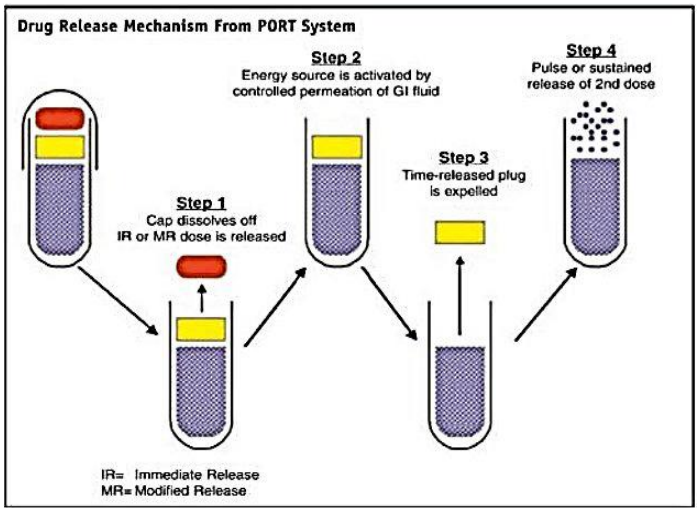

FIG 7 : DRUG RELEASE MECHANISM OF PORT SYSTEM [30].

c) Azo hydrogels

The pH sensitive monomers and azo cross linking agents in the hydrogel produce the colon specificity. During their passage through the GIT these hydrogels swell as the pH increases. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel. These hydrogels are prepared by cross linking polymerization of N- substituted (meth) acrylamides, N- tert- butyl acrylamide and acrylic acid with 4, 4-di (methacryloylamino) azobenzene as cross linking agents. The hydrogels are also prepared by crosslinking polymeric precursors, polymer- polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in NH2 groups. The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density [31].

d) Multi particulate system based drug delivery

The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, micro particles, granules and nanoparticles. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enables the drug to reach the colon quickly and retained in colon for long period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption. 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 various techniques like polymerization, nanoprecipitation, inverse micro emulsion. 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 [11].

e) CODES technology

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings [8].

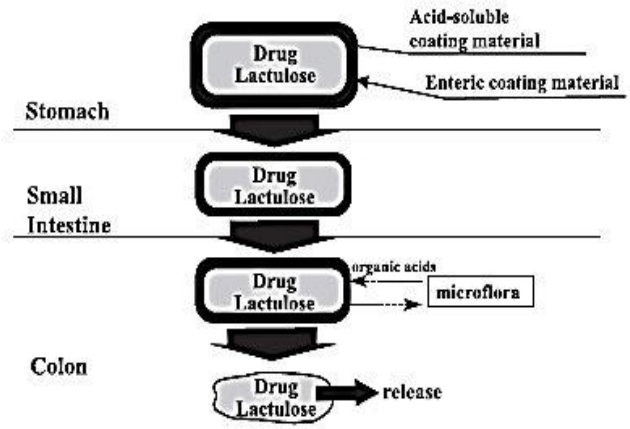

Fig 8: CODES system [8].

g) Osmotically controlled colon targeted drug delivery system

This system consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push payer. The semipermeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time[32].

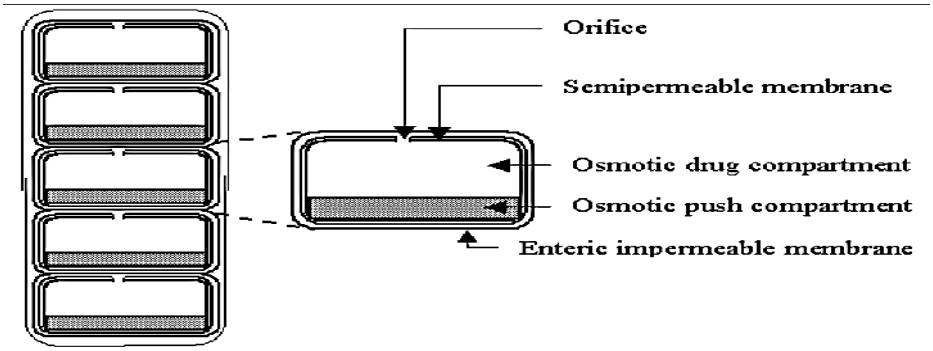

Fig9: OSMOTICALLY CONTROLLED CDDS [33].

POLYMERS USED IN COLON TARGETING

Polymer contain a large number of structural unit joined by same type linkage, form into a chain like structure. These are nowadays used in formulating various pharmaceutical products. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these
polymer many therapeutic system of body namely controlled drug delivery systems, are achieved [34,35,36].

1. Natural polymer

Guar gum, Inulin, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondrotin sulphate, Locust bean gum.

2. Synthetic polymer

Shellac, Ethyl cellulose, Cellulose acetate phthalate, hydroxy propyl methyl cellulose, Eudragit, Poly vinyl acetate phthalate

Guar gum:

Guar gum is derived from the seeds of the *cyomopsis tetragonolobus* (Fam. Leguminosae). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches . Guar gum is used in colon targeted drug delivery systems due to its drug release retarding property and susceptibility to microbial degradation in large intestine.

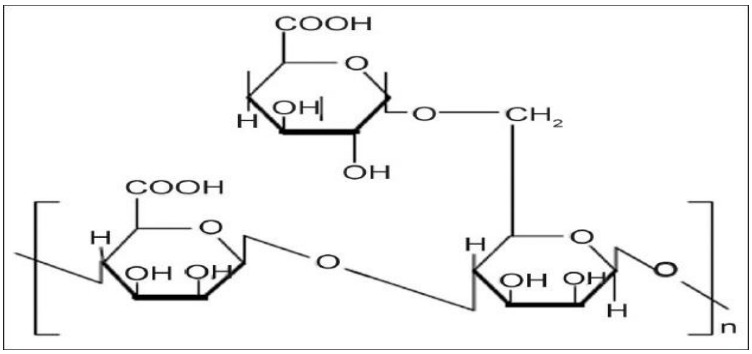

Fig10. Structure of Guar Gum [37].

The dissolution of dexamethasone and budesonide from guar gum-based formulations using reciprocating cylinder dissolution apparatus (USP Dissolution Apparatus III) and observed that the drug release in simulated colonic fluid was markedly increased at galactomannanase concentrations >0.01 mg/ml[38]. To perform a gamma scintigraphic study on guar gum matrix tablets using technetium-99m-DTPA as a tracer, in human volunteers. The scintigraphs showed that some amount of tracer present on the surface of the tablets was released in stomach and small intestine and the bulk of the tracer present in the tablet mass was delivered to the colon. These results indicated that guar gum, in the form of directly compressed matrix tablets, is a potential carrier for colon-specific drug delivery[39].

To performe the pharmacokinetic evaluation of guar gum-based colon-targeted tablets of mebendazole against an immediate release tablet in six healthy human volunteers. Colon-targeted tablets showed delayed t_{max} (9.4±1.7 h) and absorption time, and decreased C_{max} (25.7±2.6 µg/ml) and absorption rate constant when compared to the immediate release tablets. The results of the study indicated that the guar gum-based colon-targeted tablets of mebendazole did not release the drug in stomach and small intestine, but delivered the drug to the colon resulting in a slow absorption of the drug and making the drug available for local action in the colon[40].

Pectin:

Pectin is a linear, heterogeneous polysaccharide which is mainly composed of galacturonic acid and its methyl ester. These are predominantly linear polymers of mainly (1→4) linked D-galacturonic acid residue interrupted by 1,2-linked L-rhamnose residue with a few hundred to about one thousand building blocks per molecule . It is one of the major sources of dietary fiber and is extracted from fruit and vegetable cell walls [41].

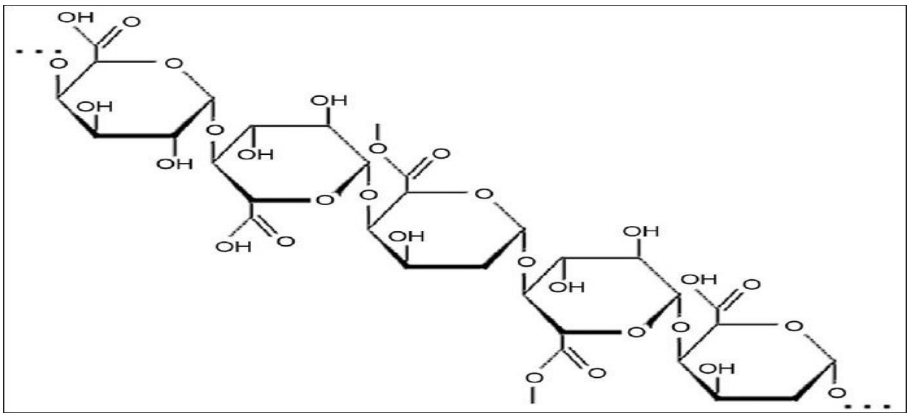

Fig11. Structure of Pectin [41].

A novel colon targeted tablet formulation using pectin as a carrier and diltiazem hydrochloride and indomethacin as model drugs has been developed [42]. *In vitro* study showed that prepared dosage forms have limited drug release in stomach and small intestine and released maximum amount of drug in the colon. The study revealed that pectin can be used effectively for colon targeting of both water soluble and insoluble drugs.

Pectin is a poor film former and therefore it is often used in combination with other polymers like hydroxypropylmethylcellulose, chitosan, ethyl cellulose. To prepared pectin-hydroxypropyl methylcellulose coated pellets for the colonic delivery of curcumin and reported that pectin-HPMC coated pellets offer a greater degree of protection from premature drug release in the upper GI tract[43].

Chondroitin Sulfate:

Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate by *Bacteroides*species in the large intestine mainly by *B. thetaiotaomicron* and *B. ovatus*. Chondroitin sulfate consist of β-1,3-D-glucuronic acid linked to N-acetyl-D-galactosamide. Natural chondroitin sulfate is cross linked and readily water soluble but it may not be able to sustain the release of most drugs from the matrix [44,45]. Chondroitin sulfate is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteroids thetaiotaoimicron* and *B. ovatus*[46].

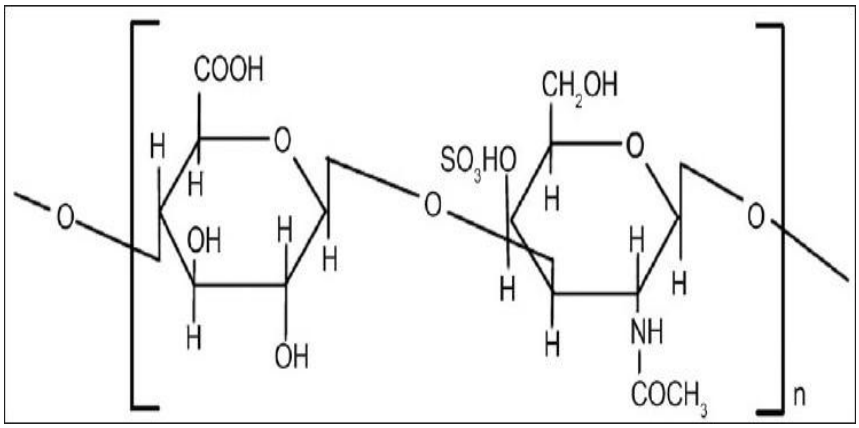

Fig12 . Structure of chondroitin sulfate.

Dextran:

Dextran is a polysaccharide consisting of α-1,6 D-glucose and side chain of α-1,3 D-glucose units (fig.13) [45,47] . These highly water soluble polymers are available commercially as different molecular weights with a relatively narrow molecular weight distribution. Dextran contains a large number of hydroxyl groups, which can be easily conjugated to drugs and proteins. Dextran gets degraded by the microbial enzyme dextranases, which is found in the colon[48]. Pharmacodynamically, conjugation with dextran has resulted in prolongation of the effect, alteration of toxicity profile, and a reduction in the immunogenicity of drug.

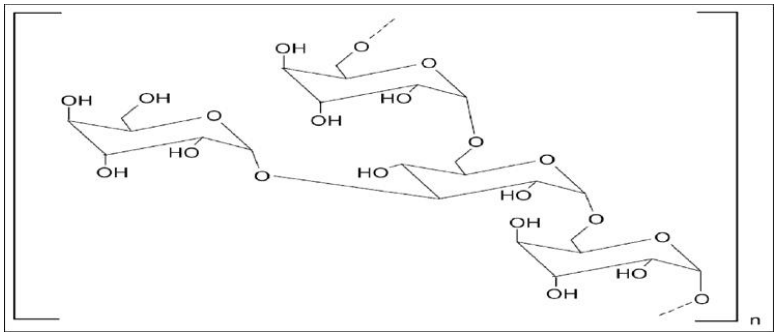

Fig13. Structure of dextran.

Chitosan:

Chitosan is functional linear polymer obtained from the alkaline deacetylation of chitin. Chitosan is consisting of the repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are linked by (1-4) β-bonds (fig.14)[45,47]. Chitosan is a nontoxic, biodegradable, biocompatible and bioactive polymer. Chitosan is used as excipient and drug carrier in drug delivery systems. Chitosan is used for the colon targeted drug delivery because it has a tendency to dissolve in acidic pH of stomach but get swollen in the intestinal pH.

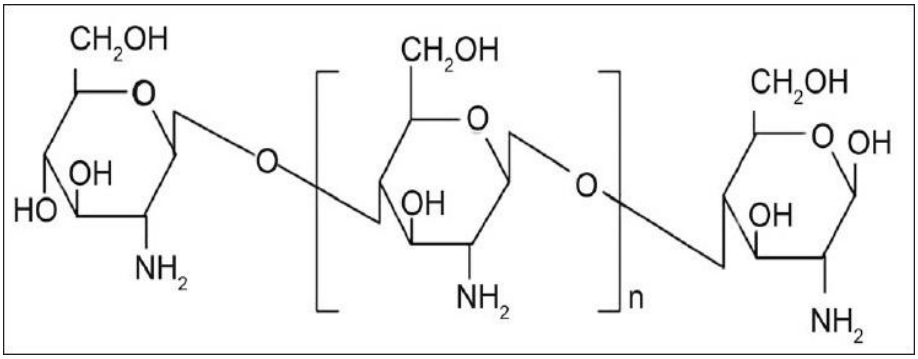

Fig14 Structure of chitosan.

Cyclodextrin:

Cyclodextrin is a cyclic oligosaccharide consisting of six to eight glucopyranose units joined by α-(1→4) glucosidic linkage (fig.15). These are potential high performance carrier molecules that have the ability to alter physical, chemical and biological properties of the drug molecule through the formation of inclusion complexes. Cyclodextrins consist of six, seven or eight glucose monomers arranged in a ring shape and these are denoted as α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, respectively.

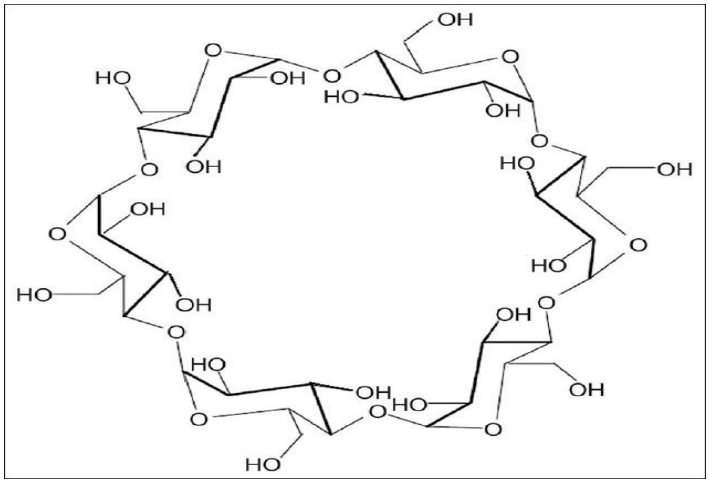

Fig.15 Structure of α-cyclodextrin.

Cyclodextrins consist an internal lipophilic cavity, which can make complex with hydrocarbon materials. Cyclodextrins are slowly hydrolysable in upper gastrointestinal tract while it gets fermented to small saccharides by colonic microflora and get absorbed in large intestine. Cyclodextrins are used to improve the drug properties such as solubility, stability, bioavailability [45,47].
Antiinflammatory drug was conjugated with primary hydroxyl groups of alpha, beta, and gamma cyclodextrins through an ester or amide linkage. The *in vivo* drug release behavior of these drug-cyclodextrin conjugates was investigated in rat. The results reveal that these conjugates were stable in stomach and in small intestine. The study suggested that cyclodextrins can be used for colon specific delivery of drug[49].

Inulin:

Inulin is a naturally occurring glucofructan and consists of β 2-1 linked D-fructose molecule having a glycosul unit at the reducing end (fig.16). It can resist the hydrolysis and digestion in the upper gastrointestinal tract. Inulin can be fermented by colonic microflora. To developed inulin hydrogels for colonic delivery of drugs and swelling property of these hydrogels was investigated. The influence of various parameters such as the degree of substitution, feed concentration of methacrylated inulin, varying concentrations of the initiators of the polymerisation reaction, the effect of pH, ionic strength on the swelling property of hydrogels were studied[50].

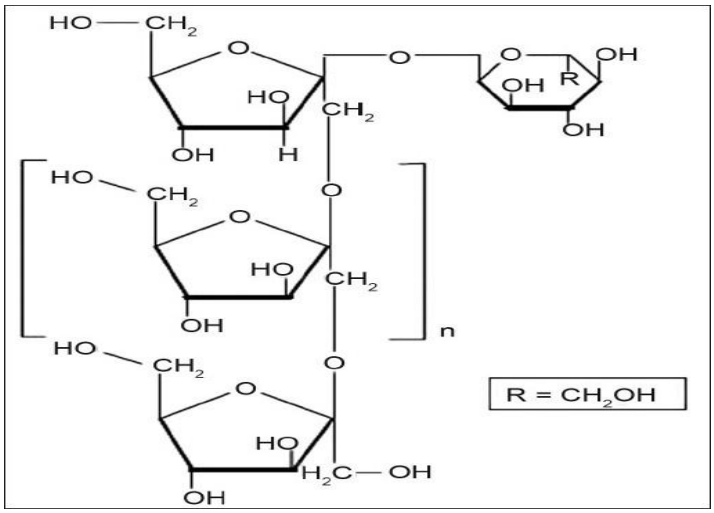

Fig.16 Structure of inulin.

Amylose:

Amylose is the polysaccharide which is obtained from the plant extracts and a component of starch. Amylose is unbranched linear polymer of glucopyranose units (α-1,4-D-glucose) linked through α–D-(1-4) linkage (fig.17). Amylose is resistant to pancreatic amylases in its glassy amorphous form but it gets degraded by the bacteroids, bifidobacterium [34].

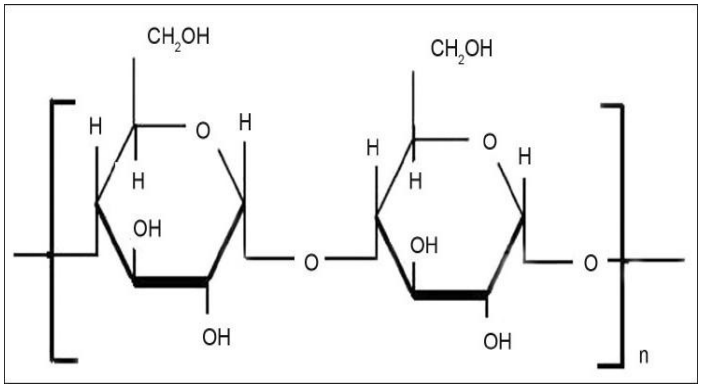

Fig.17 Structure of amylase.

Locust bean gum:

Locust bean gum contains natural polysaccharides which have a molecular weight of 310000. Locust bean gum is also known as 'Carob gum' as it is derived from the endosperm of the seed of the 'Carob' (*Ceratonia Siliqua Linne*, Fam: Leguminosae). It is irregular shaped molecule with branched β-1,4-D-galactomannan units. Locust bean contains about 88% D-galacto-D mannoglycan, 4% of pentane, 6% of protein, 1% of cellulose and 1% of ash[36].

CONCLUSIONS

In recent years CDDS has gained its importance as a site for delivery of various drugs including novel therapeutic drugs, i.e. peptides. Colon targeted drug delivery system offers benefits of local and systemic effects. The Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. The various strategies for targeting orally administered drugs to the colon includes, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bio adhesive systems etc. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs through colon. Interest in the biodegradable polymers is increasing day by day because these are safe, non-toxic, and economic and are chemically compatible with the other excipients in the formulation. This article has described the various types of biodegradable polysaccharides that have already been used in the initial approaches for colon specific drug delivery. Polysaccharides exhibit favorable properties for fabrication of colonic delivery system. Thus polysaccharides appear to be promising agents for obtaining colon-specific drug delivery systems.

REFERENCE

1. Philip AK, Dabas S, Pathak K. Optimized prodrug approach: A means for achieving enhanced anti-inflammatory potential in experimentally induced colitis. J Drug Target 2009; 17:235-241.
2. Oluwatoyin AO, John TF. In vitro evaluation of khaya and albizia gums as compression coating for drug targeting to the colon. J Pharm Pharmacol 2005; 57: 63-168.
3. Avialable from www.shodaganga.com
4. Chourasia MK, Jain S K. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Sci 2003; 6:33-66.
5. Colon Targeted Drug Delivery-Approach and Future Prospect: A Review Pooja Gupta*1, S. Mukhopadhyay1, Preeti Kothiyal1 Am.J.PharmTechRes.2015;5(4) ISSN:2249-3387.
6. Jain NK: Advances in Controlled and novel Drug Delivery. 1st edition. New Delhi, Cbs publisher and distributors; 2008. p. 86-90.
7. Sonasaniya Balvir, Dr.M.R.Patel, Dr.K.R.Patel, Dr.N.M.Patel. A Review on colon targeted drug delivery system.International Journal of Universal Pharmacy and Bio Sciences. 2013; 2(1):20-34.
8. VS Mundhe, SS Dodiya. Review article: novel approaches for colon targeted drug delivery. Ind Amer J Pharm Res. 2011; 3: 158-173.
9. P Patel, S Shukla, P Bharadia, V Pandya. Colon targeted drug delivery system- a review. IJUPLS. 2012; 2: 272-291.
10. Vyas SP, Khar RK, Gastroretentive systems. In: Vyas SP, Khar RK, editors. Controlled drug delivery: concepts and advances. New Delhi: Vallabh Prakashan, 2005: 218-253.
11. Mehta TJ et al. Need of colon specific drug delivery system: review on primary and novel approaches. Int J Pharma Res Devel 2011; 3(1): 134- 153.
12. Vinay K Gupta, G. Gnanarajan, Preeti Kothiyal. A Review Article on Colonic Targeted Drug Delivery System. 2012; 1(7): 14-24.
13. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 1988; 29:1035-1041.
14. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carr Sys 2001; 18:433-458.
15. Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches Philip AK, *et al. OMJ.* 25, 70-78 (2010); doi:10.5001/omj.2010.24
16. Anil K. Philip. Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches. OMJ. 2012; 70-78.
17. Sharma A, Jain KA. Colon targeted drug delivery using different approaches. Int J Pharma Studies Res 2010; 1(1): 60-66
18. Prasanth VV, Jayaprakash R, Mathew ST. Colon Specific Drug Delivery Systems: A Review on Various Pharmaceutical Approaches. J Applied Pharma Sci 2012; 2(1): 163-169.
19. Sinha VR, Kumria R. Polysaccharides in colon-specific drug delivery. International journal of pharmaceutics, 2001; 224: 19- 38.
20. Prasanth VV, Jayaprakash R, Mathew ST. Colon Specific Drug Delivery Systems: A Review on Various Pharmaceutical Approaches. J Applied Pharma Sci 2012; 2(1): 163-169.
21. Satpute CS *et al*., Potential Approaches of Colon Targeted Drug Delivery System: A Review. American Journal of PharmTech Research 2012.
22. Patel A et al. Novel Approaches for Colon Targeted Drug Delivery System. J Pharma Cosmetology 2011; 1(5): 85- 97.
23. Singh KI et al. Colon Specific Drug Delivery System: Review On Novel Approaches. Int J Pharma Sci Res 2012; 3(3): 637- 647.
24. Kumar Ravi, Patil M P, Sachin. A review on polysaccharides based colon specific drug delivery, International journal of pharm tech research, 1, 2009, 334-346.
25. Hay DJ, Sharma H, Irving MH. Spread of steroid containing foam after intrarectal administration. Brit Med J 1979; 1:1751-1753.
26. Watanabe S, Kawai H, Katsuma M, Fukui M. Colon specific drug release system. U. S. Patent, 1998, 09/183339.
27. Chauhan *et. al.*, Am. J. PharmTech Res. 2012; 2(3) ISSN: 2249-3387
28. Prathap M. et al. / International Journal of Research in Pharmaceutical and Nano Sciences. 3(5), 2014, 429 - 437.
29. Chauhan *et. al.*, Am. J. PharmTech Res. 2012; 2(3) ISSN: 2249-3387
30. D. Sreelatha et al/JGTPS/ Volume 4, Issue 3, pp -1174-1183, July-September 2013
31. Kothawade P. D, et.al. Conventional and novel approaches for colon specific drug delivery. E- Journal of Science and Technology. 2011; 2: 33-56.

32. S. Pradeep Kumar, D. Prathibha, R. Parthibarajan, C. RubinaReichal. Novel colon specific drug delivery system: A Review. Int. Journal of Pharmacy & Pharmaceutical Sciences. 2012; 4(1): 22-29.
33. Vishal V. Rajguru, Preeti D. Gaikwad, Vidyadhar H. Bankar, Sunil P. Pawar. An overview on colonic drug delivery system. Int. Journal of Pharmaceutical Sciences Review & Research. 2011; 6(2): 197-204
34. Available online at http//www.ijrdpl.com February - March, 2014, Vol. 3, No.2, pp 877-886 ISSN: 2278-0238.
35. Sinha .v.r, Rachna K. A Review on Polysaccharides in colon specific drug delivery. International Journal of Pharmaceutics. 2001; 224: 19-38.
36. Kumar Ravi, Patil M.P, Sachin, A review on polysaccharides based colon specific drug delivery.International journal of pharm tech research 2009; vol 1 :334-346.
37. Available from: http://en.wikipedia.org/wiki/Guar_gum
38. Wong D, Larrabee S, Clifford K, Tremblay J, Friend DR. USP Dissolution Apparatus III (reciprocating cylinder) for screening of guar-based colonic delivery formulations. J Control Release. 1997;47:173–9.
39. Krishnaiah YS, Satyanarayana S, Prasad YV, Rao SN. Gamma Scientigraphic studies on guar-gum matrix tablet for colonic drug delivery in healthy human volunteers. J Control Release. 1998;55:245–52.
40. Krishnaiah YS, Rajua PV, Kumarb BD, Satyanarayanaa V, Karthikeyana RS, Bhaskara P. Pharmacokinetic evaluation of guar gum-based colon-targeted drug delivery systems of mebendazole in healthy volunteers. J Control Release. 2003;88:95–103
41. Shirwaikar A, Shirwaikar AN, Prabu SL, Kumar GA. Herbal Excipients in Novel Drug Delivery Systems. Indian J Pharm Sci. 2008;70:415–22.
42. Ravi V, Kumar TM, Siddaramaiah Novel colon targeted drug delivery system using natural polymers. Indian J Pharm Sci. 2008;70:111–3
43. Kumar RS, Kumar M, Ganesh GN, Jawahar N, Nagasamyvenkatesh D, Senthil V, et al. Formulation and evaluation of pectin-hydroxypropyl methylcellulose coated curcumin pellets for colon delivery. Asian J Pharm. 2009;3:138–42.
44. Vyas SP, Khar RK. Systems for colon specific delivery. In: Vyas Sp, Khar RK., editors.Controlled drug delivery: Concept and advantages. 1st ed. Delhi: Vallabh Prakashan; 2002. pp. 218–56.
45. Jain A, Gupta Y, Jain SK. Perspectives of biodegradable natural polysaccharides for site specific delivery to the colon. J Pharm Pharm Sci. 2007;10:86–128.
46. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharm Sci. 2003;6:33–66.
47. Wilson CG, Mukherji G, Sha HK. Modified-release Drug Delivery Technology. In: Rathbone MJ, Had graft J, Roberts MS, Lane ME, editors. Biopolymers and Colonic Delivery. 2nd ed. Vol. 1. New York: Informa Healthcare; 2008. pp. 295–309.
48. Jain S, Jain NK. Polymers in Pharmaceutical Sciences. In: Jain NK, editor. Pharmaceutical Product Development. 1st ed. New Delhi: CBS Publisher and Distributor; 2006. pp. 218–26.
49. Minami K, Hirayama F, Uekama K. Colon-specific drug delivery based on a cyclodextrin prodrug: Release behavior of biphenylylacetic acid from its cyclodextrin conjugates in rat intestinal tracts after oral administration. J Pharm Sci. 1998;87:715–20.
50. Vervoort L, Mooter GV, Augustijns P, Kinget R. Inulin hydrogels. I. Dynamic and equilibrium swelling properties. Int J Pharm. 1998;172:127–35.