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Review on, colon specific drug delivery Strategies and *in-vitro in-vivo* evaluation

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ABSTRACT

The increase in the interest in targeted delivery of drug to the colon via the oral route. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for example, allow topical treatment of inflammatory bowel disease. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Systemic side effects could also be reduced. Colon specific systems might also allow oral administration of peptide and protein drugs, which are normally inactivated in the upper parts of the gastrointestinal tract. Colon-specific systems could also be used in diseases that have diurnal rhythms. To achieve successful colonic delivery continuous efforts have been focused on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accommodate different therapeutic needs. Among the systems developed for colon-specific delivery, four systems were unique in terms of achieving in vivo site specificity, design rationale, and feasibility of the manufacturing process i.e. coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, and osmotic controlled drug delivery systems. The focus of this review is to provide detailed descriptions of the four systems, and in vitro/in vivo evaluation of colon-specific drug delivery systems.

Introduction

Among all the routes of administration that have been explored for the development of controlled release systems the oral route has by far achieved the most attention and success. That is due in part to the ease of administration as well as to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The scientific framework required for development of a successful oral controlled drug delivery dosage form consists of an understanding of three aspects of the systems such as physiochemical characteristics of the drug, relevant gastrointestinal anatomy and physiology and dosage form characteristics. Controlled drug delivery system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and known mechanism of release [1]. Drug delivery selectively to the colon through the oral route has been the subject of new research initiatives. In recent years there has been considerable research activity within the field of colonic drug delivery. This interest has been stimulated by a number of factors. The development of new therapeutic agents for the treatment of colonic disease has required colon specific drug delivery system to maximize the effectiveness of these drugs. The introduction of once a day sustained release formulations has required a better understanding of the transit of dosage forms through the colon and of the colonic absorption of the drugs contained within them[2-5].

Rationale for Colonic drug delivery systems

❖Drugs used for local effects in colon inflammatory bowel disease like ulcerative colonitis and crohn's disease. E.g. 5-amino salicylic acid, Mebeverine hydrochloride, Sulphasalazine, hydrocortisone acetate, 5-fluorouracil, doxorubicin, Nimustine.

❖Macro molecule structures peptide and proteins for systemic effects, because colonic environments are less hostile to these drugs. e.g.: calcitonin, interleukin, interferon, insulin, growth hormone, erythropotien, analgesic peptides oral vaccines, contraceptives, peptides etc.

❖Drugs which are poorly absorbed orally, as colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.

❖For the avoidance of hepatic first pass metabolism of drugs.

❖Where the delay in systemic absorption is therapeutically desirable, especially in disease susceptible to diurnal variation, Some orally administered drugs which exhibit poor uptake in upper gastrointestinal to show enzymatic action. e.g.: Metoprolol, Nifedipine, Isosorbide, Theophylline, Bromopheniramine, Diclofenac, and Ibuprofen.

To successfully modulate a colon drug delivery for maximal gastrointestinal absorption drugs one need to have a fundamental understanding of anatomic and physiological characteristics of human gastrointestinal tract [5-6].

Permeation enhancers for colon drug delivery system:

Targeting drugs directly to the colon is advantageous in the topical treatment of colonic disease such as ulcerative colitis, crohn's disease and for the oral delivery of peptides and other

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liable drugs. Absorption of drug molecules form the colon like other regions of GIT is a result of a complex series of events. Successful colonic uptake of a drug species require both enzymatic stability and has to transport from the mucosal surface to the venous and or lymphatic capillaries located in the sub mucosa. The colonic epithelial permeability is insufficient to allow for the transport rate required for a therapeutic delivery. Then the co administration of an absorption enhancing agent offers a potential means of overcoming this barrier mostly through the use of chemical enhancers [8-9]. These agents are roughly sub characterized into categories of chelating agents, non steroidal anti inflammatory agents (NSAIDS), surfactants (mostly as mixed micelles), phenothiazenes and a general class of molecules which include fatty acids, acylcarnitive acylamino acids and dicarboxylic acid. Comparison of their rate of onset and recovery of a treated mucosa has also been made. Fatty acids have strong and fast reactivity and allow for a fast recovery of barrier functions. Bile salts and salicylates are moderate and fast acting agents with fast barrier functions recovery[10]. Strong surfactants and chelating agents have strong or moderate reactivity and a slow recovery of barrier function and solvents such as dimethyl sulfoxide and ethanol have moderate reactivity and act primarily as agents to improve drug miscibility in an aqueous environment. There are other potential enhancers which may be more colon specific such as ethylacetoacetate which must be first metabolically transformed to emanine.

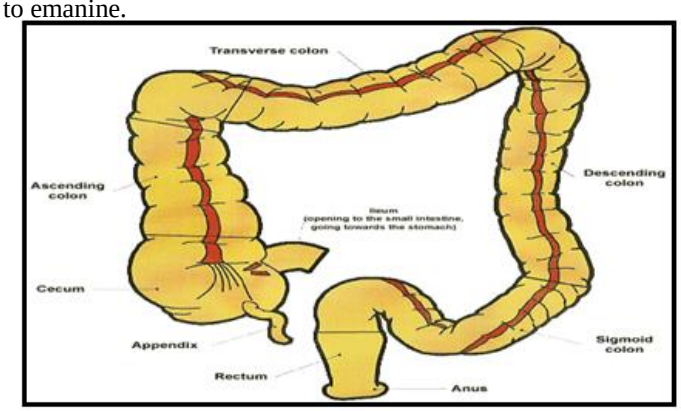

Fig 1: Anatomy of Colon

Several chemical enhancers including sodium taurocholate and Sodium ethylene diamino tetra acetate (Na-EDTA) oelic acid, Polyoxyethylated nonionic surfactants, Citric acid and dihydroxy bile salts open the paracellular OJC function. Deoxycholate, a dihydroxy bile salts, may also disrupt OJC function as well as stimulate cellular uptake through transcellular transport [11-12]. Agents which affect the local production of nitric oxide through the nerve stimulation at the ileocolonic junction will increase the epithelial permeability by decreasing the para-cellular resistance will increase the colonic drug absorption. Another component released during the nerve stimulation is substance P, possibly through activation of cycloxygenase pathway, also appears to modify the absorption across the colonic mucosa NSAIDS at high concentration can also act as cation chelators, their action appears to be more complex than a direct chelation effect [13].

Low concentration of sodium caprate, Sodium caprylate and Sodium salicylate can enhance transcellular uptake of poorly permeable compounds through colonic mucosa. It has been suggested that these enhancers might function to denature membrane proteins and / or modify their lipid protein interaction as a means of including drug uptake mixed micelles appear to produce only limited disordering of surface mucosal cells possibly by reducing the damaging effect of surfactants and somehow augmenting their enhancing activity [14-15].

Being less effective permeation enhancers, the glycocholate and taurocholate are co-formulated with lipids such as mono olein or oleic acid Glycocholate and taurocholate can produce dramatic improvements in the colonic uptake of heparin. Enhancement of colonic absorption by these chemical agents appears to be more specific to the drugs or molecules being transported. So, examples of colonic uptake of cefmetazole and insulin is enhanced by Sodium carprate, Sodium laurate and mixed micelle composed of Sodium oleate and Sodium taurocholate than EDTA, caprylate or taurocholate. Colonic uptake of fosfomycin is enhanced by polyoxyethylene lauryl ether (BL -GEX) saponin, Sodium salt of fatty acids and mixed micelle containing fasigenic lipids and taurocholate or glycocholate. Similarly mixed micelles composed of either taurocholate or glycocholate with mono olein, oleic acid, Lauric acid enhanced absorption of Gentamycin and Streptomycin [16-18]. Mixed micelles have also improved colonic uptake of the dye carboxy fluoroscin-5 Flurouracil, heparin and bleomycin. It is ascertained that absorption enhancement by surfactants, fatty acids and mixed micelles may in part be due to improved solution solubility or stability of the drug being transported.

Table No: 1 Classification of colon specific drugs

FIX	CLASS	EXAMPLES	TARGET DRUGS
I	NSAIDS	Indomethacin Diclofenac Phenylbutazone Salicylates	Ampicillin Cefmetazole Cefoxitin Insulin Levadopa, Lidocaine
II	Chelating Agents	EDTA Enamines Trisodium Citrate	Heparin Ampicillin Sulfanilic acid
III	Surfactants	Sodium lauryl sulphate Brij 35 Brij 58	Cefoxitin Lencomycin Insulin
IV	Phenothiazenes	Perphenazine Ether promazine Monoolien - Taurocholate Oleic acid -	Cefoxitin Gentamycin
V	Mixed micelles	Taurocholate Oliec acid - Polyoxy ethelene hydrogeneted caster oil (HCO - 60)	
VI	Other Agents Acylamino acids Dicarboxylic acids Acyl cametine Azone Acvl choline	Oleic acid - Glycocholate Phenylamino Non Amethylene dicarboxylic acids	Ampicillin

Stable molecules of specific molecular weight such as dextrin and polyethylene glycols have been used in a number of studies to address the size of transport window that can be opened in the colon. Muranishi and Takada have suggested that upon transport enhancement, low molecular weight drugs directed twice as often to a trans molecular pathway than the paracellular route, which molecules of 20 KDa are directly almost equally through the transcellular and paracellular routes[19-20]. This later ratio is presumed to decrease at some rate based upon the observation that molecules as large as to 70 KDa

shows only paracellular enhancement. The caparate, laurate and mixed micelles are seemed to be opening the colonic pores of 14 to 16 A°, taurocholate or caprylate opens the pores of 11 A° to 12 A°, linoliec acid opens rather sizeable molecular windows and linoleic acid-Hco-60. Mixed micelles and lipid enhancers systems can produce a significant uptake of 400 A°, colloidal gold particles from the rat colon [21].

Regarding with the fate of enhancers themselves, their rate of absorption must be same as that of the drug molecule whose absorption is been enhanced. Sometimes greater uptake ions can be seen through special mechanisms for bile salts and fatty acids, where bile salts are recycled into the liver and reprocessed in to bile component and fatty acids are metabolized by the colonic bacteria before colonic uptake. Many of other enhancers are acidic in nature, and they may affect the luminal pH and also have significant effects on colonic microbial flora, which can result in epithelial pathologies. On a positive note the colonic absorption of some molecules such as aspirin are enhanced at lower pH [22-24].

The epithelial cell membrane and the occluding junctional complex is the rate limiting barrier to transcellular and paracellular transport. These barrier functions are seemed to be altered in pathological states. In the case of Crohn's disease, increased phospholipase A_2 activity and increased colonic permeability appear to correlate with local inflammatory events although lysophospholipids enhance the mucosal permeability of proteins and peptide molecules. The repetitive delivery of lysophospho lipids to the colon as a permeation enhancer might cause unfortunate consequences since it has been suggested that the crohn's disease is due to the inability of the intestinal mucosa to compensate for the damage produced by endogenous lyso phospholipids [25-28].

The endogenous factors such as Histamines, Serotones Kenins, Arachidonic acid metabolites and Lymphakines can also have a profound effect on an absorptive or secretive function of colon by induction of the local inflammatory responses.

Increased permeability was also seen with Hemorrhage, Intestinal obstruction, Immunosuppresion, Burn trauma, Nonthermal trauma, Sepsis Radiation injury, Endotoxicosis and Clostridium difficile toxin A and also result in high local concentration of these effector molecules. The transport windows by the chemical enhancer are large enough for the passage of the bacterial toxins. So clearly number of concerns over the deleterious actions of chemical enhancers in the colon must be addressed [29].

Approaches to colon-specific drug delivery systems:

Rectal administration offers the shortest route to targeting drugs on the colon. However, reaching the proximal part of the colon via rectal administration is difficult. Rectal administration can also be uncomfortable for the patient, and compliance may be less than optimal.

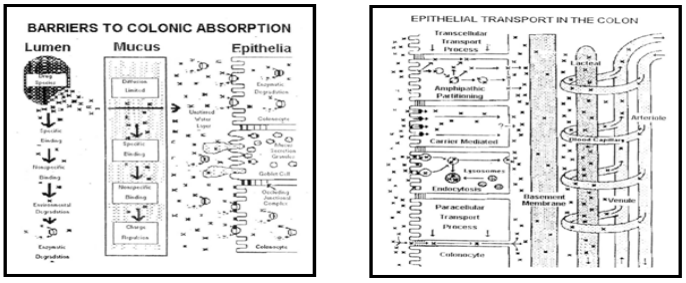

Fig 2: Barriers to colonic absorption and epithelial transport in the colon

There are several ways in which drugs can be targeted on the colon when they are given by mouth. In time-dependent formulations the drug concerned is released during the period of gastrointestinal transit time. Release from formulations that contain pH-dependent polymers takes place on the basis that pH is higher in the terminal ileum and colon than in the upper parts of the gastrointestinal tract. The colon is also home to large numbers of bacteria of many kinds. Prodrugs and dosage forms from which drug release is triggered by the action of colonic bacterial enzymes have therefore been devised [30-32].

Drug release based on variation of pH

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 and from the ileum to the colon pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6, in the descending colon 7.0. Use of pH-dependent polymers is based on these differences in pH levels. The polymers described as pH-dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. There are various problems with this approach; however, the pH in the gastrointestinal tract varies between and within individuals [33-34].

It is affected by diet and disease during acute stage of inflammatory bowel disease colonic pH has been has been found to be significantly lower than normal. In ulcerative colonitis pH values between 2.3 and 4.7 have been measured in the proximal parts of the colon. Although a pH- dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve even in the lower small intestine, and the site-specificity of formulations can be poor. Contrariwise, failure of enteric-coated dosage forms, especially single-unit dosage forms, because of lack of disintegration has been reported. 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-caecal junction or rapid transit through the ascending colon can also result in poor site-specificity of enteric-coated single-unit formulations [35].

Eudragit products are pH-dependent methacrylic acid polymers containing carboxyl groups. The number of esterified carboxyl groups affects the pH level at which dissolution takes place. Eudragit S ™ is soluble above pH 7 and Eudragit ™ L above pH 6. Eudragit™ S coatings protect well against drug liberation in the upper parts of the gastrointestinal tract and have been used in preparing colon-specific formulations. When sites of disintegration of Eudragit ™ S-coated single-unit tablets were investigated using a gamma camera they were found to lie between the ileum and splenic flexure. Site- specificity of Eudragit™ S formulations, both single- and multiple-unit, is usually poor [36-38].

Eudragit ™ S coatings have been used to target the anti-inflammatory drug 5-aminosalicylic acid (5-ASA) in single-unit formulations on the large intestine. Eudragit™ L coatings have been used in single-unit tablets to target 5-ASA on the colon in patients with ulcerative colitis or Crohn's disease. The polypeptide hormone vasopressin and insulin have been administered to rats orally in Eudrag™ S-coated single-unit capsules. Eudragit™ S-coated insulin capsules have also been administered orally to hyperglycemic beagle dogs. In the latter study it was concluded that plasma glucose levels were lowered gradually and reproducibly but that delivery by means of the oral route was not bioequivalent to delivery by means of

parenteral route (SC). Eudragit™ S has been used in combination with another methacrylic acid copolymer, Eudragit™ L100-55, in colon-targeted systems to regulate drug delivery. Dissolution studies showed that drug release profiles from enteric-coated single-unit tablets could be altered in vitro by changing the ratios of the polymers, in the pH range 5.5 to 7.0. Hydroxypropylmethylcellulose acetate succinate (HPMCAS) has been included in outer layers of single-unit press-coated tablets with a view to preventing drug release in the stomach and small intestine. Invitro dissolution studies suggested that such tablets could be useful as colon-specific formulations. No in vivo studies were undertaken [39-41].

Drug release based on gastrointestinal transit time

The time of transit through the small intestine is independent of formulation. It has been found that both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine. Transit time through the small intestine is unaffected by particle size or density, or by the composition of meals [42].

Because the time taken by formulations to leave the stomach varies greatly the time of arrival of a formulation in the colon cannot be accurately predicted. However, the effects of variation in gastric residence time can be minimized by using systems that are protected in the stomach, and thus release can be targeted on the colon by means of formulations that release the drug they contain a certain time after gastric emptying. Such formulations pass through the stomach and small intestine and drug is then released at the end of the small intestine or beginning of the colon. Accordingly, formulations that depend for drug release on time of transit through the small intestine also usually depend for drug release on changes in pH in the gastrointestinal tract. Transit times through the colon that are faster than normal have been observed in patients with irritable bowel syndrome, diarrhoea and ulcerative colitis. Systems that depend on gastrointestinal transit time for drug release are therefore not ideal for drug delivery in the colon for treatment of colon-related disease[43-45].

Combinations of hydrophilic (hydroxypropylmethylcellulose, HPMC) and hydrophobic polymers have been used as coatings for tablets that release drug from a core after a lag time. When the in vivo behaviour of such tablets was studied scintigraphically it was found that disintegration occurred in the proximal colon after about 5.5 hours (range 5 to 6.5 hours). Lag time could be adjusted by changing the thickness of the polymer layer. HPMC and hydroxypropylcellulose (HPC) have been used as swellable polymers in delayed release formulations. In such formulations enteric polymers can also be used as coatings to protect the formulation in the stomach. Using gammascintigraphy, Sangalli et al. (2001) investigated the in vivo behaviour of tablets with a drug-containing core coated with hydrophilic HPMC and an enteric polymer (Eudragit™ L3OD). The lag-time in relation to absorption was found to be 7.3 + 1.2 hours when the thickness of the polymer layer was greatest. The formulation disintegrated in the colon in all six volunteer subjects [46].

Time-controlled formulations have also been prepared using water- insoluble ethyl cellulose and swellable polymer (HPC). Each of the formulations consisted of a core, drug, swelling agent and a water-insoluble membrane. The swelling agent HPC absorbed liquid and the ethyl cellulose coat disintegrated as the core swelled. A lag time of 4.0 ± 0.5 hours in relation to absorption was found for this formulation in a human bioavailability study, and it was not influenced by food [47].

A drug delivery system (Pulsincap™), from which there is rapid drug release after a lag-time, has been developed to allow release of drug in the large intestine. The system involves an insoluble capsule body with a hydrogel plug. The plug is ejected from the capsule when it has swelled after a particular lag-time. A release profile is characterized by a period during which here is no release of drug know as lag time followed by rapid and complete drug release. Release using this system was found to be reproducible in vitro and in vivo. When gastrointestinal transit of the formulations was followed by means of gamma scintigraphy it was found in six of the eight subjects that the device reached the colon before drug was released. The formulation had been administered with the subjects in a fasting state. Effects of food and gastric retention time were not investigated. In later scintigraphic studies it was found that the site of release of drug in the gastrointestinal tract varied. In one subject the formulation even remained in the stomach for a long time, and drug was also released in the stomach [48].

A formulation that involves a plug that erodes rather than a hydrogel plug has also been developed. The aim of the studies described was to simplify the Pulsincap technology and develop a chrono pharmaceutical formulation.

Drug release based on the presence of colonic microflora

Both anaerobic and aerobic micro-organisms inhabit the human gastrointestinal tract. In the small intestine the micro flora is mainly aerobic, but in the large intestine it is anaerobic. About 400 bacterial species have been found in the colon, and some fungi. Most bacteria inhabit in the proximal areas of the large intestine, where energy sources are greatest. Carbohydrates arriving from the small intestine form the main source of nourishment for bacteria in the colon. The carbohydrates are split into short-chain fatty acids, carbon dioxide and other products by the enzymes glycosidase and polysaccharides. Protease activity in the colon can result in cleavage of proteins and peptides. In the proximal colon the pH is lower than at the end of the small bowel because of the presence of short-chain fatty acids and other fermentation products. Diet can affect colonic pH [49].

The presence of colonic microflora has formed a basis for development of colon-specific drug delivery systems. Interest has focused primarily on azo reduction and hydrolysis of glycoside bonds. However, the colonic microflora varies substantially between and within individuals, reflecting diet, age and disease. Such variations need to be taken into account in developing colon-specific formulations depending on the presence of colonic microflora. There is also significant proteoiytic activity in the colon, although this is 20 to 60 times less than in the small bowel. Even when proteolytic activity is relatively low a drug may remain much longer in the colon than in the small intestine, with the result that it is exposed longer to proteolytic activity [50]. Prodrugs have been used in targeting drugs on the large intestine. Sulphasalazine, used in the treatment of ulcerative colitis and Crohn's disease, is a colon-specific prodrug. In the colon sulphasalazine is split by bacterial azo reduction into 5-ASA and sulphapyridine. Sulphasalazine can cause side effects, and other carriers for delivery of 5-ASA to the colon have therefore also been investigated. Olsalatzine consists of two molecules of 5-ASA linked by an azo-bond. Ipsalatsine and balsalatsine are other 5- ASA containing Prodrugs. Polymers and polyamides containing azo groups have been used to convey 5-ASA to the large intestine. Azo polymers have been used as colon- specific film coatings. Colon targeting by means of azo polymers is associated with many problems.

Microbial degradation of azo polymers is usually slow, and drug delivery can be incomplete and irregular. Not enough is yet known about the safety of azo polymers. In vivo absorption studies with azo polymers have mostly been carried out using rats. No results of studies in human beings are available [51]. Although the gastrointestinal microflora of rats and humans differ, results of in vivo experiments with rats can give some indications regarding biodegradation of azo polymers.

Hydrogels containing azo-aromatic cross-links have been investigated in connection with site-specific drug delivery of peptide and protein drugs. In the low pH range of the stomach the gels have a low equilibrium degree of swelling and the drug is protected against digestion by enzymes, but at high pH levels they swell. So in the stomach a drug will be protected, but released in the colon, where cross-links become degraded.

The colonic microflora produces a wide range of glycosidases capable of hydrolysing glycosides and polysaccharides. Glycosides of glucocorticosteroids have been synthesized, and tested in rodents. The problem in these studies was that some drug was hydrolysed even in the small intestine. However, in rodent bacterial glycosidase activity in the small intestine is some 100 times greater than in human beings. It is likely that drug delivery in man would be more predictable than in rodents. Glucuronides, which are less subject to hydrolysis in the small intestine than glycosides, have also been used as drug carriers [52].

An extensive range of drug delivery systems based on polysaccharides has been investigated. The advantage of these materials is that most are easily available. Disadvantages are that most of polysaccharides are hydrophilic and gel forming. In preparing dosage forms from polysaccharides it is necessary to ensure that no drug is released until it reaches the colon.

Amylose has been used in coatings of colon-specific formulations. Amylose, a major component of starch, swells too much on its own, but amylose-ethyl cellulose coatings have been investigated in connection with targeting of drug release on the colon. From the results of in vitro studies it was concluded that amylose-ethyl cellulose coatings could be suitable for colon-specific formulations [53].

Pectin is a polysaccharide, found in the cell walls of plants. It is totally degraded by colonic bacteria but is not digested in the upper gastrointestinal tract. One disadvantage of pectin is its solubility. This can however be adjusted by changing its degree of methoxylation, or by preparing calcium pectinate. The film-coating properties of pectin have been improved through use of ethyl cellulose. Pectin has also been used with chitosan and HPMC. It has been shown in studies in which gamma camera was used that pectin-coated tablets disintegrate in the colon during transit.

Cross-linked guar gum has been used as a drug carrier in matrix tablets. It was concluded that guar gum is suitable for preparation of colon-specific formulations and is particularly suitable as a carrier of drugs that are not very soluble in water. However, the guar gum formulations mentioned have only formed the subjects of in vitro dissolution studies and in vivo evaluation in rats.

Dextran ester prodrugs have been investigated as means of transporting drugs to the colon. When the bioavailability of naproxen after administration of dextran-naproxen prodrug was assessed in pigs, lag times of two to three hours were observed. Dextran esters of fatty acids have been used to form colon-specific film coatings. The suitability of such formulations for colon-specific drug delivery in human being remains to be demonstrated in volunteers.

Chitosan is a high-molecular-weight polysaccharide that is degraded by colonic microflora. Insulin and 5-ASA have been administered to rats in enteric-coated chitosan capsules. A multiple-unit formulation containing chitosan and drug has also been prepared. This formulation depended for drug delivery on both variations in gastrointestinal pH and the presence of colonic microflora [54].

Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. (1995) have developed pressure- controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The system also appeared to depend on capsule size. When salivary secretion of caffeine after oral administration of pressure-controlled capsules was studied in human volunteers, a correlation was found between ethyl cellulose membrane thickness and the time of first appearance of caffeine in the saliva.

Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human subjects. It was concluded that the capsules disintegrated in the colon because of increases in pressure. It was also concluded that the formulation studied was advantageous in that the drug release mechanism is independent of pH. The site at which the formulations disintegrated was not demonstrated in the studies mentioned above. The mechanism of disintegration was also not clarified. As discussed above, ethyl cellulose coatings have also been used in connection with time- controlled drug delivery. Disintegration of the formulation can therefore also occur some time after administration, even in the small intestine.

Tab No: 2 Advanced research on colon specific drug delivery

Method	Advantages	Disadvantages	References
Time – dependent systems	Small intestine transit time fairly consistent	Substantial variation in gastric retention times	Davis et. al. 1986.
		Transit through the colon more rapid than normal in patients with colon disease.	Yang et. al. 2002.
pH-dependent systems	Formulation well protected in the stomach	pH levels in the small intenstine and colon vary between and within individuals	Friend 1991 Ashford and Fell 1993. Kinget et. al.
		pH levels in the end of small intestine and caecum are similar.	Yang et. al. 2002.
		Poor site specificity	Ashford et. al.
Microflora-activated systems	Good site-specificity with prodrugs and polysaccharides	Diet and disease can affect colonic microflora	Rubinstein et. al. 1997. Yang et. Al. 2002.
		Enzymatic degradation may be excessively slow	
		Few have been accepted for use in relation to medicines.	

Conclusions concerning colon-specific drug- delivery methods

During the last decade many investigations have been carried out with the aim of discovering an ideal formulation for colon-specific drug delivery. Many approaches have been demonstrated. All are having some disadvantages. The microflora of the colon can split polymers. However, such enzymatic degradation is usually excessively slow. The bio-availabilities of drugs from such formulations can be low. In addition, little is known about the safety of the polymers and few have been accepted for use in relation to medicines. Most studies relating to biodegradable polymers have been carried out only in vitro or in laboratory animals.

Time-controlled formulations have also been investigated and developed in connection with targeting of drug delivery on the colon. Formulations of this kind need to be manufactured in such a way that they remain intact in the stomach, in the presence or absence of food. Manufacture of such formulations on an scale is often complicated and expensive.

Formulations involving enteric polymers that react to changes in gastrointestinal pH have been extensively used in connection with colon specific drug delivery. Enteric polymers have been shown to be safe, and have been accepted for use in drug products. The enteric polymers that have been used are soluble above pH 6 to 7. The pH at the end of the small intestine is about 7.5. It is therefore obvious that drug release from enteric coated formulations can begin from the end of the small intestine. pH levels dissolution tests of a colon-specific formulation in various media simulating pH conditions at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment [55].

***In-vitro – in-vivo* evaluation of colon specific drug delivery**

Consecutive dissolution tests in different buffers for different periods of time best simulate the transit of a formulation through the gastrointestinal tract. In gradient dissolution studies a particular formulation unit is exposed to buffers representing successive conditions in the gastrointestinal tract. Enteric-coated capsules for colon-specific drug delivery have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4. The relationship between percentage of drug released in vitro and percentage of drug absorbed in vivo was observed when pulsatile-release tablets were tested in vitro for two hours at pH 1.2 followed by a dissolution study at pH 6.8 [56-57].

Fukui et al. (2000) kept enteric-coated tablets in a buffer at pH 1.2 for 16 hours. A dissolution study was then carried out at pH 6.8. It was concluded that the dissolution profiles of formulations that had not been kept in buffer at pH 1.2 did not differ markedly from dissolution profiles of formulations that had been kept in buffer at pH 1.2. Exposure to acid in the stomach should therefore not affect the dissolution properties of such formulations in the lower gastrointestinal tract. On the basis of these findings it is obvious that sufficient information regarding dissolution properties of formulations can often be obtained using parallel dissolution tests. Gradient dissolution tests are usually unnecessary [58].

To allow the performance of colon-specific delivery systems containing biodegradable polymers to be assessed, the contents of animal caecum have been used in dissolution studies. Such studies provide no information about the physical and chemical functionality of a system [59].

In vivo bioavailability tests in human beings are important in developing controlled-release drug delivery systems. From the results of bioavailability tests, sites of drug liberation in vivo can be determined, if the formulation has been administered to the subjects in the fasting state. However, it is impossible to predict times of arrival of formulations in the colon accurately, because gastric emptying times vary so greatly. In recent years gammascintigraphy has become the most popular means of investigating the gastrointestinal performance of pharmaceutical dosage forms; especially site-specific dosage forms Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gammascintigraphy studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphy studies (pharmacoscintigraphy). Good correlations between appearance of a drug in plasma and observed disintegration times have been recorded [60].

When gammascintigraphy was used to investigate the suitability of an Eudragit™ S-coated tablet for drug delivery to the colon results of the study were found to be in accordance with results of in vitro dissolution studies. Gammascintigraphy has also been used to determine gastrointestinal transit times and sites of disintegration of calcium pectinate tablets intended to allow colon-specific drug delivery, Although the tablets disintegrated completely in the colon it was concluded that gammascintigraphy did not allow exact information about the mechanism of disintegration to be obtained [61].

Many pharmacoscintigraphy studies have been reported. Stevens et al. (2002) used gammascintigraphy to identify the site of release from a Pulsincap™ formulation, intended to release drug after a five-hour lag time. Plasma concentrations of the model drug were also followed. A good correlation was found between release times determined scintigraphically and pharmacokinetic profiles. A correlation between pharmacokinetic and gammascintigraphy data was also found when times and anatomical locations of break-up of colon-specific formulation were determined by Sangalli et al. (2001). Different *in vitro* and *in vivo* methods are used to evaluate different carrier systems for their ability to deliver drugs specifically to the colon. The ability of the coats or carriers to remain intact in stomach and small intestine is generally assessed by conducting drug release studies in 0.1N hydrochloric acid for 2 hours followed by phosphate buffer (pH -7.4) for 3 h by using dissolution apparatus. The drug release studies may also be performed by using rat cecal contents. Another *in-vitro* method involves incubation of the drug delivery system in a fermentor with commonly found colonic bacteria. *In vivo* methods offer various animal models. Guinea pigs were used to evaluate colon- specific drug delivery from a glucoside prodrug of dexamethasone. *In vivo* gamma scintigraphic studies were carried out on the guar gum matrix tablets, using technetium 99 m- DTPA as a tracer. Scintigraphs taken at regular intervals have shown that some amount of tracer present on the surface of the tablets was released in stomach and small intestine. Radiotelemetry, Roentenograpgy are the other *in vivo* evaluation methods for colon-specific drug delivery system [62].

***In-vivo a*nimal studies:**

When the system design is conceived and prototype formulation with acceptable in-vitro characteristics is obtained, in vivo studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetics information of the delivery system.

Animal studies: Different animals have been used to evaluate the performance of colon- specific drug delivery systems such as rats, pigs and dogs. To closely simulate the human physiological environment of the colon, the selection of an appropriate animal model for evaluating a colon- specific delivery system depends on its triggering mechanism and system design. Although animal models have obvious advantages in assessing colon- specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems with visualization techniques. Various techniques used for monitoring the in vivo behavior of colon- specific delivery systems [63].

Gamma-scintigraphy:

In recent years gamma scintigraphy has become the most popular means of investigating the gastrointestinal performance of pharmaceutical dosage forms, especially site-specific dosage forms. Gamma-scintigraphy using a non-radioactive isotope used to identify the anatomical site and time of disintegration in the human gastrointestinal tract. By means of gamma-scintigraphic imaging, information can, for example, be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained Gamma-scintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behavior of dosage forms can be obtained by combining pharmacokinetic studies and gamma-scintigraphic studies (pharmaco- scintigraphy). Good correlations between appearance of a drug in plasma and observed disintegration times have been recorded. This technology is now in common use for pharmacokinetic studies because of the following advantages such as preparations are made in a non-RI (radioisotope) room. The preparation containing radiotracer can be used to track formulation performance even when used in a trace amount. The preparation is safe because it is neither dissolve in or nor absorbed from the GI tract [64].

Roentgenography:

The inclusion of a radio-opaque material into a solid dosages form enables it to be visualized by the use of X- rays. By incorporating barium sulfate into a pharmaceutical dosages form, it is possible to follow the movement, location and the integrity of the dosages after oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time points [65].

Conclusion

There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Colon specific drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc. Colon specific drug delivery has also gained increased importance for the delivery of drugs for the treatment of local diseases associated with the colon such as inflammatory bowel diseases (ulcerative colitis, Crohn's disease), some carcinomas, and gastrointestinal infections to maximize the effectiveness of these drugs. Colon is also a potential site for the systemic delivery of therapeutic peptide and proteins. A considerable amount of research work has been carried out on the development of colon- specific drug delivery systems for the last two decades. Many approaches have been demonstrated. All have some disadvantages. The large inter and intra- subject variation in G.I pH makes the pH dependent system less suitable. Time dependent system is not a feasible solution due to variable gastric and small intestinal transit times. Pressure controlled systems hold some promise but little is known about the luminal pressure of different regions of the G.I tract. Microbial controlled systems which rely on conditions which are only encountered in the colon, these systems give true site specificity. Natural polymers such as pectin, guar gum, chitosan etc are more favorable carriers for these systems, but these naturally occurring polymers have inherent water solubility which can lead to decreased biodegradability. It may be concluded that no ideal formulation for colon-specific drug deliver yet exists. Colonic drug delivery has several therapeutic advantages. The delivery of drugs to the colon is of value in the systemic disease. This can be achieved by different approaches include in matrix and coated system using polysaccharides such as Chitosan, Guar gum and Ceratonia. These polysaccharides are extensively degraded by the bacteria residing exclusively in the colon and the site specific delivery of drug is achieved at this region. The delivery of the drugs directly to the colon via the oral route has several therapeutic advantages. These polysaccharides are capable of retarding the release of the core materials until they reach the colon. Environment rich bacterial enzymes, which degrade the Guar gum and Chitosan allowing the drug release.

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