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Review Article

Recent Developments in Colon Specific Drug Delivery Systems: Approaches Promising in Targeting Colon

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ABSTRACT

Colon drug delivery is intended to target the drug molecules to the local area of colon to treat various diseases such as crohn's disease, ulcerative colitis and colon cancer etc. It is still considered as an idyllic site for the delivery of drugs by timed releasing system, coating with pH sensitive polymer, prodrug and colonic microflora activated delivery system. Amongst different types of delivery systems microflora activated delivery systems has appeared to be one of the most efficacious approaches in this direction, since the enormous bacteria population as well as associated enzymes trigger the drug release mechanism from the delivery system. In the midst of systems developed, most recently COLAL technology, CODES™, MMX™ and PHLORAL™ technologies are unique in terms of attaining the desired site *in vivo*, feasibility and design rationale of the system. The present review highlights the recent advancements made in drug delivery technologies for colon specific delivery systems to target the colon, in specific considering the transitory description of the delivery systems.

Key words: Colon targeted drug delivery system, COLAL technology, CODES™ tableting technology, microflora activated drug delivery, polysaccharides, MMX™ technology, PHLORAL™ technology.

INTRODUCTION

The site specific delivery of drugs to the colon affords major pharmacological treatments such as inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis and majorly colorectal cancer. It has been reported that one million Americans are believed to have IBD with 15,000 - 30,000 new cases diagnosed annually [1]. Moreover, colon site is specifically useful for delivery of those drugs where a delay in drug absorption is required from a therapeutic point of view e.g. in case of nocturnal asthma, angina etc. [2, 3].

It has been demonstrated that peptide drugs as well as proteins are targeted to colon and reported that insulin, calcitonin and vasopressin can be effectively absorbed in colon region [4, 5]. For protein drugs a premature release within the *upper* gastro intestinal tract (GIT) results in the rapid loss of their biological activity due to denaturation at low pH and enzymatic degradation. Thus, in both cases, an ideal dosage form should effectively suppress drug release/protect the drug in the upper GI tract (Stomach and small intestine) [6]. Therefore, it appears that, targeted drug delivery with an appropriate release pattern could be crucial in providing effective therapy for these aforementioned diseases.

An ideal colon specific drug delivery system should prevent drug release in the upper GI tract i.e. stomach and small intestine and provide onset of drug release on entry into the colonic region. To achieve this proviso, a triggering mechanism in the delivery system to be assimilated and the response to the physiological changes particular to colon is required. The pharmaceutical strategies which are commonly used to achieve a colon specific drug delivery systems includes a timed releasing system, coating with pH sensitive polymer, prodrug and colonic microflora activated delivery systems [3, 7].

Among all the systems, the microflora activated delivery systems have been found to be the most promising since the abrupt increase of the bacteria population and associated enzymatic activities in the ascending colon represents a non-continuous event independent of GI transit time and pH. The main principle in microflora activated systems is a series of polysaccharides which evade enzymatic degradation in the small intestine and are predominantly metabolized by bacteria in colon, such as xanthan gum, amylose, dextran, pectin and galactomannan [8].

Enduring to the advanced systems, the colon-specific drug delivery system CODES™ tableting technology is designed to reduce the variability associated with time or pH-dependent drug delivery. As indicated previously, COLAL technology (bacteria triggered system) is the application of amylose as the coating material, which shows the characteristics of resistant to pancreatic α-amylase but degrade by colonic bacterial enzymes. The recent development for improved colonic delivery has been the multi-matrix or MMX ™ system which shows the sustained drug release in colonic region. The concept of the MMX™ is based on pH-triggered drug release combined with a diffusion-based release mechanism to achieve sustained release.

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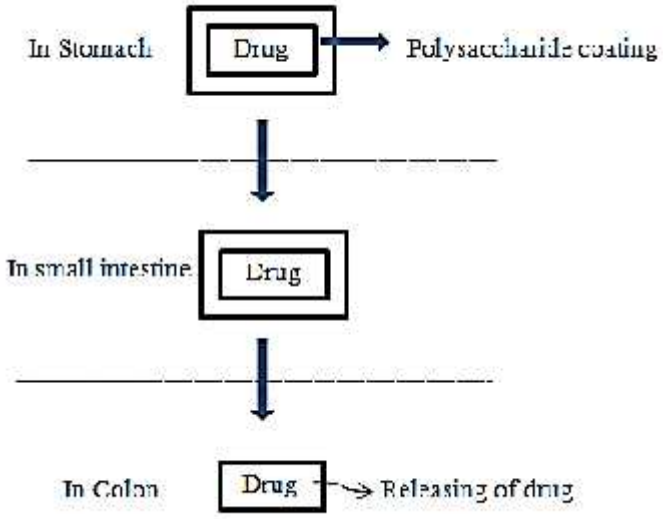

Figure 1: Schematics of the conceptual design of COLAL Technology

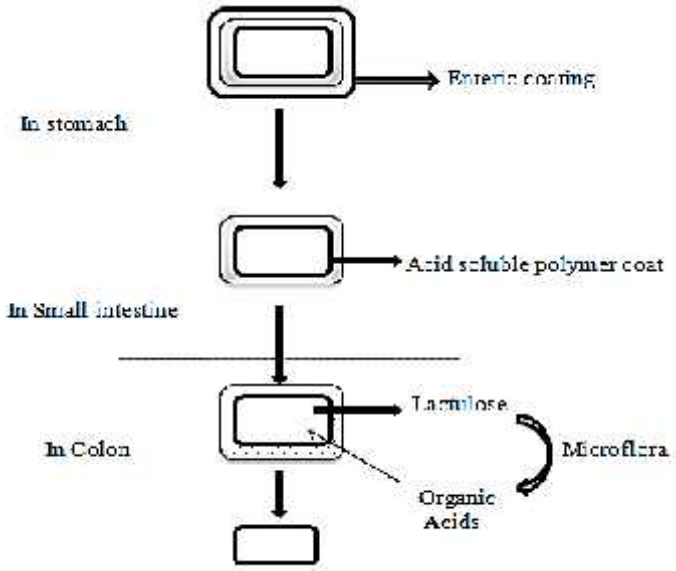

Figure 2: Schematics of the conceptual design of CODES^{TM} tableting technology

Advanced colon specific drug delivery strategies via the oral route:

COLAL Tableting Technology*:* COLAL Technology is a simple and widely used system that is based on bacteria triggered colon-specific drug delivery which is designed to avoid the inherent problems associated with pH or time dependent system [Figure. 1]. The drug core in COLAL technology was coated or compressed with a biodegradable polysaccharide, the applied coat protects the drug release in stomach and small intestine and targets the drug to the colon. As the tablet reaches to the colonic region the enormous bacteria present in the colon and secreted enzymes degrades the polysaccharide coat, causes onset of drug release.

In an early experimentation by Milojevic et al., 1996a reported that the coated 5-aminosalicylic acid pellets with amylose: ethylcellulose in a ratio of 1:4 (w/w) have been shown to be resistant to gastric and intestinal fluids but fermentable by colonic bacterial enzymes [10].

In another research Wilson and Basit, 2005 proved that the mesalazine-tablets coated with amylose: ethylcellulose blends have been also investigated exploiting gastrointestinal bacteria to trigger mesalazine release from amylose-based systems [11]. It has been concluded that the ratio of the amylose to ethylcellulose and the coating level play a major role in controlling drug release from this system. Moreover, this system was susceptible to colonic bacteria.

An ethylcellulose/glassy amylose surrounded formulation is now available as COLAL®, which has been used to coat pellets containing the corticosteroid prednisolone sodium metasulphobenzoate (COLALPRED®; Alizyme Therapeutics Ltd, Cambridge, UK). This product has achieved successful Phase II clinical trial results and is now in phase III clinical trials for the treatment of

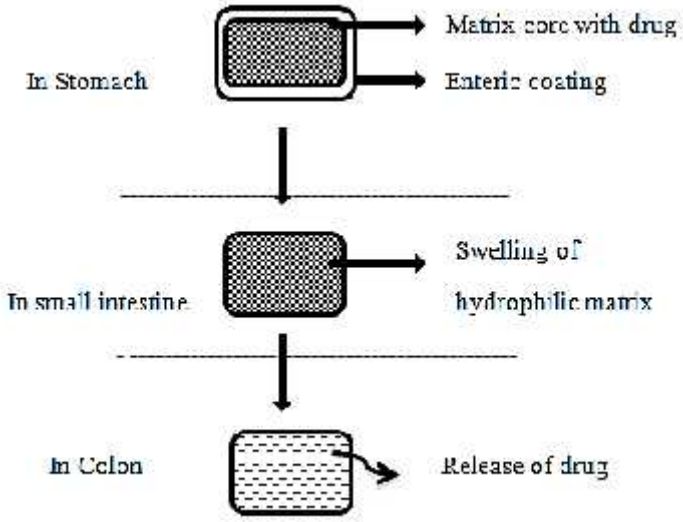

Figure 3: Schematics of the conceptual design of MMX™ tableting Technology

Table 1: Various approaches and efficacy levels of drug delivery systems

S. NO	Drug delivery type	Type of System	Triggering mechanism	Level of efficacy on colon specificity	Reference
1	*COLAL Tableting Technology*	Microflora activated	Degradation of polysaccharide coat	++	10-13
2	*CODES™ technology*	pH and microflora activated	pH responsive and degradation of polysaccharide coat	+++	14-15
3	*MMX™ technology*	pH responsive	pH and diffusion phenomenon	+	16
4	*PHLORAL™ technology*	pH and microflora activated	pH responsive and degradation of polysaccharide coat	+++	17

moderate to severe ulcerative colitis. Mixed amylose /Eudragit coating dispersion has also been used to delay drug release and target the colon [12, 13].

CODES™ technology*:* CODES™ Technology is a combination approach of pH and bacteria triggering system. This is designed to reduce the variability associated with time or pH-dependent drug delivery [Figure 2].

The strategy of CODES™ is centered on the fact that certain polysaccharides are only degraded by bacteria available in the colon. The system remains intact in the stomach due to the enteric protection during its passage through the gastrointestinal tract, but the enteric and barrier coating will dissolve in the small intestine where the pH is above 6.0. Upon entry in to the colon, the polysaccharide inside the core tablet dissolves and diffuses through the coating. The bacteria enzymatically degrade the polysaccharide into organic acids. This lowers the pH in the micro-environment surrounding the system which is sufficient to achieve the dissolution of the acid soluble coating and subsequent drug release.

Yang et al., 2003 reported the conversion of lactulose used in the tablet core to organic acids by colonic bacterial enzymes makes the microenvironment of the tablet acidic which permits the dissolution of Eudragit E. The outer coating of the CODES formulation is composed of an enteric polymer Eudragit L. As the formulation passes into the duodenum, Eudragit L dissolves exposing the undercoating, which is comprised of Eudragit E. This coating will not dissolve in the small and large intestine due to the high pH levels, but permits the lactulose within the formulation core to be released into the environment. Lactulose is metabolized to short chain fatty acids, which decrease the local pH required to dissolve Eudragit E [14, 15]. The coating thickness of Eudragit E has been found to play a decisive role in drug delivery of CODES system.

MMX™ technology: The key feature of multimatrix or MMX ™ technology is based on pH-triggered drug release combined with a diffusion-based release mechanism to achieve sustained release, but this system does not give quicker therapeutic action [Figure 3]. The technology has been designed in such a way that the drug gets release throughout the colon.

It is based on a tablet formulation in which the active ingredient is dispersed in an inner lipophilic matrix and covered by an outer hydrophilic matrix generated by in situ hydration of selected polymer chains. On to it a gastric resistant, pH-dependant film coat is applied, which makes

Table 2: Various polysaccharides used for microflora & pH activated drug delivery systems

Delivery system	Drug used	Polysaccharide used	Reference
Microflora activated type	5-Amino salicylic acid	Amylose and ethyl cellulose	18
	5-Fluorouracil	Guar gum	19
	Indomethacin	Guar gum	20,21
	5-Fluorouracil	Chitosan	22
	Mesalazine	Locust bean gum	23
	Indomethacin	Chondroitin sulfate	24,25
	Indomethacin	Calcium pectinate	26
	5-fluorouracil	calcium pectinate	27
	5-fluorouracil	guar and xanthan gum	28
	Budesonide	Dextran	29,30
	Sulphamethoxazole	Amidated pectin	31
pH and Microflora activated type	Lansoprazole	Guar gum-Eudragit	32
	Indomethacin	guar gum-Eudragit FS30 D	33
	Mebeverine	Lactulose-Eudragit	34
	Ondansetorn and Budesonide	cellulose acetate butyrate	35
	paracetamol	HPMC-Eudragit	36
	Ibuprofen	Eudragit S- Aqoat AS-HF	37

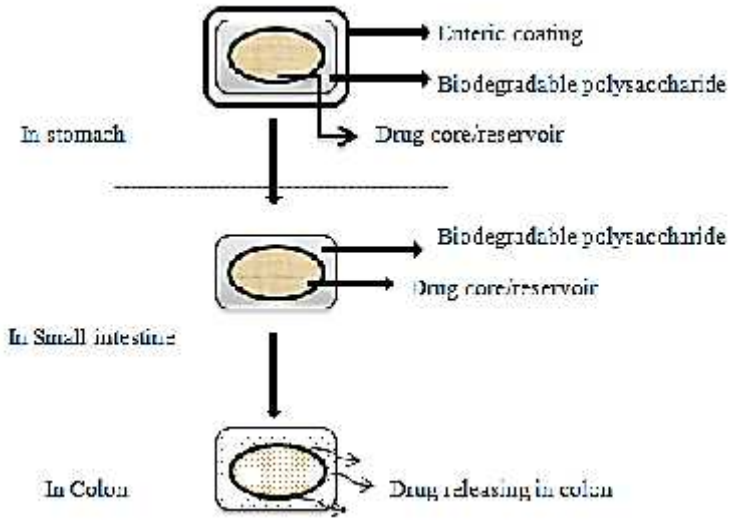

Figure 4: Schematics of the conceptual design of PHLORAL™ tableting Technology

the retardation of drug release in stomach. When the coat dissolves in the colonic region the fluid is imbibed into the core, a thick gelling layer forms through which the drug diffuses and is released in colon.

Sandborn et al., 2007 developed Lialda/Mezavant tablets, which contains hydrophilic and lipophilic compounds (sodium-carmellose, sodium carboxymethyl starch (type A), talc, stearic acid, and carnauba wax) as a matrix in which the drug is incorporated. These controlled release matrix tablets are coated with a blend of Eudragit L and Eudragit S. The Multi Matrix System (MMX™ tablet) contains 1.2 g of 5-aminosalicylic acid and indicated for the treatment of ulcerative colitis. The tablet course swells due to a hydrophilic matrix as the time increases, a thick gelling layer is formed. As this goes through the colon, fragments of the gel mass break off by bacterial fermentation in colon, roots drug release in colon [16].

PHLORAL™ technology: Among all, a new concept in colonic drug targeting introduced by combining pH responsive and bacterially triggered mechanisms in a single layer matrix film [Figure 4].

This novel system comprises a mixture of pH-responsive polymer (EUDRAGIT S) and biodegradable polysaccharide (resistant starch) as a coat. In this PHLORAL™ technology The EUDRAGIT S coating prevents the disintegration of the film in the upper gastrointestinal tract and controls swelling of starch. The resistant starch in the coating resists digestion by mammalian amylase enzyme secreted by the pancreas but is readily digestible by colonic bacterial enzymes. Once entering the colon, both pH and microflora triggering mechanism contribute to the dosage form disintegration and act as back up or fail safe to ensure appropriate drug targeting.

A gamma scintigraphy study showed that the system provides colon specificity. Consistent disintegration of tablets coated with the technology was seen at the ileocecal junction or large intestine [17].

CONCLUSION

As of the past few decades, exhilarating innovations in colon specific drug delivery have revealed unique prospective for increasing the efficacy of drugs for colonic diseases. Numerous investigations have been conceded out to find out an ideal formulation for colon specific drug delivery to treat different types of local diseases of colon. The aforementioned systems have shown that several strategies are being used for targeting the drug specifically to the colon viz. pH dependant, time-controlled, prodrug approach and those based on microbially triggering systems. Successful colon-specific drug delivery depends on the synergistic interaction between the delivery system and the gut physiology, especially for the systems triggered by colon microflora in which the non-starch polysaccharides. The anaerobic bacteria present in the colon are able to react to the constantly changing the complex mixture of different polysaccharides entering into the colon by recognizing a variety of substances and producing the appropriate digestive enzymes to trigger the system for drug releasing. This approach triggers the drug release mechanism from the dosage form, which shows a promising mechanism to target the colon over pH and time dependant and prodrug approaches.

Conflict of interest: The author has no conflict of interest

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