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Short communication

Improving the solubility and permeability of apremilast with cyclodextrin encapsulation for the development of local drug delivery systems

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Introduction

Apremilast (APR) is an orally administered small molecule that specifically inhibits the phosphodiesterase-4 (PDE4) enzyme and modulates the immune system by increasing the levels of intracellular cyclic adenosine monophosphate (cAMP) and inhibiting IL-2, -8, interferon-γ and tumor necrosis factor (TNF) production. It was approved in 2014 by the United States Food and Drug Administration (FDA) for the treatment of psoriasis, psoriatic arthritis, and, in 2019 for the systemic therapy of oral ulcers due to Behcet's disease (BD) (Nassim et al., 2020). More recently, APR has been used off-label to treat varied dermatological diseases where systemic corticosteroids or immunosuppressive agents were not effective (e.g. aphthous stomatitis, chronic actinic dermatitis, atopic dermatitis, cutaneous sarcoidosis, hidradenitis suppurativa, lichen planus, and discoid lupus erythematosus) (Nassim et al., 2020). APR is available in tablet form of 10, 20 and 30 mg, however, this route of administration presents notable disadvantages related with adverse effects, first-pass metabolism and, moreover, is not suitable for patients with swallowing difficulties (oral ulcers) (Sarango-Granda et al., 2020). Therefore, the purpose of the present study was to improve the local drug delivery of APR with the inclusion complexation with CDs, focusing on the characterization of complex formation between APR and various CDs, solubility enhancement and dissolution profile.

Materials and methods

For the CD-screening, native (α-, β-, γ-CD) and pharmaceutical grade CD derivatives [hydroxypropyl (HP-β-CD), randomly methylated (RM-β-CD) and sulfobutylether sodium salt (SBE-β-CD)] (CycloLab Ltd.) were selected. Phase-solubility analysis was performed according to the method described by Higuchi and Connors (Connors et al., 1965), and a high-performance liquid chromatography (HPLC) method for APR quantification was developed. Inclusion complexes were prepared with codissolution or heterophasic methods according to the ingredient's solubility properties in ethanol and water. Real-time monitoring of dissolution was investigated to determine the APR concentration versus time at 25 °C in phosphate buffer pH 7.4 with UV-probes attached to the

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Rainbow Dynamic Dissolution Monitor of the μDISS Profiler™ (Pion Inc., Billerica MA, USA).

Solid-state characterization of the inclusion complexes was assessed with X-ray powder diffraction (XRD), infrared spectroscopy (IR), RAMAN, differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) method to demonstrate the formation of amorphous solid dispersion.

Results and discussion

APR is categorized as a class IV drug, according to the Biopharmaceutical Classification System (BCS), due to its low solubility (10 to 14.5 μg/ml) and modest permeability (log P: 1.8) (Sarango-Granda et al., 2020). The unfavorable physicochemical properties of the drug and the local barriers hinder its topical application, hence, the incorporation of APR into cyclodextrin (CD) inclusion complex could be used as a strategy to improve its solubility and permeability in order to improve topical bioavailability and consequently to achieve the local pharmacological effect.

β-CD and its hydroxypropylated and sulfobutylated derivatives (HP-β-CD and SBE-β-CD) are dominating the market for pharmaceutical formulations containing CDs. Methylated β-CDs have been reported to have renal toxicity; therefore, they are not used in parenteral formulations, but RM-β-CD is used in topical or mucosal formulations (Rassu et al., 2021). Due to the improved its aqueous solubility and toxicological profile, these β-CD derivatives have been investigated for inclusion complexation of APR.

Previous studies have shown the dissolution rate and bioavailability enhancement by preparing an inclusion complex of oral APR with β-CD (Madan et al., 2018; Panhale et al., 2021). The present study demonstrates that the pharmaceutical grade β-CD derivatives (HP-β-CD, SBE-β-CD, RM-β-CD) represent a convenient complexing ability, improving the physicochemical characteristics of the drug. The diffraction pattern of pure APR showed a distinct series of strong peaks that indicated it was crystalline. However, the pattern of pure CD derivatives lacked strong peaks and displayed a diffuse halo that indicated it was amorphous. The physical mixture of APR and CD derivatives contained a combination of strong peaks with a diffuse halo, meaning that the sample contained crystalline and amorphous phases (APR and CDs). Also, the pattern of the inclusion complex was missing strong peaks and showed a diffuse halo, indicating that the sample lacked crystalline APR. Moreover, the characteristic absorption peaks of APR were missing in the FTIR spectra of the inclusion complexes due to the embedment of APR in the cavity of CD derivatives. The SEM images showed the different morphologies of the initial components, physical mixtures, and prepared probe, suggesting that the inclusion complex had a new form.

Taken together, the inclusion complex was successfully prepared, and the poor aqueous solubility of APR was improved by CD derivatives by about 10 folds.

Conclusion

Painful oral ulcers, which appear in almost all patients, cause difficulty eating and drinking, and impair their quality of life (Takeno 2020). Standard therapies for oral ulcers include topical steroids and oral agents such as colchicine, although these therapies are not very effective in some patients. APR has been approved for systemic treatment of recurrent oral ulcers in BD patients (Takeno et al., 2020), however, with the development of local formulations, an effective alternative therapy could be achieved with minimal systemic adverse effects. Complexation of APR with CD derivatives improves drug solubility and bioavailability and can be exploited to promote local drug delivery development for severe, non-responsive dermatological diseases.

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