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Review

Biorelevant dissolution testing of colon-specific delivery systems activated by colonic microflora

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Abstract

The fermentation of non-starch polysaccharides by colonic microflora is popular as a triggering mechanism to achieve colon-specific drug delivery in that the existence of colonic microflora is independent of gastrointestinal transit time, pH, and disease conditions, and various delivery systems were developed using this strategy. One of such delivery systems, COLAL technology, has advanced into late stage of product development. However, *in vitro* characterization of these delivery systems remains a challenge in part because the critical performance indicator is colonic specificity of drug release. Moreover, the dynamic and ecologically diverse features of the colon are difficult to be incorporated into USP dissolution methods. As a result, alternative dissolution approaches have been designed to better represent the colonic conditions, such as utilizing polysaccharide-degrading enzymes, rat caecal contents, human fecal slurries, and multi-stage culture systems. The primary focus of this article is to summarize and review the dissolution testing currently used in characterizing colon-specific delivery systems activated by microflora. A brief description of physiological parameters of the colon relevant to colonic drug release is also presented.

Keywords: Colon-specific delivery system; Colonic microflora; *In vitro* dissolution testing; Polysaccharide fermentation; Biorelevant dissolution

Contents

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1. Introduction

Dissolution testing is probably the most widely used methodology for evaluating oral modified release delivery systems including those for colon-specific drug delivery. A rationally developed dissolution method can be used to assess drug release kinetics, the implications of formulation and manufacturing process changes, the impact of pH and hydrodynamic conditions on drug release characteristics, to elucidate drug-release controlling mechanism, to ensure batch-to-batch consistency in manufacturing, and possibly to act as an *in vivo* surrogate. This necessitates that the dissolution method be discriminative, reproducible, scientifically justifiable, and more importantly biorelevant. The development of such dissolution methodology, the rationale of specification establishment, and the application as a tool of quality control are an essential part of drug product applications to regulatory agencies. Currently, USP dissolution apparatus I (basket), II (paddle method), and III (reciprocating cylinder) are routinely employed to evaluate orally modified release delivery systems. However, certain constraints associated with USP dissolution methods were recognized in the dissolution evaluation of complex drug delivery systems, and some modification of USP dissolution methods was deemed necessary [1].

Colon-specific drug delivery is intended to improve the efficacy and reduce side effects by exerting high drug concentrations topically at the disease site. Because of the distal location of the colon in the gastrointestinal (GI) tract, an ideal colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and effect an abrupt onset of drug release upon entry into the colon. This requires a triggering mechanism built in the delivery system responsive to the physiological changes particular to the colon. However, the physiological similarity between distal small intestine and the proximal colon presents very limited options in selecting an appropriate drug release triggering mechanism. Commonly used pharmaceutical strategies to achieve a colon-specific drug delivery include timed-release approximating the GI transit time, pH-sensitive polymer coating, prodrug, and colonic microflora activated delivery systems [2–4]. Of these systems, microflora activated delivery systems are considered to be preferable and promising since the abrupt increase of the bacteria population and associated enzymatic activities in ascending colon represents a non-continuous event independent of GI transit time and pH. The critical component in microflora activated systems is a series of polysaccharides which evade enzymatic degradation in the small intestine and are predominantly metabolized by colonic bacteria, such as xanthan gum, amylose, dextran, pectin, galactomannan [5]. In particular, a colonic release product of steroid prednisolone metasulphobenzoate based on amylose/ethylcellulose coating (COLAL technology), COLAL-PRED™, is in a pivotal Phase III clinical trial for the indication of ulcerative colitis [6]. Phase II clinical trial of COLAL-PRED™ in 33 mild-to-moderate ulcerative colitis patients showed that there was a clinical response in 63% of patients in the 60 mg dose group and in 35% of patients in the 40 mg dose group. More importantly, no steroid-related adverse events and change in cortisol levels associated with oral administration of prednisolone were observed [7]. These clinical trial results further demonstrated that the *in vivo* performance of COLAL technology was not affected by the pathophysiological and histological changes in the colonic mucosa as well as the alterations in mucosa-associated microflora in the patients with ulcerative colitis [8,9].

When developing a colon-specific drug delivery system, the proof-of-concept is usually conducted in human via γ-scintigraphy imaging to ascertain its specificity of drug release [10–14]. Subsequent formulation optimization and process development are to be assessed with the aid of an appropriate dissolution methodology. Because of the involvement of colon microflora as the mechanism in triggering drug release, the dissolution testing should be performed under a condition that the dynamic and ecologically diverse features of the colon can be incorporated into. It appears that this can hardly be accomplished with the existing USP dissolution methods. Consequently, alternative approaches have been utilized and described in the literature. The focus of this article is to summarize and review the dissolution testing currently used in characterizing the colon-specific delivery systems activated by microflora. A brief description of physiological parameters of the colon relevant to colonic drug release is also presented.

2. Physiological considerations of the colon

2.1. Colonic microflora

The human colon is a dynamic and ecologically diverse environment, containing over 400 distinct species of bacteria with a population of 10^{11} to 10^{12} CFU/mL [15,16], with *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Lactobacillus*, etc greatly outnumbering other species. For example, it was reported that *Bacteroides*, *Bifidobacterium* and *Eubacterium* could constitute as much as over 60% of the total cultivable flora [17]. These bacteria produce a wide spectrum of enzymes that, being reductive and hydrolytic in nature, are actively involved in many processes in the colon, such as carbohydrate and protein fermentation, bile acid and steroid transformation, metabolism of xenobiotic substances, as well as the activation and destruction of potential mutagenic metabolites. Nitroreductase, azoreductase, N-oxide and sulfoxide reductase are the most extensively investigated reductive enzymes, while glucosidase and glucronidase are the most extensively studied hydrolytic enzymes. The primary source of nutrition for these anaerobic bacteria is carbohydrates such as non-starch polysaccharides (i.e., dietary fibers) from the intestinal chime. It is well established that non-starch polysaccharides are fermented during transit through the colon and the breakdown in the stomach and small intestine is negligible [18]. Enzymes responsible for the degradation of polysaccharides include α-L-arabinofuranosidase, β-D-fucosidase, β-D-galactosidase, β-D-glucosidase, β-xylosidase, with the last three enzymes being the most active [19]. Additionally, the composition of colonic bacteria and corresponding enzymes can be influenced by many factors, including age, diet, diseases, medication such as antibiotics, and geographic regions [20–23]. A unique feature