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EDITORIAL

Enteric coatings for colonic drug delivery: state of the art

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Colon delivery systems for oral administration have grown in popularity since the 1990s, primarily because of the increasing incidence of inflammatory bowel disease (IBD) that has broadly been demonstrated to benefit from topical pharmacological treatment [1]. Moreover, selective release of biotechnological drugs to the large bowel has been proposed as a viable strategy to have their oral bioavailability enhanced with respect to gastric and/or small intestinal delivery as yielded by conventional peroral dosage forms [2,3].

So far, a wide range of targeting formulation approaches have been explored, which are generally based on physiological parameters typically differing between the large bowel and more proximal regions of the digestive tract [4]. Enteric-coated systems, in particular, are intended to pursue colon delivery by exploiting differences in the pH of gastrointestinal fluids. Polymethacrylates with a pH-dependent dissolution threshold ranging from pH 6.0 to 7.0 are mainly used as coating agents aimed at protecting the drug core from gastric and small intestinal contents, Eudragit® S (EuS), Eudragit® L (EuL), and Eudragit® FS (EuFS) (Evonik Industries) being popular brands thereof [5]. This is notably the formulation strategy behind most of anti-inflammatory drug products that are commercially available worldwide for the therapy of ulcerative colitis and Crohn's disease (IBD).

It is well known, however, that the dissolution pH thresholds of the employed enteric-soluble polymers may physiologically be exceeded within the small bowel, particularly in its distal portions.

In addition, acidic pH values were disclosed in the right colon of healthy subjects by a radiotelemetry study performed almost 30 years ago [6]. The fall in pH would be due to accumulation of short-chain fatty acids in the cecum and proximal large intestine resulting from bacterial fermentation activities. It ensues that exposure of the coating polymers to fluids having pH above their dissolution threshold may not be long enough to enable drug release within the target site, particularly in the presence of high coating levels that are generally resorted to in order to prevent drug release into the upper gut. Such issues may become especially challenging in the case of ulcerative colitis sufferers, who reportedly undergo pathology-related alterations in the pH of colonic contents [7].

Indeed, the reliability of pH-dependent formulations has recurrently been questioned over the last decades.

In the early 1990s, the time and site of disintegration for EuS-coated tablets dosed to fasted healthy volunteers were found to be highly variable [8]. It was thereby concluded that enteric-coated formulations would be unsuitable for consistent colonic release.

In a more recent γ-scintigraphy investigation, it was demonstrated that EuS films, irrespective of whether they were applied as an organic solution or an aqueous dispersion of the polymer, were unfit to provide selective drug release into the colon [9]. When organic coating systems were used, the dosage forms were subject to disintegration failure, whereas aqueous EuS-coated units always disintegrated before the target site had been reached. In agreement with this evidence of early release, a newly identified goal of ileo-colonic targeting was proposed.

The risk of a lack of timely disintegration for organic EuS-coated tablets was confirmed under fasted, fed and pre-feed administration regimens, the latter consisting in a standard breakfast taken 30 min post-dose [10]. By concomitant radiotelemetric measurements, remarkable variability was highlighted in intestinal pH values. This finding, along with possibly insufficient residence time within regions having pH above the dissolution threshold of the coating polymer and paucity of water available, was deemed to hinder attainment of predictable performance from such formulations. Importantly, the duration of exposure to the acidic gastric fluid, which may penetrate the enteric layer and then delay neutralization of carboxyl groups upon pH rise, was also shown to impact on the release profile.

Lately, by administering differing marketed mesalazine products for modified release to fasted healthy volunteers and measuring drug concentrations in gastrointestinal fluid and feces samples, it was hypothesized that tableted systems coated with EuS may in some cases fail to completely release its drug load [11].

Issues of poorly site-selective disintegration would concern not only single- but also multiple-unit EuS-coated formulations. Indeed, either early drug absorption or disintegration failure was observed from pellets coated with an organic solution of the polymer [12].

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Coatings based on EuFS were more specifically proposed for colonic release. In spite of a slightly higher dissolution pH threshold, which helped overcome the risk of premature release into the small intestine, a tendency to early disintegration was still demonstrated for dosage forms coated with such a polymer [9,13]. However, an intact unit was also seen in the descending colon at the end of imaging [9].

In view of the limitations encountered, much effort has been devoted to improving the colon targeting effectiveness of the pH-based approach. Particularly, the risk of delivery failure has been faced by exploiting further physiological characteristics of the large bowel, such as the enzymatic activity of the resident bacteria, as a synergistic trigger for *in situ* release, or promoting dissolution of the enteric-soluble coating polymer when its pH threshold has been reached.

High-amylose maize starch (resistant starch) was blended with EuS because of its susceptibility to selective colonic microbial degradation [14]. Tablets coated with this mixture were consistently shown to disintegrate at the ileo-cecal junction or in the colon irrespective of the feeding regimen.

In order to promote a rapid disintegration of EuS layers, swelling agents were added to the organic coating solution as solid particles [15]. The time elapsed between 5% and 70% *in vitro* release (pulse time) at pH 7.5 from hard-gelatin capsules coated according to this technology was reduced with respect to a EuS-coated reference formulation. Through the use of $^{13}C_6$-glucose and ^{13}C-urea as markers of the time and site of release, it was besides demonstrated that disintegration in fasted healthy volunteers would occur in the cecum and colon and not be slowed down as compared with an uncoated capsule [15,16].

A dual EuS coating was also designed aiming to face the problem of incomplete release. The dual coating included an outer layer obtained from an organic solution of the polymer and an inner one resulting from an alkaline aqueous solution thereof that also contained a buffering agent [17]. The internal layer was expected to accelerate dissolution of the overlaid one in pH > 7 intestinal fluid by creating an additional dissolution front at its inner surface. This coating technology proved advantageous to expedite release from EuS-coated tablets intended for ileo-colonic release [17,18].

Expert opinion

The earliest attempts to pursue oral colon targeting were based on a pH-dependent approach exploiting luminal pH differences that occur throughout the gastrointestinal tract. Such a strategy is still in use and has so far yielded numerous anti-inflammatory drug products approved for various IBD treatment options. Most of them are mesalazine dosage forms provided with a polymer coating soluble at pH above 7.

It is by now clearly evident, however, that while neutral to slightly alkaline pH values are reached in the small intestine, an acidic environment is found in the cecum and proximal colon. Such circumstances imply major risks of premature drug release into the small bowel on the one hand, and of release failure on the other, which need to be taken into proper account especially in the case of IBD sufferers and may impact on the successful outcome of the anti-inflammatory therapy. Nevertheless, it is generally believed that, in spite of diverse release patterns, there would not be any clinical differences among the various enteric-coated oral formulations for topical treatment of IBD [19,20].

Irrespective of the outcome of mesalazine products based on gastrointestinal pH, it is undeniable that the targeting effectiveness of the approach concerned still requires to be improved. In this respect, notable benefits could arise from exploitation of further regional colonic characteristics that, by a combination of release-triggering mechanisms, may help overcome patho-physiological variability issues related to each single parameter.

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Declaration of interest

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