Colon Specific Drug Delivery by pH Sensitive Polymers & Pulsatile Drug Delivery System

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ABSTRACT: The colon is a highly vascular organ and a site where lack of digestive enzymes and long transit time occur, which provided an environment to the dosage form better systemic absorption of drug and a good bioavailability. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review mainly compares the primary approaches for CSDD (Colon Specific Drug Delivery) namely pH sensitive systems, and Pulsatile drug delivery system. Although oral delivery has become a widely acceptable route of administration, GI tracts presents several formidable barrier to drug delivery. In addition life cycle management, patient compliance, improved stability and optimization of drug absorption process are some key drivers for developing alternative delivery system of drugs. © 2014 iGlobal Research and Publishing Foundation. All rights reserved.

KEYWORDS: Colon Specific Drug Delivery System (CSDD); pH Sensitive; Pulsatile Drug Delivery System.

INTRODUCTION

The major goal of any drug delivery system is to supply a therapeutic amount of drug to a target site in a body. Oral control drug delivery offers a number of advantages over conventional immediate release preparations. Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non target sites[1]. Oral route is the most convenient and preferred route but other routes for CSDD may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal. A targeted drug delivery system is preferred in drugs having instability, low solubility and short half life. The colon specific drug delivery system (CSDD) should be capable of protecting the drug to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon[2]. There is definitely an increasing interest in colonic targeting of drugs, because targeted API directly to the colon shows better absorption and bioavailability due to high systemic circulation. The colon is believed to be a suitable absorption site for drugs which shows following reasons;

(i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CSDD protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability[3], and finally because the colon has a long residence time which is up to 24 hour and is highly responsive to absorption enhancers[3, 4].

The high water absorption capacity of the colon and colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low[5]. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules[4, 5].

ADVANTAGES OF CSDD OVER CONVENTIONAL DRUG DELIVERY

- CSDD avoid hepatic first pass metabolism, thus increasing bioavailability and efficacy of drug.
- Less frequency of administration and Improves patient compliance.
- Reduction in gastrointestinal side effects.
- Colon drug delivery system delivers medicines via the colon portal to systemic circulation at a predetermined rate over a prolonged period of time.
- Minimizes inter and intra patient variability.

Colon drug delivery is controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effects of drug. Colon drug targeting maintain drug concentration within the therapeutic window for prolonged period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration[5, 6].

Chronic colitis, namely ulcerative colitis, and Crohn's disease are currently treated with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption.Thus selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses[7].

CHALLENGES/LIMITATION FOR CSDD

i) It should be however noted that GI fluids might pass through the coat while the dosage form transits through the small intestine. This could lead to premature drug release in the upper parts of GI tract and as a result loss of therapeutic efficacy may occur. One approach to overcome these problems to apply higher coating levels of enteric polymers; however, this also allows influx of GI fluids through the coat, and the thicker coats often rupture under the influence of contractile activity in the stomach.

ii) One challenge in the development of colon-specific drug delivery system is to establish an appropriate dissolution method in designing in-vitro system. Due to the rationale after a colon delivery system is quite diverse. As, a site for delivery offers a near neutral pH, reduced digestive enzymes activity, a long transit time, and increased responsiveness to absorption enhancers, hence targeting is complicated, with reliability and delivery efficiency[8].

(iii) Limiting factors for poorly soluble drug as the fluid contents in colon is much lower and it is more viscous than in upper part of GI tract, for successful delivery through this site, drugs require to be in solution form before it arrives to colon and/or it should dissolve in luminal fluid of colon[9].

(iv) Resident microflora could also affect colonic performances via metabolic degradation of drug[8, 9].

(v) Lower surface area and relative 'tightness' of the tight junction in the colon can also restrict drug transport across the mucosa and into the systemic circulation[7, 8].

COLON DRUG TARGETING

Colon specific drug delivery by pH sensitive polymer and pulsatile drug delivery approaches.

pH Sensitive Polymer for CSDD
In pH sensitive system drugs can be intended to a solid dosage forms like tablets, capsules, pellets and coated with pH sensitive polymers as enteric coating or micropellets and microsphere can be filled into capsule shell made up of pH sensitive polymer[10]. The pH dependent system based upon the phenomenon that the pH of human GIT increases progressively from the stomach pH 1-2 which increases to 4 during digestion and it increases to 7-8 in distal cecum. In the stomach, pH ranges between 1 and 2 during fasting but increases after eating[11, 12]. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. Solid formulations for colonic delivery that are based on pH-dependent drug release mechanism are similar to conventional enteric-coated formulations but they differ in target site for delivery and therefore type of enteric polymers. In contrast to conventional enteric-coated formulations from the ileum to the colon, pH declines significantly[13]. It is about 6.4 in the cecum.

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 7.0 in the descending colon. 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[16]. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor[14]. 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-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations[14, 15].

There are various polymers which are used for colon drug delivery system[15].

pH sensitive polymer for CSDD
These are the polymers which have been used for the colon drug delivery because these have ability to withstand an environment ranging from low pH (~1.2) to neutral pH (~7.5) for several hours. These polymers have the ability to maintain their physicochemical properties and physical and chemical integrity during passes through stomach and small intestine and highly desirable for disintegrate to release the drug according to their pH-dependency[16].

Apparently, it is highly desirable for pH-dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally. It should be however noted that GI fluids might pass through the coat while the dosage form transits through the small intestine. This could lead to premature drug release in the upper parts of GI tract and as a result loss of therapeutic efficacy may occur. One approach to overcome this problem is to apply higher coating levels of enteric polymers; however, this also allows influx of GI fluids through the coat, and the thicker coats often rupture under the influence of contractile activity in the stomach[17]. In general, the amount of coating required depends upon the solubility characteristics (solubility, dose/solubility ratio) of the drug, desired release profile and surface area of the formulation, and composition of the coating solution/dispersion. Coating approach is one of the simplest formulation technologies available for colon-specific delivery. It also offers significant advantage in terms of cost and ease of manufacture. From formulation standpoint, coated dosage forms may be either single-unit system or a multi-particulate system, and each of these may be a single layer product or a multi-layer product. In case of single layered products, the coating may be composed of a single enteric polymer that has a pH-dependent solubility or a mixture of two polymers one of which is pH-dependent while other is pH independent[18]. On the other hand, in case of multilayer products, the coating is applied in successive layers which could be either based on two enteric polymers that have different pH-dependent solubility profiles, or two polymers one of which is enteric while other has a pH independent solubility but permeable to intestinal fluids. In either case, the coating can be applied to a wide variety of solid core formulations such as tablets, capsules, minitablets, pellets or granules. When coated pellets or granules are filled into a gelatin capsule or compressed together with conventional excipients in the form of tablets, the formulation is regarded as multi-particulate dosage form[17, 18].

S.No.	Name of the Polymer	pH for dissolution
1	Shellac	7
2	Eudragit S-100, S-12.5	7
3	Methyl acrylic acid co polymer Type (B)	>7
4	Eudragit L-100 and Eudragit L12.5	6
5	Methyl acrylic acid Copolymer- Type-A	>6
6	Methyl acrylic acid Copolymer dispersion (Eudragit L30 D-55)	>5
7	Methyl acrylic acid Copolymer Type-C (Eudragit L100-55)	6
8	Hydroxyl propyl methyl cellulose acetate succinate (HPMCAS)	>6
9	Hydroxyl propyl methyl cellulose phthalate (HPMCP)	>5.5
10	Cellulose acetate trimalate (CAT)	5.5
11	Polyvinyl acetate phthalate (PVAP)	5

The tablets or capsules containing coated pellets or granules can be further coated with a suitable enteric polymer which may be same or different than that used for coating of pellets or granules. Modified-release formulations that are based on the combination of a pH-dependent and pH-independent polymer are described in a European patent assigned to Aktiebolaget Hässle. The approach involves coating of an active ingredient (e.g., mesalazine) with a mixture of an anionic acrylic polymer soluble just at pH 5.5 (e.g., Eudragit L) and a cationic acrylic polymer insoluble in water (e.g., Eudragit RS or RL) [19]. The quantities of anionic acrylic polymers can range from 10 to 85% while that of pH independent polymers may vary from 15 to 90%. The blending with one or more polymers having a pH independent solubility thus prevents the active ingredient from being released too rapidly, once the soluble polymer has reached the optimum pH of solubilisation. eg: Mesalazine (also known as mesalamine, 5- aminosalicylic acid or 5-ASA) tablets coated with Eudragit L-100 are commercially available as Claversal, Salofalk, Mesasalâ and Rowasa. These tablets can effectively deliver mesalazine to the terminal ileum and proximal colon in patients with inflammatory bowel disease. It is important to recognize that drug release from Eudragit-L coated products may start in the proximal small intestine, which has a luminal pH of 6.6. Consequently, a relatively thick coating may be needed to delay the drug release until the formulation reaches the terminal ileum and proximal colon. An alternate approach to overcome above issues is to use a polymer which is insoluble below pH 7.0. Rhodes and Evans described a non-sustained release solid formulation in the form of a capsule or tablet containing a pharmacologically active agent, for example mesalazine, for the treatment of ulcerative colitis and Crohn's disease[20].

Pulsatile drug delivery system

Colon specific drug delivery offers a number of advantages over conventional immediate release preparations. A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies[21]. These systems are designed to deliver the drug at controlled and predetermined rate thus maintaining their therapeutic effective concentration in systemic circulation for prolonged periods. Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems[22]. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro-intestinal tract such as pH or enzymes. Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve, erode or rupture during/after a certain lag time, after which the drug is released rapidly from the inner reservoir core[23]. The rupturing of the barriers is induced by an expanding core upon water penetration through the barrier coating. Thus it is important to develop new drug delivery systems to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems, while minimizing undesired side effects. Therefore, pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts[23, 24].

Methods for pulsatile drug delivery system

Capsular system: Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. Example: Pulsincap system[25].

In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable and swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position and dimensions of plug and control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added[26]. Plug material is generally made up of following:

a) Swellable materials coated with but permeable polymer (polymethacrylates).

b) Erodible compressed polymer (HPMC, polyvinyl alcohol).

c) Congealed melted polymer (glyceryl monooleate).

d) Enzymatically controlled erodible polymer (pectin).

Osmotic system: This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation[27]. This system shows good *in-vivo* and *in-vitro* correlation in humans and used to deliver methylphenidate to school age children for the treatment of Attention Deficit Hyper activity Disorder (ADHD) [27, 28]. Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semi permeable capsule supported by an expending osmotic layer after the barrier layer is dissolved. The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation[29]. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure

that ejects the plug after a lag time. The lag time is controlled by coating thickness[30].

Erosion of membrane/ solubilisation: These systems are based up on a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time.e.g. The "Time Clock® system" consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, PH, enzyme and gastric residence[30, 31].

Rupture of membrane: These systems are based up on a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent[32]. Citric acid and sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs[33]. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch glycollate or low substituted hydroxyl propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane[34].

CONCLUSION

There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms. CDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified time lag. Colon drug delivery is one such system that, by and in right amounts, holds good promises of benefit to the patients suffering from chronic problems. Thus designing of proper colon drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article represent attempts conducted over the past decade to achieve colon drug delivery. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives delivering drug at the right time, right place. A significant progress has been made toward achieving CDDS that can effectively treat diseases with non-constant dosing therapies.

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