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High-dose Mesalamine Oral Colon delivery systems: Innovative Approach to Enhance Therapeutic Management of Inflammatory Bowel Disease

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Riassunto

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Ulcerative colitis is a chronic pathological condition that primarily affects the mucosa of the colon and rectum. This is a form of inflammatory bowel disease (IBD) that leads to long-lasting inflammation and ulcers in the large bowel [1]. As such, it can strongly impair the general health status and life quality of patients due to debilitating symptoms, including persistent diarrhea, abdominal pain and rectal bleeding. The need for targeted drug delivery systems to manage intestinal inflammation effectively while reducing systemic side effects is of crucial importance, particularly in the case of first-line medication, *i.e.* mesalamine or 5-aminosalicylic acid [2]. The aim of this study was to develop and characterize an oral delivery system intended to deliver this drug at a high dose (1200 mg) to the colon using a combination of approaches for more reliable site targeting. The delivery system consisted in a tablet core containing the drug and two overlaid functional polymer coatings. Mesalamine granules were prepared by wet granulation, using a PVP-based binding solution, to increase the total payload of drug. Moreover, different fillers (Startab®, Avicel® PH200) and disintegrants (starch, Explotab® CLV) were evaluated. Oblong punches 22x10 mm in size were employed to attain the tablet core. Among the different formulations tested, the one using Avicel® PH200 and Explotab® CLV exhibited satisfactory physico-technological properties. These tablet cores underwent subsequent coating for colon targeting purposes [3]. An inner layer of hydroxypropyl methylcellulose (HPMC) was applied to prevent premature release in the upper gastrointestinal tract through swelling/erosion phenomena undergone by the hydrophilic polymer in contact with aqueous media. Moreover, an outer coating comprising Eudragit® S and guar gum, selected for their pH-sensitivity and biodegradability, respectively, was added to synergistically protect the core before colon arrival and to avoid release failure *in situ*, thanks to bacterial breakdown of the polysaccharide component. Both the HPMC and Eudragit® S/guar gum coating processes were carried out by tangential-spray fluid bed (GPCG 1.1., Glatt, DE). Given the peculiar shape and size of the substrate, the coating conditions needed to be set up attentively. The resulting HPMC and Eudragit® S/guar gum layers showed 105.74±7.94 µm and 149.45±29.97 µm thickness as well as 4.25 and 6.25 weight gain, respectively. The coated systems were tested for release using a dissolution and an adapted disintegration apparatus, in HCl 0.1 N for 2 h followed by phosphate buffer pH 7.4. The *in vitro* release data showed the desired pulsatile release profiles, with consistent lag times obtained in the dissolution and disintegration equipment settings. Further studies are needed to assess the performance of the delivery systems in simulated colonic fluid, *i.e.* in the presence of fecal bacteria. However, the combination colon targeting strategy in use coupled with the particular formulation of the drug core here described would represent a promising approach to provide the inflamed colonic mucosa with the required high mesalamine concentration, for improved healing and clinical management of ulcerative colitis.

References:

1. Ungaro R et al., 2017, Ulcerative colitis, Lancet, 389(10080):1756-1770.
2. Karagozian R, Burakoff R., 2007, The role of mesalamine in the treatment of ulcerative colitis. Ther Clin Risk Manag, 3(5):893-903.
3. Moutaharrik S et al., 2024, Guar gum as a microbially degradable component for an oral colon delivery system based on a combination strategy: Formulation and *in vitro* evaluation. Drug Deliv Transl Res, 14(3), 826-838.

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