Review Article

Available online through
www.ijrap.net

IJRAP
ISSN 2229-3566

# COLON TARGETED DRUG DELIVERY SYSTEM: A REVIEW

Koteshwara K.B.*, Naha Anup, Nampoothiri Madhavan
Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India -576104

Received on: 28/12/2010 Revised on: 24/01/2011 Accepted on: 11/02/2011

**ABSTRACT**
Site specific drug delivery has gained a lot of interest in the last decade for formulations. One such specific target is colon wherein both local and systemic drug delivery can take place. General approaches for Colon targeted drug delivery include use of prodrugs, pH dependent system, time dependent systems and clonic microflora activated systems. Here in this review we give an overview of all these methods tried so far including some information on marketed and patented drug delivery dosage forms.
**KEYWORDS:** colon, drug delivery, target

***Address for Correspondence**
K.B Koteshwara, Associate Professor, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal, Karnataka, India -57610

## INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for providing both systemic as well as local effects in various regions of the gastro intestinal tract. Conventional oral dosage forms provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. Traditionally, solid oral dosage forms have been designed to release their drug load in the upper regions of the gastrointestinal tract, where conditions are generally more suited to drug dissolution and absorption. Recently, greater emphasis has been placed on controlling the site and/or rate of drug release from oral formulations for the purposes of improving treatment efficacy and patient compliance. Over the last three decades, many novel oral drug therapeutic systems have been invented like fast release preparations, controlled release preparations, targeted release preparations, colon specific drug delivery system etc.,

During the last decade there has been interest in developing site-specific formulations for targeting drug delivery to the colon. The colon is a site where both local and systemic drug delivery can take place[1]. A local means of drug delivery could allow topical treatment of diseases associated with the colon such as amoebiasis, ulcerative colitis, crohn's disease and colon cancer. Treatment may be more effective if the drug substances are targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced. Site-specific means of drug delivery could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of the gastrointestinal tract[2].This is because of the favorable environment in colon in comparision to the upper gastrointestinal tract[3] with the low diversity and intensity of the digestive enzymatic activities as well as the near neutral pH. Vaccines, insulin and growth hormone are examples of such drug candidates. Colon-specific systems could also be used in conditions in which a diurnal rhythm is evident, e.g. asthma, rheumatic disease, ulcer disease and ischaemic heart disease[4]. Because dosage forms remain longer in the large intestine than in the small intestine, colon-specific formulations could be used to prolong drug delivery. For oral administration to succeed, however, many physiological barriers have to be overcome. Absorption or degradation of the active ingredients in the upper part of the gastrointestinal tract is a main obstacle and must be circumvented for successful colonic drug delivery. 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[5]. Several reviews have been published reporting the research that has gone into the development of perorally delivered single unit colon targeted drug

delivery systems[6]. In general four primary approaches have been proposed for colon targeted delivery namely prodrugs, pH dependent system, time dependent systems and colonic micro flora activated systems[7].

**APPROACHES FOR COLON TARGETED DRUG DELIVERY**

**Colonic Microflora dependent drug delivery**

Both anaerobic and aerobic micro-organisms inhabit the human gastrointestinal tract[8]. In the small intestine the microflora is mainly aerobic, but in the large intestine it is anaerobic. Most bacteria inhabit in the proximal areas of the large intestine, where energy sources are greatest[2]. Carbohydrates arriving from the small intestine form the main source of nourishment for bacteria in the colon. 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[8].

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 [9]. 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. Because of the presence of the biodegradable enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo degradation by enzyme or break down of the polymer structure leading to release of the drug in the colon.

**Prodrug approach**

Prodrugs have been used in targeting drugs to the colon. Prodrug are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the drug carrier. Subsynthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. These have been shown to be susceptible to cleavage by the azoreducatase enzyme in the large bowel.

Sulphasalazine, used in the treatment of ulcerative colitis and Crohn's disease, is a colon-specific prodrug [10]. In the colon sulphasalazine is split by bacterial azoreduction into 5-ASA and sulphapyridine [11]. Polymers and polyamides containing azo groups have been used to convey 5-ASA to the large intestine[12]. Hydrogels containing azo-aromatic cross-links have been investigated in connection with site-specific drug delivery of peptide and protein drugs[13]. 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. Colon targeting by means of azo polymers is associated with many problems[14]. 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.

**Polysaccharide approach**

An extensive range of drug delivery systems based on polysaccharides has been investigated. The advantage of these materials is that most are easily available, are found in abundance, have wide availability, are inexpensive and are available in a verity of a structures with varied properties 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 formulation. Amylose, a major component of starch, swells too much on its own, but amylose-ethylcellulose coatings have been investigated in connection with targeting of drug release on the colon. 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 [15]. The film-coating properties of pectin have been improved through use of ethylcellulose. Pectin has also been used with chitosan [16] and HMPC[17]. 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[18,19]. 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. Chitosan is a high-molecular-weight polysaccharide that is degraded by colonic microflora[20].

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[21]. This formulation depends for drug delivery on both variations in gastrointestinal pH and the presence of colonic microflora. Disadvantages are that most of polysaccharides are hydrophilic and gel forming.

**Gastrointestinal Transit Time dependent drug delivery**

Transit time through the small intestine is independent of type 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[22,23]. 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 release the drug after a certain time of gastric emptying. 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. 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 [24]. 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). Gammascintigraphy[25] has been used to investigate the in vivo behaviour of tablets with a drug-containing core coated with hydrophilic HPMC and an enteric polymer (Eudragit™ L30D). 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 ethylcellulose and swellable polymer (HPC)[26]. Each of the formulations consisted of a core, drug, swelling agent and a water-insoluble membrane. The swelling agent HPC absorbed liquid and the ethylcellulose 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 [27]. 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. The release profile is characterized by a period during which there is no release followed by rapid and complete drug release. When gastrointestinal transit of the formulations was followed by means of gamma scintigraphy it was found that the device reached the colon before drug was released[27]. A formulation that involves a plug that erodes rather than a hydrogel plug, has also been developed[28]. The aim of the studies described was to simplify the Pulsincap™ technology and develop a chronopharmaceutical formulation.

**pH dependent drug delivery**

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[29]. The pH declines significantly from the ileum to the colon. 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 and 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.

Eudragit, and more specifically Eudragit L and S are the principal group of polymers utilized for the preparation of colon-targeted dosage forms. The polymers form salts and dissolve above pH 6.0 and 7, respectively. Eudragit L 100-55 disperses in water to form latex and thus avoids the use of organic solvents in the coating process (Eudragit L 30 D-55 is a ready-to-use aqueous dispersion of Eudragit L 100-55). 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[30].

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 [30]. 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 (Hardy et al. 1987). 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 [31]. 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). DanBioSyst has developed a simple-to-manufacture colon targeting system (TARGIT) that is based on injection-molded starch capsules coated with a mixture of Eudragit L and S. The mixture of Eudragit is chosen to provide a coating that begins to dissolve as the capsule enters the small intestine from the stomach as per US Patent 6228396. Eudragit L 100-55 and Eudragit S 100 combinations have been reported to be superior to tablets coated with either of them alone. Dissolution studies performed on the mesalazine tablets further confirmed that the release profile of the drug could be manipulated by changing the ratios of Eudragit L 100-55 and S-100 within the pH range of 5.5 to 7.0 in which the individual poly-mers are soluble. They also confirmed that a coating formulation consisting of a combination of two copolymers can overcome the issue of high gastrointestinal pH vari-ability among individuals, and a formulation can be adjusted to deliver drug at any other desirable site of the intestinal region of the gastrointestinal tract on the basis of pH variability[32].

**Pressure dependent drug delivery**

Pressure controlled colon delivery capsules (PCDs) rely on the relatively strong peristalsis wave in the colon that leads to luminal pressure. PCDs consist of capsule shaped suppositories coated with a water soluble polymer. Once taken orally they behave like an ethyl cellulose balloon because their base liquefies at body temperature. In the upper part of the GIT PCDs are not directly subjected to luminal pressure. The reabsorption of water in the colon causes the viscosity of the luminal contents to increase. As a result, the increased intestinal pressure directly affects the system via colonic peristalsis. In response to raised pressure the capsule ruptures and releases the drug in the colon[33].

## EVALUATION OF COLON TARGETED DRUG DELIVERY

***In vitro* dissolution test**

Controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces. The conventional method involving dissolution in various buffers is useful for assessing the ability of an enteric-coating to prevent drug release in the stomach and small intestine. Dissolution studies of this kind can be used in relation to both time-release systems and formulations with enteric coatings.

Dissolution tests relating to colon-specific drug delivery systems may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behaviour of formulations at different pH levels. Rudolph et al. carried out 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

***In vivo* evaluation tests**

Guinea pigs, dogs, pigs and rats are generally used to evaluate the drug delivery to colon as they have anatomical and physiological similarities in addition to similarities with human GIT microflora. For evaluation of colon drug delivery a new model has been proposed where in the human fetal bowel is transplanted into a subcutaneous tulle on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host.

**Clinical evaluation tests**

Colonoscopy and intubation can be used to monitor the absorption of drugs from the colon. At present, gama scintigraphy and high frequency capsules are the most preferred techniques used to evaluate colon drug delivery systems.

## CONCLUSION

Colon drug delivery systems are beneficial for local and system treatment of patients. Although various approaches were proposed for colon targeted drug delivery there is a need to develop novel approaches which are specific for colon targeting. Systems that uses natural materials which gets degraded by colonic bacterial enzymes can be considered for developing colon targeted drug delivery systems. Challenges remain for pharmaceutical scientists to develop and validate a dissolution method that depicting the physiological features of the colon

## REFERENCES

1. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 2001;18:433-458.
2. Watts P. Illum L. Colonic drug delivery. Drug Dev. Ind. Pharm.1997;23: 893-913.
3. Reddy MS, Sinha RV and Reddy DS. Drugs of Today. 1999; 35(7): 537
4. Yang L, Chu J and Fix J. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. Int. J. Pharm.2002;235:1-15.
5. Zahirul M, Khan I, Prebeg Z and Kurjakovih N. A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. I. Manipulation of drug release using Eudragit™

L100-55 and Eudragit™ S 100 combinations. J. Controlled Release.1999; 58: 215-222.
6. Chourasia MK, Jain SK. Pharmaceuticalapproaches to colon targeted drug delivery systems. J Pharm Pharm Sci;2003;6:33-66
7. Laila F, Ali A and Sajeev Ch. Multiparticulate Formulation Approach to Colon Specific Drug Delivery: Current Perspectives., J Pharm Pharmaceut Sci.2006;9 (3): 327-338,
8. Kinget R, Kalala W, Vervoort L. and Van den Mooter G. Colonic drug delivery. J. Drug Target.1998;6:129-149
9. Rubinstein A, Radai R, Ezra M, Pathak S and Rokem S. In vitro evaluation of calcium pectinate: A potential colon-specific drug delivery carrier. Pharm. Res.1993;10:258-263
10. Friend DR. Colon-specific drug delivery. Adv. Drug Deliv. Rev.1991;7:149-199.
11. Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5- aminosalisylic acid. Clin. Pharmacokinet,1985;10:285-302.
12. Schacht E, Gevaert A, Kenawy ER, Molly K, Verstraete W, Adriaensens P., Carleer R. and Gelan J. Polymers for colon specific drug delivery. J. Controlled Release.1996;39:327-338.
13. Bronstedt H. and KopeMek J. Hydrogels for site-specific drug delivery to the colon: in vitro and in vivo degradation. Pharm. Res.;1992;9:1540-1545.
14. Van den Mooter G, Maris B, Samyn C, Augustijns P and Kinget R. Use of azo polymers for colon-specific drug delivery. J. Pharm. Sci.1997;86:1321-1327
15. Asford M, Fell JT, Attwood D, Sharma H. and Woodhead PJ. An in vivo investigation into the suitability of pH-dependent polymers for colonic targeting. Int. J. Pharm.1993;95: 193-199.
16. Munjeri O, Collett JH and Fell JT. Hydrogel beads based on amidated pectins for colonspecific drug delivery: the role of chitosan in modifying drug release. J. Controlled Release 1997; 46:273-278.
17. Turkoglu M, Takka S, Baran H and Sakr A. Pectin-hydroxypropyl methylcellulose drug delivery system for colon targeting. Pharm. Ind.,1999; 61:662-665.
18. Gliko-Kabir I, Yagen B, Penhasi A and Rubinstein A. Low swelling, crosslinked guar and its potential use as colon-specific drug carrier. Pharm. Res.1998;15:1019-1025.
19. Rama Prasad YV, Krishnaiah YSR. and Satyanarayana S. In vitro evaluation of guar gum as a carrier for colon specific drug delivery. J. Controlled Release;1998;51:281-287.
20. Tozaki H, Komoike J, Tada C, Maruyama T et. al. Chitosan capsules for colon-specific drug delivery: Improvement of insulin absorption from the rat colon. J. Pharm. Sci.1997; 86:1016-1021.
21. Lorenzo-Lamosa M, Remunan-Lopez C, Vila-Jato J. and Alonso M. Design of microencapsulated chitosan microspheres for colonic drug delivery. J. Controlled Release.1998;52:109-118.
22. Davis SS, Hardy JG and Fara JW. Transit of pharmaceutical dosage forms through the small intestine. Gut.1986; 27:886-892.
23. Adkin DA, Davis SS, Sparrow RA and Wilding IR. Colonic transit of different sized tablets in healthy subjects. J. Controlled Release.1993;23:147-156.
24. Pozzi F, Furlani P, Gazzanica A, Davis SS and Wilding IR. The time clock system: A new oral dosage form for fast and complete release of drug after a predetermined lag time. J. Controlled Release.1994;31:99-108
25. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F and Gazzanica A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J. Controlled Release.2001;73:103-110.
26. Hata T., Shimazaki Y., Kagayama A., Tamura S. and Ueda S. Development of a novel drug delivery system, time-controlled explosion system (TES). Part 5. Animal pharmacodynamic and human bioavailability study. Int. J. Pharm.1994;110:1-7.
27. Wilding IR, Davis SS, Bakhshaee M, Stevens HE, Sparrow RA and Brennan. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation. Pharm. Res.1992;9:654-657.
28. Krogel I and Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm. Res.1998;15:474-481
29. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ and Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut, 1998;29:1035-1041
30. Dew MJ, Hughes PJ, Lee MG, Evans BK and Rhodes J. An oral preparation to release drugs in the human colon. Br. J. Clin. Pharmac.1982;14:405-408.
31. Hosny E, Al-Shora H and Elmazar M. Oral delivery of insulin from enteric-coated capsules containing salicylate: effect on relative hypoglycemia of diabetic beagle dogs. Int. J. Pharm.2002; 237:71-76.
32. Khan M, Prebeg Z and Kurjakovi MN. A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. I. Manipulation of drug release using Eudragit™ L100- 55 and Eudragit™ S100 combinations. J. Controlled Release. 1998;58:215-222.
33. Takaya T, Ikeda C, Imagawa N, Niwa K. and Takada K. Development of a colon delivery capsule and the pharmacological activity of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in beagle dogs. J. Pharm. Pharmacol.1995;47:474-478
34. Dipiro JT, Posey LM, and Bowden TA. In: Pharmaco Therapy, A Pathophysiologic Approach, Dipiro J.T. (Eds), Elsevier, New york.1989.p. 444

**Table 1: Advantages and Disadvantages of Various Oral Colon-Specific Drug Delivery Methods**

| Method | Advantages | Disadvantages |
|---|---|---|
| Time dependent systems | Small intestine transit time fairly consistent | Substantial variation in gastric retention times<br><br>Transit through the colon more rapid than normal in patients with colon disease |
| pH dependent systems | Formulation well protected in the stomach | pH levels in the small intestine and colon vary between and within individuals pH levels in the end of small intestine and caecum are similar Poor site Specificity |
| Microflora activated systems | Good site specificity with prodrugs and polysaccharides | Diet and disease can affect Colonic microflora. Enzymatic Degradation maybe excessively slow |

**Table 2: Marketed Colon Specific Drug Delivery Systems**

| Drug | Trade Name | Formulation | Dose |
|---|---|---|---|
| Mesalamine | Asacol | Eudragit S coated Tablets | 0.8-2.4g/day |
| Mesalamine | Salofac | Eudragit L coated tablets | 1-4g/day |
| Mesalamine | Pentaza | Controlled release EC coated pellets | 1.5-4g/day |
| Mesalamine | Claversal | Eudragit L coated tablets | 1-2g/day |
| Budesonide | Entocort | Eudragit L coated beads | 9mg/day |
| Olsalazine | Dipentum | 5-ASA Dimer as capsules and tablets | 1g/day |
| Sulfasalazine | Salazopyrin | 5-ASA linked to sulfapyridine as tablets | 1-2g/day |

**Table 3: Patents registered on colon-targeted drug delivery**

| Patent No & Year | Title | Summary |
|---|---|---|
| Patent no: 5,482,718 Shah , et al. 1996 | Colon-targeted delivery system | A novel delivery system for colon targeting is a tablet comprised of three parts: (1) an enteric coating (2) an erodible polymer layer (3) a core, which is a conventional tablet or beadlet containing an active ingredient(s) |
| Patent no: 7,485,294 Bourgeois , et al., 2009 | Galenic pectinate formulation for colon-targeted delivery of antibiotic-inactivating enzymes and method of use thereof | Colonic delivery of active ingredients selected from the group comprising enzymes capable of inactivating macrolide antibiotics and related compounds, enzymes capable of inactivating quinolones, and beta.-lactamases. |
| Patent no: 6,039,975 Shah , et al. 2000 | Colon targeted delivery system | A novel delivery system based on a time-dependent explosion mechanism for targeting drugs to the colon is herein described This delivery system is particularly suitable for delivering viral protease inhibitors to the colon. |

Source of support: Nil, Conflict of interest: None Declared