Review Article

Novel Pharmaceutical Approaches For Colon-Specific Drug Delivery: An Overview

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ABSTRACT

Colon specific drug delivery has gained increased importance not just for the delivery of drugs in the treatment associated with the colon, but also as a potential site for the systemic delivery of therapeutic peptide and proteins. To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon. The necessity and advantages of colon-specific drug delivery systems have been well recognized and documented. The primary approaches to obtain colon-specific delivery are based on prodrugs, pH- and time-dependent systems or microflora-activated systems and have achieved limited success only. Precise colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological conditions particular to the colon. Hence, continuous efforts have been focused on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs. Among the systems developed most recently for colon-specific delivery, four systems were unique in terms of achieving in vivo site specificity, design rationale, and feasibility of the manufacturing process (pressure-controlled colon delivery capsules (PCDCs), CODES™, colonic drug delivery system based on pectin and galactomannan coating, and Azo hydrogels). The focus of this review is to provide detailed descriptions of the above mentioned approaches.

Key words : Colon specific drug delivery, Novel Approaches, Pressure-controlled colon delivery capsules, CODES™, Colonic drug delivery system based on pectin and galactomannan coating and Azo hydrogels

INTRODUCTION

By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e., colon). The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel diseases (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. [1, 2]. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine. [3, 4].

Formulations which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, in particular, therapeutic proteins and peptides are suitable for colonic deliverys. [5, 6, 7]. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systemically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics (e.g., nisin), which are useful in the treatment of inflammatory bowel diseases and GI infections, respectively. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissues. Therefore, the uptake of antigens through the colonic mucosa will lead to rapid and local production of antibodies. There is also an increasing interest in the colonic delivery for improving the oral bioavailability of drugs that are substrates of cytochrome P450 3A class, as the activity of this class of metabolizing enzymes is comparatively lower in the colonic mucosa than in the small intestine[8]. Increasing bioavailability via a colonic formulation approach has also been found to be effective in minimizing unwanted side-effects [9].

Delayed systemic absorption of drugs via colonic delivery is desirable for chronotherapy of diseases such as asthma, hypertension, cardiac arrhythmias, arthritis or inflammation, which are affected by circadian biorhythms. These diseases are characterized by night-time or early morning onset. For treatment of these diseases, it is therefore highly desirable to have a delayed-release delivery system that can provide nocturnal release of a drug, which in turn may provide considerable relief to the patients while they are in resting[3].

So, the colon, as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity and offers a much greater responsiveness to absorption enhancers. These criteria favor this distal part of the gastrointestinal tract (GIT) as a site for the delivery of various drug molecules, including proteins and peptides. Colon-specific delivery systems should prevent the release of the drug in the upper-part of GIT and require a triggering mechanism to release the drug on reaching the colon.

It's caliber is higher near the cecum and gradually diminishes to the rectum, where as it enlarges just above the anal canal. The colon is the upper 5 feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube lined by a moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2 to 3 inches in diameter [10]. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoidal colon, rectum, and the anal canal [11]. Unlike the small intestine, the colon does not have any villi. However, because of the presence of plicae semilunares, which are crescentic folds, the intestinal surface of the colon is increased to approximately 1300 cm^2 [12]. The physiology of the proximal and distal colon differs in several respects that can have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also changes, liquid in the cecum to semisolid in the distal colon. The major functions of the colon are:

1) The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and to store the feces until excretion. The absorptive capacity is very high; each day about 2000 ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.

2) Creation of a suitable environment for the growth of

FACTORS TO BE AFFECTED IN THE DESIGN OF COLON-TARGETED DRUG DELIVERY SYSTEMS

Anatomy & Physiology of Colon

The large intestine extends from the distal end of the ileum to the anus. The human large intestine is about 1.5 m long. (Table 1)

Table 1. Summary of anatomical and physiological features of small intestine and colon.

Region of GI Tract	Length (cm)	Internal Diamater (cm)
Entire GI Tract	500-700	
Small Intestine		3-4
Duodenum	20-30	
Jejunum	150-200	
Ileum	200-350	
Large Intestine		6
Cecum	6-7	
Ascending colon	20	
Transverse colon	45	
Descending colon	30	
Sigmoid colon	40	
Rectum	12	
Anal canal	3	

colonic microorganisms, such as Bacteroides, Eubacterium, and Enterobacteriaceae.

3) Expulsion of the contents of the colon at a suitable time.

4) Absorption of water and Na^+ from the lumen, concentrating the fecal content, and secretion of K^+ and HCO_3-[11].

pH in The Colon

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state, and food intake influences the pH of the gastrointestinal fluid. The changes in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery [13]. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine [14]. The right, mid, and left colon have pH values of approximately 6.4, 6.6 and 7.0 respectively. The pH of the colon is often lower than the pH of the small intestine, which is as high as 8 or 9[14]. The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by the way of pH-sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids produced by bacterial fermentation of polysaccharides. For example, lactose is fermented by colonic bacteria and produce large amount of lactic acid, resulting in drop of pH to about 5.0[15].

Colonic Microflora & Their Enzymes

Intestinal enzymes are used to trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug). Over 400 distinct bacterial species have been found, 20% to 30% of which are of the genus Bacteroides[10].The upper region of the GI tract has a very small number of bacteria and predominantly consists of Gram-positive facultative bacteria. The concentration of bacteria in the human colon is around 1000 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium, and Clostridium[16]. A summary of the most important metabolic reactions carried out by intestinal bacteria is provided in Table 2.

Transit of Material in the Colon

Gastric emptying of dosage forms are highly variable and depend primarily on whether the subject is fed or fasted and on the properties of the dosage forms, such as size and density. The transit times of different dosage form in the GI tract are provided in Table 3. The effect of transit abnormalities has been examined using gamma scintigraphy. Whole gut transit times were relatively long, ranging from 56 to 78 hours. Colonic transit times (estimated from the difference in mouth to cecum and whole gut transit times) ranged from 50 to 70 hours. Stool weights increased significantly with the presence of active disease presumably due to exudates from inflamed epithelium, increased mucus secretion, and reduction in reabsorption of fluid and electrolytes[18].

RATIONAL FOR THE DEVELOPMENT OF ORAL COLON TARGETED DRUG DELIVERY

- Treatment of local pathologies
- Chronotherapy (asthma, hypertension, cardiac arrhythmias, arthritis or inflammation)
- Greater responsiveness to the absorption enhancers
- Less enzymatic activity
- Site for delivery of delicate drugs (Proteins and Peptides)
- Oral delivery of vaccines as it is rich in lymphoid tissues

ADVANTAGES

- Drugs are directly available at the target site
- Comparatively lesser amount of required dose
- Decreased side effects
- Improved drug utilization

GENERAL CONSIDERATIONS FOR DESIGN OF COLONIC FORMULATIONS

Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release' [19] or a sustained/ prolonged release once they reach the colon. The proper selection of a formulation approach is dependent upon several important factors, which are listed below.

- Pathology and pattern of the disease, especially the affected parts of the lower GI tract or, physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment
- Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and
- The desired release profile of the active ingredient.

The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GI tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH = 6.6 ± 0.5) to the terminal ileum (pH = 7.5 ± 0.4), a decrease in the cecum (pH = 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 suggest that alterations in GI pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations[20].

Formulation of drugs for colonic delivery also requires careful consideration of drug dissolution and/ or release rate in the colonic fluids. Generally, the dissolution and release rate from colonic formulations is thought to be decreased in the colon, which is attributed to the fact that less fluid is present in the colon than in the small intestine. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water-soluble and/or require higher doses for therapy. Consequently, such drugs need to be delivered in a presolubilized form, or formulation should be targeted for proximal colon, which has more fluid than in the distal colon [21].

PHARMACEUTICAL APPROACHES FOR TARGETING DRUGS TO COLON

- pH sensitive systems
- Microbially triggered systems
  - ✓ Prodrugs
  - ✓ Polysaccharide based systems
- Timed release systems

NOVELPHARMACEUTICAL APPROACHES FOR TARGETING DRUGS TO COLON

- Pressure-controlled colon delivery capsules (PCDCs)
- CODES™
- Colonic drug delivery system based on pectin and galactomannan coating
- Azo hydrogels

NOVELPHARMACEUTICAL APPROACHES FOR TARGETING DRUGS TO COLON

Pressure-controlled colon delivery capsules (PCDCs)

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems.

Intestinal pressure-controlled colon delivery capsules (PCDCs), relies on the relatively strong peristaltic waves in the colon that lead to an increased luminal pressure. PCDCs were originally prepared by coating the inner surface of gelatin capsules with a water-insoluble polymer, ethylcellulose (EC),[22, 23] and the drug was introduced along with the suppository base. The thickness of the EC membrane determines the disintegration characteristics of PCDCs. In PCDCs, the drug is dissolved with a suppository base. Therefore, after administration, the system behaves like an EC balloon containing drug solution, since suppository base dissolves at body temperature. Due to the reabsorption of water in the colon [24], the viscosity of luminal content increases. As a result, increased intestinal pressures directly affect the system via colonic peristalsis (high-amplitude propagated contractions). In response to the raised pressure, PCDCs rupture and release the drug load in the colon. Therefore, the thickness of EC membrane is the most important factor for the colon delivery of drugs for colon specific diseases as well as protein drugs. However, it should be noted that our understanding of this raised pressure phase is very limited. It was reported that in healthy subjects this pressure

Table 2. Drug metabolizing enzymes in the colon that catalyze reactions [17]

Enzymes Catalyzed	Microorganism	Metabolic Reaction
Nitroreductase	*E. coli*, Bacteroids	Reduce aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. Coli	Reductive cleavage of azo compounds
N-Oxide reductase, sulfoxide reductase	*E. coli*	Reduce N-Oxides and sulfoxides
Hydrogenase	Clostridia, Lactobacilli	Reduce carbonyl groups and aliphatic double bonds
Esterases and amidases	*E. coli*, P. vulgaris, B. subtilis, B. mycoides	Cleavage of esters or amidases of carboxylic acids
Glucosidase	Clostridia, Eubacteria	Cleavage of , b-glycosidases of alcohols and phenols
Glucuronidase	*E. coli*, A. aerogenes	Cleavage of , b-glucuronidases of alcohols and phenols
Sulfatase	Eubacteria, Clostridia, Streptococci	Cleavage of O-sulfates and sulfamates

can be as high as110 mmHg with duration of 14 s [25, 26]. But the activity followed the circadian rhythm, with the occurrence of maximum frequency after waking, after meals or with defecation [26].

Based on limited in vivo evaluation [27], it has been demonstrated that the performance of this system appears to be dependent on the capsule size and the thickness of ethyl cellulose coating. Hu et al. used the biomagnetic measurement system (BMS) to estimate the GI transit characteristics of this system in healthy volunteers [28]. It was found that the capsule arrived at the ascending colon 4 and 5 h after oral administration in two subjects, while a model drug, caffeine, was first detected in the saliva of the same two subjects 6 and 5 h following oral administration, respectively. This indicated that PCDCs were able to deliver the drug to the colon.

CODES™ technology

CODES™ is a unique colon-specific drug delivery technology that was designed to avoid the inherent problems associated with pH- or time-dependent systems [29, 30]. The design of CODES™ exploited the advantages of certain polysaccharides that are only degraded by bacteria available in the colon. This is coupled with a pH-sensitive polymer coating. Since the degradation of polysaccharides occurred only in the colon, this system exhibited the capability to achieve colon delivery consistently and reliably.

As schematically presented in Fig. 1, one typical configuration of CODES™ consists of a core tablet coated with three layers of polymer coatings. The first coating (next to the core tablet) is an acid-soluble polymer (in the present case, Eudragit E® was used) and outer coating is enteric with a HPMC (hydroxypropylmethylcellulose) barrier layer in between to prevent any possible interactions between the oppositely charged polymers. The core tablet is comprised of the active, one or more polysaccharides and other desirable excipients. The polysaccharides, degradable by enterobacteria to generate organic acid, include mannitol, maltose, stachyose, lactulose, fructooligosaccharide etc. During its transit through the GI tract, CODES™ remains intact in the stomach due to the enteric protection, but the enteric and barrier coating will dissolve in the small intestine, where the pH is above 6. Because Eudragit® E starts to dissolve at pH 5, the inner Eudragit® E coating is only slightly permeable and swellable in small intestine. Upon entry into the colon, the polysaccharide inside the core tablet will dissolve and diffuse through the coating. The bacteria will enzymatically degrade the polysaccharide into organic acid. This lowers the pH of the surrounding system and result in the dissolution of the acid-soluble coating and subsequent drug release.

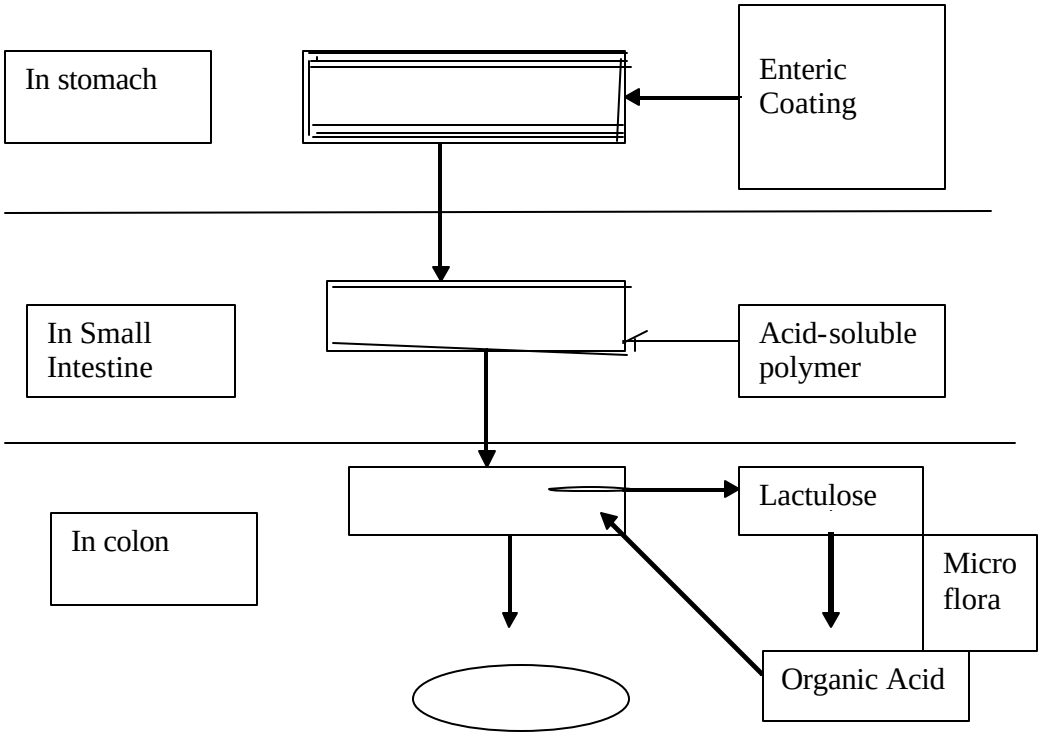

Figure 1. Schematics of the conceptual design of CODES™

Colonic drug delivery system based on pectin and galactomannan coating

This technology was recently proposed by Lee et al. [31] and Pai et al. [32]. It consists of a conventional tablet or capsule coated with two specific polysaccharides, namely pectin and galactomannan. By itself, neither pectin nor galactomannan can be used as a drug carrier for colon-specific delivery due to their high water solubility/swelling characteristics. However, the solubility of the coating produced from the mixture of the two polysaccharides was found to predominantly depend on the pH of coating solution. The coating from a pH 7 aqueous solution of pectin and galactomannan was shown to be strong, elastic and insoluble in simulated gastric and intestinal fluids. Accordingly, such coating could protect drug from being released in the upper GI tract. On the other hand, the coating from the identical solution with pH 7 was dissolved readily in the simulated intestinal fluids. Even though the mechanism of this observation remains to be investigated, it was proposed that a complex between the two polysaccharides might be formed at pH 7 due to the hydrogen bonding, hydrophobic force, and the formation of an inter junction zone from conformational changes of polysaccharides at the higher pH.

Results indicated that the bacterial degradability of films produced by this method was still preserved in the colon. It was also demonstrated that the extent of film resistance to hydration and subsequent solublization, the rate of film degradation by enzymes, and the resultant drug release rate depend on the ratio of pectin to galactomannan. Higher percentage of galactomannan results in decreased bacterial degradation in the colon and prolonged duration of action and also of negligible drug release in the upper GI tract. The site specificity of drug release was pharmacoscintigraphically confirmed in human subjects [32]. Compared with the combination of pectin and ethyl cellulose [33] or amylose and ethyl cellulose [34], this technology might have the advantage of faster degradation in vivo since both pectin and galactomannan are readily degradable by microflora in the colon.

Azo hydrogels

The synthesis and characterization of a series of novel azo hydrogels for colon-targeted drug delivery have been described [35, 36 and 37]. The colon-specificity is achieved due to the presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure. During the transit through the GI tract, the swelling capacity of the hydrogels increases as the pH increases, being highest around pH 7.4. Upon arrival in the colon, the hydrogels have reached a degree of swelling that makes the cross-links accessible to the enzymes (azoreductase) or mediators. Subsequently, the hydrogel network is progressively degraded via the cleavage of the cross-links, and the drug entrapped is thus released. The swelling characteristics of the hydrogels can be further controlled by incorporating the hydrolyzable moieties in the hydrogel structure.

Different synthetic approaches were developed to prepare the hydrogel systems. They can be obtained by cross-linking polymerization of *N*-substituted (meth)acrylamides, *N-tert*-butylacrylamide and acrylic acid with 4,4'-di (methacryloylamino) azobenzene, 4,4'-di (*N*-methacryloyl-6- aminohexanoylamino) or 3,3',5,5'-tetrabromo-4,4, 4',4'-tetrakis (methacryloylamino) azobenzene as the cross - linking agents (35, 36). An alternative approach is cross-linking polymeric precursors. In this case, a reactive linear polymeric precursor was first prepared by copolymerization of *N*, *N*-dimethacrylamide, *N-tert*butylacrylaminde, acrylic acid, and *N*-methacryloylglycylglycine *p*-nitrophenyl ester. The precursors were then cross-linked with *N, N'* (aminocaproyl)-4, 4'-diaminoazobenzene on the nitrophenyl ester to form the hydrogel structure [37]. The hydrogels were also prepared by polymer–polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH_2 groups.

The degradability of these hydrogels has been well characterized both in vitro and in vivo. The rate of hydrogel degradation was shown to be largely associated with the equilibrium degree of swelling and being inversely proportional to the crosslinking density. It appears that the degradation mechanism of the hydrogel was dependent on to a great extent the synthetic methodology. For hydrogel of the same polymer composition and cross-link structure, those prepared by cross-linking polymerization primarily exhibited a bulk degradation- like process, while the hydrogel from cross-linking polymeric precursors followed predominantly a surface-erosion process at a low density of cross-linking and became a bulk-degradation- like process when the cross-linking density increased. Hydrogels obtained from polymer– polymer reaction showed the degradation pattern similar to that of the hydrogel from cross-linking polymeric precursors. To make the hydrogel approach more effective for colon-specific delivery, the hydrogel should be further optimized, since preliminary studies in rats indicated that the enzymatic degradation occurred over several days [36].

CONCLUSION

A successful colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological conditions particular to the colon. Due to the lack of discontinuity in physiological parameters along the GI tract, only few mechanisms has been incorporated into a delivery system to effect colon-specific drug release. So far, four approaches were proposed for colon-specific drug delivery: prodrugs, pH- and time-dependent systems and microflora activated systems. Among the four approaches, microflora-activated system appears more promising since there is a increased amount of bacterial population and associated enzyme activity in the colon represent a non-continuous event, independent of GI transit time. Compared with the colon-specific drug delivery systems previously reported, the recently designed systems detailed in this article exhibit the following advantages: commonly used pharmaceutical excipients, feasible processing, site specificity of drug release and versatile drug release kinetics, if so desired.

REFERENCES

[1] Davis S, (1990) Overcoming barriers to the oral administration of peptide drugs. Trends Pharm Sci, 11: 353-355.

[2] Van den Mooter G. V., Kinget R, (1995) Oral colon-specific drug delivery: a review. Drug Deliv, 2: 81-93.

[3] Singh BN, Kim, KH. In: Swarbrick J, Boylan JC (Eds.), (2002) Encyclopedia of Pharmaceu t i c a l

Technology, New York, Marcel Dekker, Inc., 886-909.

[4] Ashford M, Fell J T, (1994) Targeting drugs to the colon: delivery systems for oral administration. J Drug Target, 2: 241-258

[5] Luck, M., Crabb, J. (2000): US20006074689.

[6] Watts, P.J., Illum, L. (2001): US20016200602.

[7] Yang, H., Nguyen, V.A., Dong, L.C., Wong, P.S.L.(1999):US6008187.

[8] Basit A, Bloor J. (2003) Perspectives on colonic drug delivery. Business Briefing: Pharmatech: 185-190.

[9] Dolan, T.F., Humphrey, M.J., Nichols, D.J. (2000): US20006106864.

[10] Sarasija S, Hota A. (2002) Colon-specific drug delivery systems. Ind J Pharm Sci. 62(1):1-8.

[11] Macfarlane GT, Cummings JH. (1991) The colonic flora, fermentation, and large bowel digestive function. In: SF Phillips, JH Pemberton, RG Shorter,eds. The Large Intenstine: Physiology, Pathophysiology and Disease. New York, NY: Raven Press: 51.

[12] Mrsny RJ. (1992). The colon as a site for drug delivery. J Controlled Release. 22: 5-34.

[13]Thomas P, Richards D, Richards A, Rojers L,Evans BK, Drew MJ, Rhodes J. (1985) Absorption of delayed-release prednisolone in ul cerative coliti and Crohn's disease. Int J Pharm.37:757.

[14]Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. (1988) Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut.29:1035-1041.

[15]Tomlin J, Read NW. (1988). The relation between bacterial degradation of viscous polysaccharides and stool output in human beings. Brit J Nutr.60:476.

[16] Krishnaiah YSR, Styanarayana S. (2000) Colon-specific drug delivery systems. In: Jain NK, ed. Advances in Controlled and Novel Drug Delivery. New Delhi, India: CBS Publishers and Distributors: 89-119.

[17]Lee VHL, Mukherjee SK. (2002) Drug Delivery: Oral Colon-Specific. Ency Pharm Tech. Dekker Encyclopedia: 871-885.

[18]Rao SSC, Read NW, Bruce C, Brown C, Holdsworth CD.(1987) Studies on the mechanism of bowel disturbance in ulcerative colitis. Gastroenterol. : 93: 934-940.

[19]Pinhasi, A., Gomberg, M., Avramoff,(2004)A.: US20046703044.

[20] Nugent SG, Kumar D, Rampton DS, Evans DF.(2001) Intestinal luminal pH in inflammatorybowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut;48:571-577.

[21] Takaya, T., Ikeda, C., Imagawa, N., Niwa, K.,Takada, K. (1995). Development of a colon delivery capsule and the pharmacological activity of recombinant human granulocyte colony-stimulatingfactor (rhG-CSF) in bea gle dogs. JPharm. Pharmacol. 47:474–478.

[22] Hu, Z., Mawatari, S., Shimokawa, T., Kimura, G., Yoshikawa, Y., Shibata, N., Takada, K. (2000a). Colon delivery efficiencies of intes tinal pressure-controlled colon delivery capsules prepared by a coating machine in human subjects. J. Pharm. Pharmacol. 52: 1187–1193.

[23]Shibata, N., Obno, T., Shimokawa, T., Hu, Z.,Yoshikawa, Y., Koga, K., Murakami, M.,Takada,K. (2001). Application of pressure-controlled colon delivery capsule to oral administration of glycyrrhizin in dogs. J. Pharm. Pharmacol. 53: 441–447.

[24]Debongnie, J.C., Phillips, S.F. (1978). Capacity of the human colon to absorb fluid. Gastroenterology 74: 698–703.

[25]Bassotti, G., Gaburri, M. (1988). Manometric investigation of high-amplitude propagated contractile activity of the human colon. Am. J. Physiol. 255:G660–G664.

[26]Rao, S.S.C., Sadeghi, P., Beaty, J., Kavlock, R., Ackerson, K. (2001). Ambulatory 24-h colonic manometry in healthy humans. Am. J. Physiol Gastrointest. Liver Physiol. 280 (4):G629–G639.

[27] Hu, Z., Kimura, G., Mawatari, S., Shimokawa, T., Yoshikawa, Y., Takada, K. (1998). New preparation method of intestinal pressure-controlled colon delivery capsules by coating machine and evaluation in beagle dogs. J.Control. Release 56:293–302.

[28] Hu, Z., Mawatari, S., Shibata, N., Takada, K., Yoshikawa, H., Arakawa, A., Yosida, Y. (2000). Application of a biomagnetic measurement system (BMS) to the evaluation of gastrointestinal transit of intestinal pressure-controlled colon delivery capsules (PCDCs) in human subjects. Pharm. Res. 17:160–167.

29. Watanabe, S., Kawai, H., Katsuma, M., Fukui, M. (1998). Colon specific drug release system. US

patent application (09/183,339).

[30] Takemura, S., Watanabe, S., Katsuma, M., Fukui, M. (2000). Human Gastrointestinal transit study of a novel colon delivery system (CODES™) using ?-scintigraphy. Proceedings of the International Symposium on Controlled Release Bioactive Material, vol. 27.

[31] Lee, S.S., Lim, C.B., Pai, C.M., Lee, S.J., Park, I., Seo Moon, G., Park, H.N. (1999). Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides. EP 974344 A2.

[32] Pai, C.M., Lim, C.B., Lee, S.J., Park, I.,Seomoon, G.,Connor,A.L.,Wilding,I.R.(2000). Pharmacoscintigraphicn and pharmacokineticevaluation of colon specific deliverysystem in healthy volunteers. Proceedings of the International Symposium on Controlled Release Bioactive Materials, vol. 27.

[33] Wakerly, Z., Fell, J.T., Attwood, D., Parkins, D.(1996). Pectin/ethycellulose film coating formulations for colonic drug delivery. Pharm. Res.13, 1210–1212.

[34] Basit, A.W. (2000). Oral colon-specific drug delivery using amylose-based film coatings. Pharm. Tech. Eur. 12 (2):30–36.

[35] Brondsted, H., Kopecek, J. (1991). Hydrogels for site-specific oral drug delivery: synthesis and characterization. Biomaterials 12:584–592.

[36] Brondsted, H., Kopecek, J. (1992). Hydrogels for site-specific drug delivery to the colon: in vitro and in vivo degradation. Pharm. Res. 9:1540–1545.

[37] Kopecek, J., Kopecekova, P., Brondsted, H., Rathi, R., Rihova, B., Yeh, P.Y., Ikesue, K. (1992). Polymers for colon-specific drug delivery. J. Control. Release 19:121–130.

[38] Yeh, P.Y., Kopecekova, P., Kopecek, J. (1994). Biodegradable and pH-sensitive hydrogels: synthesis by cross-linking of N,Ndimethacrylamidecopolymer precursors. J. Polym. Sci. 32, 1627–1637.

[39] Yeh, P.Y., Berenson, M.M., Samowiz, W.S., Kopecekova, P., Kopecek, J. (1995). Site specific drug delivery and penetration enhancement in the gastrointestinal tract. J. Control. Release 36:109–124.

[40] Ghandehari, H., Kopeckova, P., Kopecek, J. (1997). In vitro degradation of pH-sensitive hydrogels containing aromatic azo bonds. Biomaterials 18:861–872.

[41] Akala, E.O., Kopeckova, P., Kopecek, J. (1998). Novel pHsensitive hydrogels with adjustable swelling kinetics. Biomaterials 19, 1037–1047.