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Review Article

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Implications of Biodegradable and Bioadhesive Systems in Colon Delivery

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ABSTRACT
Oral or non-parental drug delivery systems are widely used for the administration of therapeutic drugs. However, the gastrointestinal tract presents several barriers to anticancer drugs in targeting colon cancer. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. To achieve successful colonic delivery, which is considered to be the optimum site for colon-targeted delivery of drugs, colon targeting is of prime importance for the topical treatment of diseases of colon such as Chorn's diseases, ulcerative colitis, colorectal cancer and amebiasis. Peptides, proteins, oligonucleotides and vaccines pose potential candidature for colon targeted drug delivery.

Keywords: Anticancer drugs, Chorn's diseases, amebiasis.

INTRODUCTION

The oral route is considered to be most convenient for the administration of drugs to patients. Oral administration of conventional dosage from normally dissolves in the stomach fluid or intestinal fluid and absorption of drugs from three regions of the GIT depends upon the physiochemical properties of the drug. It is a serious drawback in condition where localized delivery of the drugs in the colon is required or in condition where a drug needs to be protected from the hostile environment of upper GIT. Oral delivery of drugs to the colon is valuable in the treatment of disease of colon (ulcerative colitis, chrons's disease, carcinomas and infections) whereby high drug concentration can be achieved while minimizing side effect that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. [1] The colon is attracting interest as a site where poorly absorbed drug may have an improved bioavailability. This region of the colon is recognized as less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a longer retention time and highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of per orally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after per oral application. The simplest method for targeting of drugs to the colon is to obtain slower release rate or longer release period by the application of thicker layers of conventional enteric coatings or extremely slow releasing matrices.

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Colonic Drug Delivery

Site-specific drug delivery to the colon has attracted considerable attention for the past few years in order to develop drug delivery systems that are able to release drugs specifically in the colon in a predictable and reproducible manner. Colonic drug delivery in general has been reviewed by Basit [2] and Chourasia and Jain. [3] A chronic inflammatory disease such as ulcerative colitis requires daily treatment with aminosalicylates, and in some cases even daily treatments with corticosteroids such as prednisolone. [4] The site-specific drug delivery to colon is important for the

treatment of diseases associated with the colon, reducing the side effects of the drug and reducing the administered dose. The pharmaceutical formulations available for this treatment are slow release oral formulations or enemas and foams for rectal administration. The formulations, however, are not truly site-specific, and the treatments are connected with a high frequency of systemic side effects. The side effects appear to be more frequent after administration of oral formulations compared with rectal formulations because of the large degree of systemic absorption from the upper gastrointestinal tract. Drugs for which the colon might appear as a potential absorption site (e.g., peptides and vaccines) may also advantageously be delivered to this region for systemic absorption because; the enzymes which are responsible for the degradation of the peptides or vaccines are significantly present in the upper part of the GIT. Relevant drugs for colon-specific are presented diagrammatically in Figure 1.

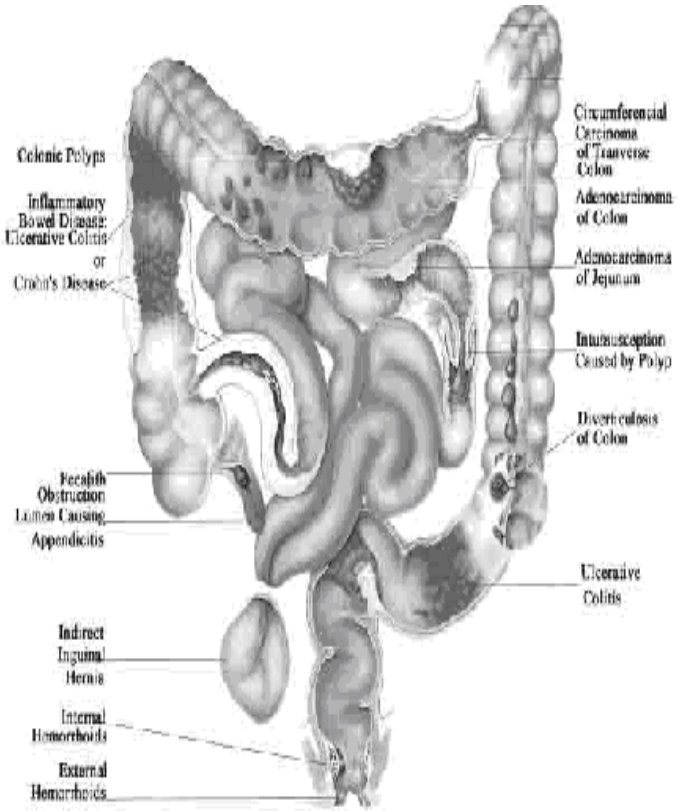

Fig.1: Relevant drugs for colon-specific

Colon-specific drug delivery has been approached by a number of methods exploiting changes in the physiological parameters along the gastrointestinal tract. [6-91 The GIT transit time was utilized to formulate colon specific drug delivery systems which are so designed that their drug release is delayed to the time required for transiting drug from mouth cavity to distal part of small intestine i.e., ileum and subsequently drug release in the colon. [10-13] Factors influencing the transit time of pharmaceutical dosage forms in the various regions of the gastrointestinal tract appear to depend on diet, gastrointestinal motility and physical activity of the person, fasted or fed state of the person. [14-16] The change in pH along the gastrointestinal tract was also used to develop colon specific drug delivery systems by applying coatings that were intact at low pH and dissolved at neutral pH. The pH of the colon is, however, often lower than the pH of the small intestine, which in turn may be as high as 8 or 9, resulting in a too early release of a drug. [12] Other reports conclude that pH is useful as a trigger for drug release in the colon. [9, 11] A number of specific regional characters of the colon can be explored for site specific drug delivery to the colon. In the colon, an extensive growth of anaerobic microorganisms is observed. [10, 14] Hence, drug delivery systems based on polysaccharide can also be used for colon specific drug delivery.

Strategies used in delivery of drugs to colon

The microparticualte system consisted of Budesonide-containing hydrophobic cores, microencapsulated with in an enteric polymer, which solubilizes at above pH 7, thus combining pH-sensitive and controlled release properties. [17] Colonic injury and inflammation were assessed by measuring colon/body weight ratio, myeloperoxidase activity and by scoring macroscopic and histological damage in colotic rats treated orally with budesonide were included in the developed system, once a day for 4 days after the induction of inflammation. A Budesonide suspension and budesonide containing enteric microparticals were included as a control formulation in the experimental design. The administration of the new Budesonide delivery system significantly reduced the colon /body weight ratio as compared to the administration of control formulations. Similarly, myeloperoxidase activity and macroscopic and histological damage of the inflamed colonic segments got decreased significantly when the Budesonide formulation was administered in comparison to oral administration of the drug suspension. There were no significant differences, however when the new treatment was compared with the control formulation consisting of simple enteric microparticles. A multi-unit dosage form was developed containing 5-ASA for the treatment of ulcerative colitis. Pellets were prepared by a granulation and spheronization process and then coated with a new pH sensitive poly (meth) acrylate copolymer (eudragit® FS 30D) to achieve site-specific drug release close to the ileocecal valve. [18] From the dissolution studies it was concluded that pellets released rapidly at pH values above 7.5. Between pH 6.8 and 7.2, drug release was found to be zero order, while at pH 6.5 and below no release occurred. In a biorelevant medium, which simulates the fasting proximal small intestine fluid, it was shown that neither surfactants (sodium taurocholate and lecithin) nor changes in ionic strength trigger drug release. As compared to 5-ASA pellets coated with the well established Eudragit® S, and currently marketed products licensed for the treatment of ulcerative colitis, the multi unit dosage from coated with the new polymer exhibited an in vitro dissolution profile more appropriate to the pH profile of the ileum and the colon observed in ulcerative colitis patients.

Biodegradable polymers in colon delivery

The bioenvironment inside the human GIT is characterized by the presence of complex microflora especially the colon that is rich in microorganism that are involved in the process of reduction of dietary component or other materials. Drugs that are coated with the polymers, show degradability due to the influence of colonic microorganism, can be exploited in designing drugs for colon targeting. These bacterial degradable polymers (especially azo polymers) have been explored in order to release an orally administered drug in the

colon. Actually, upon passage of the dosage from through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is quiet insufficient for cleavage of polymer coating. Release of the drugs from azo polymer coated formulation is supposed to take place after reduction and the degradation of the azo bonds occur by the azo reductase enzymes released by the azo bacter present in the colonic microflora. Since, the concept of the strategy is based on the metabolic activity of azo reductase produced by azo bacters of colon; the bacterial degradation of polymeric coating may be effected by several other factors e.g. dietary fermentation precursors, type of food consumed and co administrations of chemotherapeutic agents. Linear type segmented polyurethanes azo groups in the main chain have been synthesized as coating material. [19-21] Since, this polymer degraded specifically by the action of intestinal flora, the dosage form coated with the polymer would be effective for colon targeting of orally administered drugs. However, this polyurethane based on m-xylene diisocynate (XDI), was soluble only in limited solvents and has been thought to be clinically inapplicable due to the trace amount of remaining solvent. Therefore a segmented was synthesized polyurethane containing azo aromatic groups in the main chain using a fixed ratio of isophorone disocyanate with a mixture of m, m'–di (hydroxymethyl) azobenzene, poly (ethylene glycol) and 1, 2 propanediol. This polyurethane was soluble in various solvents and showed a good coating and film forming property. A solution cast film of this polyurethane was found to be degraded in a culture of intestinal flora with the azo group reduction to hydroazo groups, not to amino groups. The film degradation was attributed to the decreased cohesive energy in the hydroazo polymer compared with that of original azo polymer. The drug pellets containing water-soluble drugs were undercoated with (carboxymethyl) (ethyl)–cellulose and over coated with the azo polymer in order to examine the drug releasing profiles in the culture of intestinal flora. The release rate of drug from these double pellets was found to be dependent on the molecular weight, the composition of the polyurethane used as the overcoat and the hydrophilicity of the incorporated drugs. Since, the polyurethane was glassy and its segment motion or conformational change was frozen, the structure change should be retarded even after partial reduction of the drug leakage. Further, a urethane based analogue was synthesized containing an azo aromatic linkage in the backbone for use in the colon–specific delivery system by reacting toluence 2, 6 diisocyanate with a mixture of an aromatic azo dial, (bis-4 hydrocyanate)-4,4'–diazobiphenyl,poly (ethylene glycol and 1,2-propanediol (propylene glyol). [22] The compounds exhibited low molecular weight, lacked film forming properties and crystallinity in the structure. In vitro bacterial degradation test was conducted to demonstrate the susceptibility of azo bond to bacterial enzymes using media inoculated with lactobacillus culture. The result indicated degradation of films by Azoreducatase. In vitro permeation of 5-ASA was studied in control and lactobacilli treated films. The permeability of the lactobacilli treated films was significantly increased suggesting the potential of these compounds for application in colonic targeting. Further, a suspension of natural polygalactomannans in polymethacrylate solutions to form degradable coating. [231 The polygalactomannans form a swellable layer around the drug core thus delaying the release of drug in the small intestine. They are destroyed enzymatically in the colon and consequently the drug is released. In order to formulate inulin as a biodegradable coating material, it was incorporated as a suspension in Eudragit® S films, since inulin itself has no films forming properties. Eudragit® S copolymer of acrylic acid esters with a low content of quaternary ammonium groups was chosen as film-former because it gives water-insoluble, pH-independent, low permeable films which are inert to endogenous digestive secretions and enzymes. [24] There was a fall in pH after incubation with human fecal medium for 24 h due to the formation of degradation products such as lactic acid, acetic acid and other volatile fatty acids. A significant increase in the permeability coefficient was detected after incubation within the control medium and on increasing the amount of insulin HP in the film, the permeability coefficient showed a tendency to increase. Paracetamol cores were coated using aqueous dispersion consisting of pectin and EC. From the results, it was concluded that drug release was controlled by the reaction of EC to pectin in the film coat. [25] Application of glutaraldehyde crosslinked dextran as a capsule material for colon-specific drug delivery has been also exploited. A reaction mixture containing dextran, magnesium chloride, glutaraldehyde and PEG 400 in water was applied onto moulding pins of nylon producing capsule caps and bodies. [7] The capsule materials were characterised by measuring the mechanical strength in compression and equilibrium degree of swelling. Based on these results an optimal composition for the capsule material was selected. The release was about 10 % in the first 3 h in a buffer solution and over a period of 24 h, 35 % drug release was observed. However, when the dextran capsules were challenged with a dextranase solution, simulating the arrival of the drug delivery system to the colon, the capsules were quickly broken and the drug was released as a dose dump. Proposed ester based dextran with molecular weight of approximately 250 kD and degree of solubilization ranging from 0.11 to 0.4 as film forming which were stable between pH 1.0 and 7.4. The tablet cores with theophylline were coated using conventional equipment with dispersion of 4 % laury1 dextran to theoretical polymer weight of 5, 0 and 15 mg/cm2. The dissolution of theophylline was carried out in a buffer of pH 5.5 for 4 h, after which dextranase was added to simulate the colonic environment. The release was inversely proportional to the amount of ester applied on the coatings. The entire degradation of coating was observed within 2 h after the addition of dextranase in the dissolution medium. A novel oral delivery system for the treatment of IBD, based on the microencapsulation of anti-inflamammatory drugs, sulfasalazine and betamethasone using different biodegradable polymers, poly (caprolactone), polylactic acid and poly (lactic-co-glycolic acid), was prepared either by the water in oil-in –water (w-o-w) or the solid in oil in water (s/o/w) solvent evaporation method. Microparticles were characterized for their size, morphology, encapsulation efficiency and drug release In vitro release studies showed a controlled release of sulfasalazine and betamethasone from microparticles prepared by the s/o/w method while a pronounced burst release of sulfasalazine was observed from microparticles prepared by the w/o/w method.

Biodegradable matrices and bydrogels

Polysaccharides, the polymer of monosacccharides retains their integrity because they are resistant to the digestive

action of gastrointestinal enzymes. The matrices of polysaccharides get intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharidase resulting in the degradation of the matrices. This family of natural polymers has an appeal to the area of drug delivery as it is comprised of Polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, and for the most part, a low toxicity and, biodegradability, yet a high stability. The most favorable property of these materials is that they are already approved as pharmaceutical excipients. A large number of polysaccharides such as amylase, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans and locust bean gum have been investigated for their use in colon targeted drug delivery systems, The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they need to be made water insoluble by crosslinking or hydrophobic derivatisation using an optimal proportional of the hydrophobic and hydrophilic parts respectively and the number of free hydroxyl groups in the polymeric molecule. Pectin is a polysaccharide consists of α-1, 4 D-galacturonic acid and 1, 2 D-rhamnose with D-galactose and D-arabinose side chains. A novel colonic drug delivery system based on the polysaccharide pection has been investigated. In vitro experiments have demonstrated that high methoxy pectin, when applied as a compression coat, is capable of protecting a core tablet during stimulating gastrointestinal environment and was susceptible to enzymatic attack. In vivo gamma scintigraphic studies confirmed the in vitro findings. In all the volunteers, the pectin-coated tablets disintegrated in the colon indicating the site-specificity and thus illustrating the potential of a colonic drug delivery system utilizing pectin. However, in the in vivo conditions, a coat of considerable thickness was required to protect the drug core. This necessitates the development of such derivatives of pectin, which were less water-soluble but were degraded by the colonic microflora. Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of indomethacin. The use of calcium pectinate as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but retains its integrity in the physiological environment of small bowel. In spite of reduction of water solubility, calcium pectinate compressed with indomethacin into tablets was shown to degrade by enzymes of Aspergillsn and colonic bacteria bacteroides ovatus as reflected from the in vivo performance studies. Various variables like pectin, the presence of calcium and the solubility of the calcium salt influenced the release of drug. It was observed that either a high methoxy pectin formulation or low methoxy pectin with a carefully controlled amount of calcium, maximized the colonic specificity by providing optimal protection of drug during its transit to the colon and a high susceptibility to enzymatic degradation. Combination of the pectin along with either chitosan or HPMC has been successfully used for the formulation of colon targeted drug delivery systems. Combination of pectin and ethyl cellulose film was used for colonic delivery of paracetamol. Aqueous dispersions of pectin and ethyl cellulose were used for film coating of paracetamol tablet cores. The drug release mechanisms were assessed using flow through dissolution testing in the presence and absence of enzymes. Drug release from the coated systems was complex and dependent on the nature and characteristics of the mixed film as well as the composition of the dissolution medium. Drug release profiles were comparable with a mechanism involving the formation of channels in the film caused by pectin dissolution. Channel formation was accelerated in the most of the cases by the presence of pectinolytic enzymes showing that the pectin in the mixed film was susceptible to enzymes attack. The mechanical and permeability properties of mixed ethyl cellulose/pectin films cast from dibutyl sebacate plasticized aqueous dispersions of Aqua coat and Pectin USP has been investigated. The films were subjected to tensile testing, elongation at break and elastic modulus. Increasing concentrations of pectin imparted increasing brittleness and decreasing toughness to the films. Despite the inclusion of increasing quantities of the hydrophilic pectin into the films, the permeability to moisture remained essentially the same. The results imply that there is a limit to the amount of pectin that can be included in the coating material to produce a satisfactory film, but the protective nature of the ethyl cellulose to moisture is not compromised. Pectin and chitosan mixtures were also used as coatings for colon-specific drug delivery of indomethacin and paracetamol, as model drugs to represent poorly soluble and soluble compounds respectively. Pectin alone was able to protect the cores from permature release, but only when a substantially thick coat was present. Pectin/chitosan mixtures achieved better protection at a lower coat weight. The use of pectinolytic enzymes to simulate breakdown in the colon showed that the pectin/chitosan mixture was susceptible to enzymatic breakdown and allowed drug release to occur. A study was carried out to assess the potential of pectin/chitosan films for colonic drug delivery. Drug dissolution/ system erosion/degradation studies were carried out in pH 1.2 and 6.8 buffers using a pectinolytic enzyme. The system was designed based on the gastrointestinal transit time concept, under the assumption of colon arrival time of 6 h. It was found that pectin alone was not sufficient to protect the core tablets and HPMC addition was required to control the solubility of pectin. The optimum HPMC concentration was 20 % and such system protected the cores up to 6h that corresponded to 25-35 % erosion and after that under the influence of pectinase the system degraded faster and delivered 5-ASA to the colon. Theophylline pellets were coated with cellulosic (Aquacoat ECD 30, Surelease clear) or acrylic (Eudragit® NE30D, RS30D) polymer aqueous dispersions, containing 10% (related to the insoluble polymer content) of pectin HM or calcium pectinate, using a Uni-Glatt fluidized-bed coating apparatus. The results were examined with regard to the validity of the approach based on the combination of pectin and the insoluble polymer aqueous dispersions intended for specific- delivery of drugs to the colon. Amidated pectins are low-methoxy pectins in which some of the carboxylic acid groups are amidated. They are more tolerant to pH variations and calcium levels than conventional pectins, which could make them useful in colonic delivery systems. Gelation of droplets in the presence of calcium may provide a valuable approach to the formation of a multiparticulate system for colonic delivery. The properties of such amidated pectin beads may be altered by the formation of a polyelectrolytes complex membrane

around the bed using cationic polymers such as chitosan. Despite the presence of chitosan in the amidated pectin beads, it retained its ability to degradation by pectinolytic enzymes and significantly reduced the release of sulfamethoxazole and indomethacin in simulated gastric and intestinal fluid as compared with non-amidated beads. Similarly, calcium pectinate gel (CPG) beads of indomethacin, by dispersing the drug in a solution of pectin and then dropping the dispersion into calcium chloride solution. The droplets instantaneously converted into gelled spheres by ionotrophic gelation. The effect of several factors such as pectin type, the presence of a hardening agent and the drug loading were investigated on the percentage of drug entrapped, size distribution and drug release from the CPG beads. Oral delayed release system was proposed based on Zinc-pectinate gel microparticles as an alternative carrier to calcium pectinate beads for colonic drug delivery. The system which consists of ketoprofen-loaded Zinc-pectinate gel (ZPG) microparticles together with pectin/dextran mixtures in a tablet form has been investigated, in vitro, using conditions chosen to simulate the pH and time likely to be encountered during transist to the colon. In order to find the suitable ZPG microparticles, the formulations were prepared utilizing 2(3) factorial degisn and the effect of various formulation factors on the release and surface characteristics of the microparticles was studied. The results implied that the release of keptoprofen from ZPG microparticles was greatly extended with the pectinate microparticles, which were prepared with 2.5 or 3 % w/v pectin, 2.75 % w/v zinc acetate and 2.5 % w/v drug. Additionally, the analysis of variance results showed that the release of ketoprofen in simulated intestinal fluid (pH 7.4) was strongly affected by crosslinking agent concentration and initial drug amount, but not affected by the amount of pectin added. The investigated drug concentration factor has significantly increased the drug entrapment efficiency. The optimum colonic drug delivery ZPG/tablet system provided the expected delayed-release sigmoidal patterns with a lag-time of 4.125-4.85 h and $t_{50\%}$ (the time for 50 % of the drug to be released) at 7.45-8.70 h, depending on pectin/dextran ratio employed. The results also demonstrated that the untableted ZPG microparticles exhibited drug release profiles that retarded the release of ketoprofen in simulated intestinal fluid (pH 7.4) by 5.28-37.82 times depending on formulation parameters) which were lower than the conventional calcium pecitinate beads. Hydrogels are usually formed by the covalent crosslinking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble. Heterogeneous polymer mixtures may also be used to form hydrogels without the need for covalent crosslinking. Various hydrogels based on the azo polymeric networks have been developed for site-specific delivery of drugs to the colon. Inulin is a naturally occurring polysaccharides found in many plants. It consists of 2-1 linked D-fructose molecules having a glycosyl unit at the reducing end. Various inulin and dextran hydrogels have been developed that serve as potential carrier for introduction of drugs into the colon. Poly vinyl alcohol of different molecular weights were cross-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel forming polymers and their suitability as colon -specific drug delivery systems was determined. The results indicated the ability of the cross-linked polymers to slow the release of the drugs with respect to the pure drug dissolution at each pH. The lengthening of the cross-linker acyl chain was observed to decrease drug release further. A new series of water insoluble acrylic polymers based on cellobiose-derived monomers for colon targeting was reported. In addition, water-soluble acrylic polymers such as carbopol 947P were also evaluated for the controlled intestinal delivery of mesalamine. Guar gum is a polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* and many reports in the literature has proved its efficacy for colonic drug delivery. It consists of linear chains of (1-4)- β -D-manopyranosyl units with α -D-galactopryanosyl units attached by (1-6) linkages. Guar gum is hydrophilic in nature and swells in cold water forming viscous colloidal dispersions or sols. This gelling property retards release of the drug from the dosage from as well as it is susceptible to degradation in the colonic environment. Homogenized and diluted feces from human source were incubated with the guar gum to investigate the polysaccharide by intestinal microflora. It produces a rapid decrease in viscosity and fall in pH while no such results were observed when it was incubated with autoclaved fecal homogenates. Guar gum was crosslinked with increasing amounts of trisodium trimetaphosphate to reduce its swelling properties for use as a vehicle in oral delivery formulations. As a result of the crosslinking procedure, guar gum lost its non-ionic nature and become negatively charged. This was demonstrated by methylene blue adsorption studies and swelling studies in sodium chloride solutions with increasing concentrations in which the hydrogels network collapsed. Crosslinked guar gum products were analysed to check the efficacy as colon-specific drug carrier and it was found that the product which was crosslinked with 0.1 equivalent of trisodium trimetaphosphate was able to prevent the release of 80% of its hydrocortisone load in 6 h in PBS (pH 6.4). When a mixture of a-galactosidase and–mannanse was added to the buffer solution, an enhanced release was observed. In vivo degradation studies in the rat caceum showed that despite the chemical modification of guar gum, it retained its enzyme-degrading properties in a crosslinker concentration dependent manner. A novel tablet formulation for oral administration using guar gum as the carrier and indomethacin as a model drug has been investigated for colon targeted drug delivery using in vitro methods. Drug release studies under conditions simulating the gastrointestinal transit have shown that guar gum protects the drug from being released completely in the physiological environment of stomach and small intestine. Studies in pH 6.8 PBS containing rat caecal contents have demonstrated the susceptibility of guar gum to the colonic bacterial enzyme action with consequent drug release. The guar gum matrix tablets of albendazole were found degraded by colonic bacteria of rat caecal contents and released about 44 % of albendazole in simulated colonic fluids (control study) at the end of 24h indicating the susceptibility of the guar gum formulations to the rat caecal contents. Compression coated tablets of 5-ASA and matrix tablets of membendazole have been prepared using guar gum as a carrier. Matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder. The tablets were evaluated for drug content uniformity, and were subjected to in vitro drug studies. The results revealed that matrix tablets containing either 20 % or 30 % of guar gum are most likely to provide targeting of mebendazole for local action in the colon. A novel colon

specific drug delivery system based on guar gum matrix tablets was evaluated by conducting gama scintigraphy studies using technetium-99m-DTPA as a tracer, in six healthy male human volunteers. Scintigraphy taken at regular intervals showed that some amount of tracer present on the surface of the tablets was released in the stomach and intestine and bulk of the tracer present in the tablet mass delivered to the colon. Amylase is a polysaccharide obtained from plant extracts and a component of starch. It consists of D-glucopyranose residues linked by alpha-(1-4) bonds. It is a poly (1-4-alpha-D-glucopyranose). Colon-specific drug delivery may be possible by the application of dried amylase films to pharmaceutical formulations. Amylose, one of the major fractions of starch, possesses the ability to form films through gelation, when prepared under appropriate conditions. The microstructure of the film is potentially resistant to the action of pancreatic alpha-amylase but is digested by amylases of the colonic microflora. However, under simulated gastrointestinal conditions, coatings made solely of amylose will become porous and allow drug release. Incorporation of insoluble polymers into the amylose film, to control amylose swelling provides a solution to this problem. A range of cellulose and acrylate based copolymers were assessed, of which a commercially available ethylcellulose (Ethocel) was found to control the swelling most effectively. The in vitro dissolution of various coated pellets under simulated gastric and small intestinal conditions, using commercially available pepsin and pancreatin was determined and demonstrated the resistance of the amylose-Ethocel coat (1:4) to such conditions over a period of 12 h. Glucose as a model drug was incorporated into pellets that were prepared by extrusion and spheronization to assess the colonic drug delivery capability. The behaviour of different glucose containing pellets coated with an amylose-Ethocel mixture was investigated in vitro and formulation was found to gastric and small intestine resistant. In vitro fermentation studies revealed that the formulation was susceptible to bacterial enzymatic attack. Epichlorhydrin treated crosslinked amylose was introduced as a matrix for controlled release of theophylline. A mixture of amylose was used as surrogate for drug delivery. Chodroitin sulphate is a mucopolysaccharide, which consists of D-glucronic acid linked to N-acetyl-D-galactosamide. It is degraded by the anaerobic bacteria of the large intestine mainly by Bacteriods theaiotaoimicron and B. ovatus. The high water solubility of chondroitin sulphate put hurdles in the formation of colon targeted drug delivery systems and hence crosslinking has been reported in the literature to alleviate this problem. Chondroitin sulphate was cross-linked with 1, 12 diaminododecane using dicylohexylcarbodiimide as a catalyst and formulated in a matrix with indomethacin as a drug market. The indomethacin release kinetics from the various formulations was analysed in PBS with and without rat caecal content at 37°C under carbon dioxide atmosphere and it was concluded that release of indomethacin was dependent upon the biodegradation action of the caecal content. Chitosan is a high molecular weight polycationic polysaccharides derived from naturally occurring chitin by alkaline deacetylation. Chemically, it is a poly (N-glucosamine). Chitosan has favorable biological properties such as nontoxicity, biocompatibility and biodegradability. Similar to other polysaccharides it undergoes degradation by the action of colonic microflora and hence poses its candidature for colon targeted drug delivery. The naturally occurring polymer chitosan was reacted separately with succinic and phthalic anhydrides. The resulting semisynthetic polymers were assessed as potential matrices for colon-specific, orally administrated drug delivery using sodium diclofenac as the dispersed model drug. The prepared matrices were incorporated into tablets, evaluated in vitro which resisted dissolution under acidic conditions. On the other hand, improved drug release profiles were observed under basic conditions that suggest the suitability of the prepared matrices in colon-specific, orally administered drug delivery system. Therapeutic effect of R-68070, a new thromboxane synthetase inhibitor on 2, 4, 6 trinitrobenzene sulfonic acid sodium salt induced ulcerative colitis was studied using chitosan capsules to achieve its colon-specific drug delivery in rats. A pH-sensitive drug delivery carrier has been reported for chitosan based hydrogels. A multiparticulate system of chitosan hydrogel beads has been investigated for colon-specific drug delivery of macromolecules using fluorescein isothiocanate-labeled bovine serum albumin as a model protein. The hydrogel bead was formed by polyelectreolyte complexation of chitosan with its counter ion, tripolyphosphare. The protein release experiments were carried out in vitro under different conditions to simulate the pH and times likely to be encountered during intestinal transit to the colon. The results show that hydrogel beads were degraded by rat cecal and colonic enzymes resulting in a marked acceleration in the release of protein. Chitosan dispersed drug delivery system which was composed of active ingredient reservoir and the outer drug release regulating layer dispersing chitosan powder in hydrophobic polymer, was newly developed for colon-specific drug delivery. [2] Different chitosan salts were prepared by dissolving in aqueous solutions containing aspartic, glutamic, hydrochloric, lactic and citric acid. The in vitro evaluation was carried out to the study the influence of acid type on the release behavior of incorporated diclofenac sodium from the physical mixture during gastrointestinal transit. The physical mixture of chitosan salts with diclofenac sodium provided slower drug release than the pure drug both in acidic and alkaline pH. In addition the presence of B-glucosidase at pH 7.0 enhanced the release rate.

Bioadhesive systems

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Dissolution of dosage from and simultaneous absorption from upper GIT lead to low intracolonic drug concentration as well as absorption of drugs result in the generation of side effects. Bioadhension is a process by which a dosage from remains in contact with particular organ for an augmented period of time. This longer resistance time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropyline oxide copolymers have been investigated as materials for bioadhesive systems. [1] Bioadhension has been proposed as a means of improving the performance and extending the mean resistance time of colonic drug delivery systems. In vitro bioadhension has been confirmed from many studies and few reports are available in the literature

regardsing the in vivo bioadhension studies. The chemical structure of the synthesized series of copolymers was examined by infrared spectroscopy and nuclear magnetic resonance data. The thermal properties of the materials were assessed using a combination was evaluated at physiologically relevant buffers designed to mimic the gastrointestinal environment. These networks were subjected to in vitro degradation and mucoadhension (before and after degradation) testing in order to model their performance in the gastrointestinal tract. Advanced surface characterization techniques (SEM, AFM, FTIR microscopy) were used to examine the network morphology prior to and after degradation. These studies indicate that there is an optimum crosslinking density to allow non-adhesive particles to reach the colon. Within the colonic environment, the azo network degrades to produce a structure capable of developing mucoadhesive interactions with the colonic mucosa. Amino acids and polymers were used as drug carriers for colon targeted delivery of 5-ASA. Water –soluble polymer containing salicylate residues azo linked at the 5-position to the polymer backbone was synthesized for the treatment of IBD. [5] A new concept of oral drug delivery was proposed based on a combination of site-specific delivery of 5-ASA to the colon bioadhesive properties of the carrier. HPMA copolymers containing saccharide units complementary to mucosal lectins of the GIT are used as carriers. They also contain side chains terminated in salicyclic acid bound via an azo bond. Cleavage experiments were carried out using an isolated strain of bacteria commonly found in the colon. When inoculated with *Streptococcum faecium in vitro* 5-ASA was released. Body distribution in guinea pigs after oral administration has shown that HPMA copolymers containing fucosylamine associate with the colon. HPMA copolymers were evaluated as colon-specific drug carriers. Their design was based on the concept of site-specific binding of carbohydrate moieties complementary to colonic mucosal lectins and on the concept of site-specific binding of carbohydrate moieties complementary to colonic mucosal lectins and on the concept of the site-specific drug (5-ASA) release by the microbial azoreductase activitity present in the colon (3). A new 5-aminosalicyclic acid-containing monomer was synthesized and incorporated into the copolymer together with the fucosylamine bioadhesive moiety containing comonomer by radical copolymerization. The in vitro release rate of 5-ASA from HPMA copolymers by azoreductase activity in guinea pig caceum was approximately 2.5 times lower that of a low molecular weight analogue. The azoreductase activities in caceum contents of guinea pig, rat and rabbit as well as in human faeces were determined. The relative activities for ratguniea pig:human:rabbit were 100:65:50:28. Both in vitro and in vivo HPMA copolymer containing side chains terminated in fucosylamine showed a higher adherence to guinea pig colon as compared to HPMA copolymer without fucosylamine moieties. The incorporation of 5-ASA containing aromatic side-chains into HPMA copolymer further increased their adherence probably by combination of non-specific hydrophobic binding with specific recognition.

To target the drugs specifically to colon, it need to be coated with either hydrophilic or hydrophobic polymer along with enteric polymer, at the neutral or slightly alkaline pH of the terminal ileum, the enteric coating breaks and the coating of second polymer would carry the drug to the target site. The colon is rich in harboring excellent micro flora, which can be used to the target the drug release in the colon. The formulation coated with microbially degradable polymers (azo polymers) passes intact from hostile environment of upper GIT and liberates the drug after reduction due to degradation of azo bonds by azo reductase enzymes present exclusively in the colon. Polysaccharides represent class of material that exhibits favorable properties for fabrication of colonic delivery system formulation protected with polysaccharides remain intact in the adverse enzymatic environment of stomach and small intestine. Releases of drug from such formulation take place after degradation of polysaccharides due to the cleavage of polysaccharides found in the colon. The most frequently encounter problem with the use of polysaccharides is their high water solubility, which causes the partial release of drugs in the upper GIT. Cross-linking of polysaccharides with agent such as gluaraldehyde, epichlorhydrin and sodium trimetaphosphate, which renders them hydrophobic, can rectify this. Multiple coated dosage from provides promising approach for the delivery of drugs to the colon. It is expected that film coated formulation composed of an enteric polymer and a hydrophilic polymer provides release of drugs at target site by delaying release in the upper GIT. All the approaches provide means for treatment of local diseases associated with the colon or for systematic absorption of poorly absorbable drugs.

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