Chapter 4
Colonic Bacterial Enzymes:
Pharmaceutical Significance and Applications

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ABSTRACT

This chapter reviews various enzymes produced by the colonic microflora and their utilization in the development of pharmaceutical dosage forms to achieve colon-specific drug delivery. This chapter discusses the applications of colonic bacterial enzymes in order to surrogate colonic conditions in vivo *so as to evaluate* in vitro *drug release from microbially triggered/enzymatically triggered colon-specific drug delivery systems. This chapter also discusses different methods to produce colonic bacterial enzymes as well as use of probiotics as a source to produce colonic bacterial enzymes.*

INTRODUCTION

The human colon comprises of a wide range of microflora representing approximately 10^{11}-10^{12} CFUs/ml with more than 400 bacterial species such as Bifidobacteria, Bacteroides, Clostridia etc. These bacterial species residing in the colon are capable of producing more than 500 different types of enzymes. The fermentation of various substrates that are left undigested in the small intestine after reaching the colon acts as a source of energy for the colonic bacteria in order to maintain their cellular functions. These substrates include disaccharides and trisaccharides such as lactulose, cellobiose, raffinose, stachyoseas well as partially fermented residues of polysaccharides such as pectins, galactomannans, xylans, etc. The colonic microflora produces wide range of bacterial enzymes such as α-D-galactosidase, β-D-glucosidase, β-xylosidase, β-arabinosidase, β-D-glucuronidase etc., to carry out fermentation of substrates (polysaccharides or dietary fibers). These bacterial enzymes are also capable of degrading the various polysaccharide-based coatings/matrices as well as break the bonds between the inert carrier and an ac-

tive drug moiety resulting in the release of active drug in the colon without being affected in the upper gastrointestinal tract (GIT). Taking this into consideration, several formulations have been developed to achieve colon targeting by using polysaccharides and carriers that are readily degraded by the colonic microflora but unaffected by the microflora present in the upper part of GIT. These systems, after reaching the colon are fermented (polysaccharide-based systems) or broken down (prodrug-based systems) by the colonic bacterial enzymes, thereby causing complete drug release in the colon. These approaches have been utilized in the treatment of various colonic conditions such as Crohn's disease, ulcerative colitis, diarrhea, constipation, amoebiasis and colorectal cancer. Additionally, these systems are utilized to avoid first pass metabolism of the drugs that are degraded in the upper gastric environment. Colonic bacterial enzymes have also found its applications in the *in vitro* release evaluation of colonic formulations serving as a discriminatory and biorelevant method to evaluate drug release from enzymatically/ microbially triggered colonic formulations. Colonic bacterial enzymes that are specific to the substrate e.g. pectinases for pectin-based colonic formulations or a mixture of several colonic bacterial enzymes representing the entire colonic microflora are employed during the dissolution studies under anaerobic conditions in order to simulate colonic conditions and assess drug release from the colonic formulations. This chapter reviews the importance of colonic bacterial enzymes, their production methods as well as their utilization to develop various formulations for achieving colon-specific drug delivery.

BACKGROUND

The human gastrointestinal tract (GIT) represents dynamic and ecologically diverse environment containing variety of microorganisms that contributes to its physiology and functions including its importance in the metabolism of ingested material. The upper part of the GIT including the upper region of the gastrointestinal tract, the stomach, duodenum, jejunum and upper ileum possess very small number of bacteria, mostly Gram-positive facultative organisms (Simon et al., 1982). However, the bacterial concentration increases significantly in the colon. The count of the colonic bacteria is 10^{11}-10^{12} colony forming units/mL (CFU/mL) (Moore, & Holdeman, 1975) and the anaerobic bacteria outnumber the aerobic bacteria by the factor of 1000 (Simon, Gorbach, & Bustos-Fernandez, 1983). This is because in the lower gut, the conditions are highly reducing and the oxygen tension is so low that even very-oxygen-sensitive (VOS) anaerobes can flourish and under these conditions facultative organisms compete poorly for nutrients (Hillman, 2004). The most predominant species of anaerobic bacteria in the colon are: Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococccus, Propionibacterium, Veillonella and Clostridium whereas; Escherichia coli and lactobacillus are important facultative bacteria in the colon (Simon, Gorbach, & Bustos-Fernandez, 1983; Drasar, & Hill, 1974). These bacteria produce wide range of hydrolytic and reductive metabolizing enzymes (Rowland, 1988). Various roles of the enzymes of bacterial origin in the colon are listed in Figure 1. The most widely exploited reductive colonic enzymes in drug delivery are azoreductases, nitroreductases, N-oxide reductases, sulfoxidereductases, deaminases and the most extensively investigated hydrolytic colonic enzymes are glucosidases, β-xylosidases, α-L-arabinosidases and glucuronidases (Scheline, 1973). These intestinal enzymes are used to trigger drug release from devices in various parts of gastrointestinal tract to degrade the polymeric coatings/matrices as well as to break bonds between an inert carrier and an active molecule (release of the drug using prodrug approach) (Tomlin, & Read, 1988; Prasanth, Jayaprakash, & Mathew, 2012). Such drug delivery systems are called as 'enzymatically triggered or

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