Review Article

AN OVERVIEW ON COLONIC DRUG DELIVERY SYSTEM

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ABSTRACT

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. Natural polysaccharides have been used as a tool to deliver the drugs specifically to the colon. Formulation coated with enteric polymers releases drug, when pH move towards alkaline range while as the multicoated formulation passes the stomach, the drug is released after a lag time of 3-5 hours that is equivalent to small intestinal transit time. Drug coated with a bioadhesive polymer that selectively provides adhesion to the colonic mucosa may release drug in the colon. Historically, the clinical applications of colonic drug delivery have been limited to the local treatment of inflammatory bowel disease with little consideration of the possibility for systemic absorption. The physiology and environmental conditions in the colon extremely low surface area due to lack of villi and lack of fluid would seem to support this view. Nevertheless, other local diseases of the large intestine could benefit from topical delivery to the colonic mucosa. The potential of the colon for systemic delivery of drugs including vaccines, proteins and peptides, is gaining renewed interest. The review is aimed at understanding Pharmaceutical approaches to colon targeted drug delivery systems for better therapeutic action without compromising on drug degradation or its low bioavailability.

Keywords: Colon drug delivery, polymers, approaches, recent techniques.

INTRODUCTION

Oral controlled release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including Pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate or sustained release products.[1,2]

By definition, colonic delivery refers to targeted delivery of drugs into the lower gastrointestinal tract, which occurs primarily in the large intestine (i.e. colon). The site-specific delivery of drugs to lower parts of the gastrointestinal tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction.[3,4] It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon.

These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules, where they are needed most and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the Gastrointestinal tract, namely stomach and small intestine.[5]

Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may need to be delivered in a pre-solubilized form or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug.[6]

To understand the mechanism of colon targeted drug delivery system[7], the anatomy of stomach and intestine is given in figure no.1 and the ranges of pH for the different regions[8] of Gastrointestinal tract is given in table no 1.

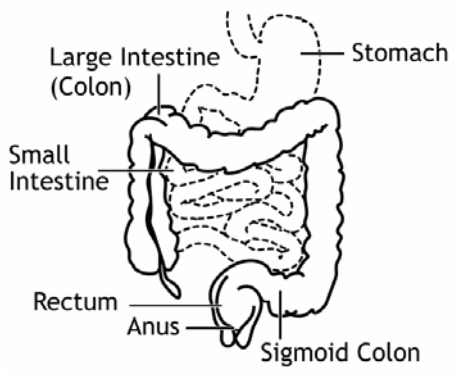

Figure 1: Anatomy of Stomach and Intestine

Table No. 1: Ranges of pH of Gastrointestinal Tract

Region	pH
Stomach (before meal)	1-2
Stomach (during digestion)	4
Small intestine	6-7
Duodenum	6.6 +0.5
Ileum	7.5 +0.4
Cecum	6.4 +0.4

Why Colon Targeted Drug Delivery is Needed?

a) Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.

b) To delay the drug absorption.

c) To prevent asthma, arthritis attacks in early morning.

d) 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.

e) Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.

f) The colon is a site where both local and systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, for example Ulcerative Colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).

g) 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.

h) 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 gastrointestinal tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides[9].

General Considerations for Design of Colonic Formulations

Formulations for colonic delivery are, in general, delayed-released dosage forms which may be designed either to provide a 'burst release' or a sustained / prolonged / targeted.

i. Pathology of disease, especially the affected parts of the lower GIT.

ii. Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery.

iii. The preferred release data of the drug.

Very common physiological factor which is considered in the design of delayed release colonic formulations is pH gradient of the gastrointestinal tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH is 6.6±0.5) to the end of the ileum (pH is 7.5 ± 0.4), a decrease in the cecum (pH is 6.4 ± 0.4) and then a slow rise from the right to the left colon with a final value of 7.0 ± 0.7. Some reports suggested that alterations in gastrointestinal pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations.[10]

Limitations and Challenges in Colon Targeted Drug Delivery

I. One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system *in-vitro*. This is due to the rationale after a colon specific drug delivery system is quite diverse.

II. As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.

III. Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.

IV. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may

potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.

V. The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation[11].

The literature also suggested that the cytochrome P-450 (3A) class of drug metabolizing enzymes have lower activity in the colonic mucosa. A longer residence time of 3 to 5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

There are some of the diseases and drugs which are generally used for the colon targeting sites which is shown in table no 2.[12]

Table 2: Colon Targeting Sites, Diseases and Drugs

Target site	Diseases	Drugs
Topical action	Inflammatory Bowel disease, Irritable Bowel disease and Crohn's disease, Chronic pancreatic	Hydrocortisone Budesonide, Prednisolon, Sulfasalazine, Olsalazine
Local action	Pancreactomy and cystic fibrosis, cororectal cancer	Digestive enzymes, supplements, 5-Fu
Systemic action	To prevent gastric irritation To prevent first pass metabolism	NSAID Steroids

APPROACHES TO DELIVER THE INTACT MOLECULE TO THE COLON

1. 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. 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. The pH in the gastrointestinal tract varies between and within individuals.

It is affected by diet and disease, for example. During acute stage of inflammatory bowel disease colonic pH has been has been found to be significantly lower than normal. In ulcerative colitis 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. 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. 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 units, is usually poor. Eudragit S coatings have been used to target the anti-inflammatory drug of 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 Eudragit S-coated single-unit capsules. Eudragit S-coated insulin capsules have also been administered orally to hyperglycaemic 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 of 5.5 to 7.0. Hydroxy propyl methyl cellulose 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. *In-vitro* dissolution studies suggested that such tablets could be useful as colon-specific formulations as shown in table no 3.

Table 3: Polymers used in Colonic Drug Delivery System

Polymer	pH
Eudragit L100	6.0
Eudragit S100	7.0
Polyvinyl acetate phthalate	5.0
Hydroxy propyl methyl cellulose phthalate	4.5
Cellulose acetate phthalate	5.0

2. Drug release based on gastrointestinal transit time

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. 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 drug release can be targeted on the colon by means of formulations that releases the drug which contain a certain time after gastric emptying. Such formulations pass through the stomach and small intestine and drug is 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 of the gastrointestinal tract. Transit times through the colon that is faster than normal that 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. Combinations of hydrophilic (hydroxyl propyl methyl cellulose, 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 hydroxyl propyl cellulose (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 gamma scintigraphy, investigated *in-vivo* behavior of tablets with a drug-containing core coated with hydrophilic HPMC and an enteric polymer (Eudragit L30D).[13] 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. 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.

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.[14] 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 no release 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 carried out by gamma scintigraphy, it was found that 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.[15] 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 chronopharmaceutical formulation.

3. Drug release based on the presence of colonic micro flora

Both anaerobic and aerobic micro-organisms inhabit the human gastrointestinal tract. In the small intestine, the microflora 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 polysaccharidase. 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. 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 proteolytic 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. 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 azoreduction into 5-ASA and sulphapyridine. Sulphapyridine 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 of 5-ASA containing prodrugs. Polymers and polyamides containing azo groups that 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. 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 it swells. 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. 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 amylase ethylcellulose 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 amylase ethylcellulose coatings could be suitable for colon-specific formulations. 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 ethylcellulose. Pectin has also been used with chitosan and HMPC. 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.[15] 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.

4. Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya have developed pressure controlled colon-delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems, drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The system also appeared to depend on capsule size. 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.

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 sometime after administration, even in the small intestine[16-21].

There are some of the advantages and disadvantages of colon drug delivery system which are given in below table no. 4. [22-27]

Table 4: Advantages and Disadvantages of Colonic Drug Delivery System

Advantages	Disadvantages
Reduced dose frequency.	Low dose loading.
Improved patient compliance.	Higher need of exipients.
Delivery of drug in its intact form as close as possible to the target sites.	Lack of manufacturing reproducibility and efficacy.
Reduction in dose size.	Multiple formulation steps.
Improve bioavailability.	Large number of process variables.
Flexibility in design.	Need of advanced technology.
Reduced incidence of adverse side effects improved tolerability.	Skilled personal needed for Manufacturing of colonic drug delivery system.
Protection of mucosa from irritating drugs.	----------
Drug loss is prevented by extensive first pass metabolism.	----------
Lower daily cost to patient due to fewer dosage units are required by the patient.	----------

The table below shows drugs which are used for the targeting of colon which are given on the basis of targeting technique which is used [28, 29].

Table 5: List of Drugs which are used for the Targeting of Colon

Drugs used	Targetting technique
Paracetamol	pH- dependent
5-aminosalicylic acid	pH- dependent / Enzyme controlled (Polysaccharide based / prodrug based)
Diclofenac sodium	pH- dependent / Enzyme controlled (Polysaccharide based) / Time dependent
Mesalazine	pH- dependent
Indomethacin	Time - dependent/ Enzyme controlled (Polysaccharide based)
Naloxone	Enzyme controlled (Prodrug based)
Budesonide	Enzyme controlled (Prodrug based)
Prednisolon	pH- dependent
Pseudoephedrine HCl	Time – dependent
Theophylline	Time – dependent
Dexamethasone	Enzyme controlled (Polysaccharide based)
Fludrocortisone	Enzyme controlled (Prodrug based)
Diltizem HCl	Time – dependent
Mebendazole	Enzyme controlled (Polysaccharide based)
5- Fluorouracil	Enzyme controlled (Polysaccharide based)

NEW TECHNOLOGIES

A new concept in colonic drug targeting, recently described by uses a combined pH-responsive and bacterially triggered drug delivery technology. The technology combines the bacterial and pH mediated approaches used previously for colonic delivery. The combination of these independent but complementary release mechanisms should overcome the limitations associated with the single trigger systems and improve site specificity. The technology involves the combination of a pH-sensitive polymer with resistant starch. This mixture is used as a film coating matrix, which can be applied to tablets, capsules or pellets. The results of testing tablets with the new coating in healthy volunteers to assess the site of disintegration using gamma scintigraphy. In contrast to the performance of the pH-responsive polymer coatings mentioned reported that the coated tablets were able to resist breakdown in the stomach and small intestine. Consistent disintegration of the dosage form was observed at the ileocaecal junction/large intestine and this was unaffected by food.

The success of the system was attributed to the role of starch, which is not digestible by mammalian pancreatic amylase but is readily digested by colonic bacterial enzymes. Thus, even if the pH-responsive polymer component of the film remains intact, the colonic bacterial enzymes will still digest the starch component allowing dosage form disintegration.

It is claimed that the starch provides a back-up or 'fail-safe' for dosage form disintegration. One of the physiological constraints to the colonic delivery of drugs is the low volumes of fluid available for disintegration of dosage forms and subsequent dissolution. A combination of the new colonic drug targeting technology with liquid filled hard capsule technology, where the drug is delivered as a solution, suspension or self-emulsifying system, has yet to be investigated, but may well prove to be an ideal platform technology for the delivery of drugs to the colon.[30-32]

CONCLUSION

The advantages of targeting drugs specifically to the diseased colon are reduced incidence of systemic side effects, lower dose of drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. The various strategies for targeting orally administered drugs to the colon include coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bioadhesive systems. All the approaches provide means for treatment of local diseases associated with the colon

or for systemic absorption of poorly absorbable drugs. The colon is rich in microflora, which can be used to target the drug release in the colon. The need is to identify the appropriate approach, which can results in the delivery of drugs in a safe, effective and less expensive manner with minimum fluctuation in terms of release of drugs at target site.

Lastly the patents which are taken on colon drug delivery system from the date year 1994 to 2007.[33]

Table 6: List of Patents on Colon Targeted Drug Delivery Approaches

Patent No	Title	Patenting Date
5302397	Polymer-based drug delivery system	12/4/1994
5407682	Process for the preparation of azo-and /or disulfide polymer matrix drug delivery system for the site specific delivery of an active agent in the colon	18/4/1995
5525634	Colonic drug delivery system	11/6/1996
5536507	Colonic drug delivery system	16/7/1996
5626877	Polymer-based drug delivery system	6/5/1997
5866619	Colonic drug delivery system	2/2/1999
6200602	Composition for enhanced uptake of polar drugs from the colon	13/3/2001
6228396	Colonic drug delivery composition	8/5/2001
6322819	Oral pulsed dose drug delivery system	27/11/2001
6319518	Colon selective drug delivery composition	20/11/2001
6231888	Local delivery of non steroidal anti inflammatory drugs (NSAIDS) to the colon as a treatment for colonic polyps	15/5/2001
6413494	Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides	2/7/2002
6368629	Colon-specific drug release system	9/4/2002
6605300	Oral pulsed dose drug delivery system	12/8/2003
6506407	Colon-specific drug release system	14/1/2003
20050118268	Timed pulsatile drug delivery systems	2/6/2005
20070243253	Colonic drug delivery formulation	18/10/2007
20070178108	Colon Specific Gene and Protein and Cancer	2/8/2007

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