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ORIGINAL ARTICLE

Augmented bioavailability of felodipine through an α-linolenic acid-based microemulsion

Mahendra Singh[1] · Jovita Kanoujia[1] · Poonam Parashar[1] · Malti Arya[1] · Chandra B. Tripathi[1] · V. R. Sinha[2] · Shailendra K. Saraf[3] · Shubhini A. Saraf[1]

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Abstract

The oral bioavailability of felodipine, a dihydropyridine calcium channel antagonist, is about 15%. This may be due to poor water solubility, and a lower intestinal permeability than a BCS class I drug, and hepatic first-pass metabolism of the drug. Many drugs are unpopular due to solubility issues. The goal of this study was to develop and optimize a felodipine-containing microemulsion to improve the intestinal permeability and bioavailability of the drug. The felodipine microemulsions were developed with the selected components, i.e., α-linolenic acid as the oil phase, Tween 80 as a surfactant, and isopropyl alcohol as co-surfactant using Box-Behnken design and characterized for in vitro release and particle size. The optimized felodipine-loaded microemulsion was investigated for physicochemical interaction, surface morphology, intestinal permeability, rheology, cytotoxicity, cellular uptake, pharmacodynamic (electrocardiogram and heart rate variability), and pharmacokinetic studies to explore its suitability as a promising oral drug delivery system for the treatment of hypertension. The optimized felodipine-loaded microemulsion showed significantly higher ($P < 0.05$) apparent permeability coefficients (Papp) at 7.918×10^{-5} cm/s after 1 h, when compared with conventional formulations that are marketed tablet, drug oily solution, and drug emulsion, which showed a maximum Papp of 3.013, 4.428, and 5.335×10^{-5} cm/s, respectively. The optimized felodipine-loaded microemulsion showed biocompatibility and no cytotoxicity. Cellular uptake studies confirmed payload delivery to a cellular site on the J774.A1 cell line. The rheology study of the optimized felodipine-loaded microemulsion revealed Newtonian-type flow behavior and discontinuous microemulsion formation. In pharmacodynamic studies, significant differences in parameters were observed between the optimized felodipine-loaded microemulsion and marketed formulation. The optimized felodipine-loaded microemulsion showed significantly higher ($p < 0.01$) C_{max} (7.12 ± 1.04 μg/ml) than marketed tablets (2.44 ± 1.03 μg/ml). It was found that AUC_{last} obtained from the optimized felodipine-loaded microemulsion (84.53 ± 10.73 μg h/ml) was significantly higher ($p < 0.01$) than the marketed tablet (27.41 ± 5.54 μg h/ml). The relative bioavailability (Fr) of the optimized felodipine-loaded microemulsion was about 308.3% higher than that of the marketed formulation. The results demonstrate that the prepared microemulsion is an advanced and efficient oral delivery system of felodipine for the management of hypertension.

Keywords Microemulsion · α-Linolenic acid · Cytotoxicity · Cellular uptake · Electrocardiogram · Heart rate variability

Introduction

Felodipine (FEL) is a dihydropyridine calcium antagonist widely used as a selective vasodilator in cardiovascular disorders, primarily in arterial hypertension [1]. It is a crystalline drug and practically insoluble in water [2].

It is a biopharmaceutical classification system (BCS) class-II drug, lipophilic in nature, highly photosensitive and exhibits poor aqueous solubility, undergoes extensive first-pass metabolism, and exhibits poor bioavailability [3]. Even though FEL is rapidly absorbed after oral administration, it is important to enhance the

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✉ Shubhini A. Saraf
shubhini.saraf@gmail.com

[1] Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University (A Central University), Vidya Vihar, Raebareli Road, Lucknow, UP 226025, India

[2] University Institute of Pharmaceutical Sciences, Sector-14, Panjab University, Chandigarh, UT 160014, India

[3] Faculty of Pharmacy, B.B.D.N.I.I.T, Lucknow, India