Development and Evaluation of Self-Emulsified Freeze Dried Nasal Powder for Peptide Delivery

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Abstract

Cyclosporine-A (CsA) is a peptide agent which shows immunosuppressant activity so it is used in treatment of lung transplantation having Bronchiolitis obliterans syndrome. The small alveoli are compressed due to fibrosis in bronchiolitis obliterans syndrome. Cyclosporine-A is administered by oral and intravenous route but these routed shows side effect like systemic toxicity, pain at sight of injection, first pass metabolism and highly metabolized in oral route due to enzymes secretion. So the aim of the present investigation was to formulate and evaluate self-emulsified freeze dried nasal powder for treatment of bronchiolitis obliterans. Fourier Transform Infrared spectroscopic (FTIR) studies were performed to study drug and excipients compatibility. Selection of oil and surfactant was carried out by solubility study of cyclosporine-A in various oils and surfactants. The self-emulsified formulation of Cyclosporine-A was prepared using olive oil (1.5 gm), tween-80 (1 gm), sodium alginate bio-gel adhesive (0.5 gm) and water (50 gm). Different concentration of oil, surfactant, bio-gel adhesive and water were optimized using Box Behnken Design. Optimized self-emulsified formulation was converted into powder form by lyophilization using mannitol: microcrystalline cellulose: respitose (1:1:1) for better stability. Developed self-emulsified powder of cyclosporine-A was evaluated for globule size, zeta potential and poly dispersity index (PDI) using Malvern zetasizer NS90. Self-emulsification time and drug content was measured for prepared self-emulsified freeze dried powder. Flow properties of developed self-emulsified freeze

dried powder were evaluated by measuring carr's index, angle of repose, hausner's ratio. *In-vitro* drug release study was performed on goat nasal mucosa using Franz diffusion cell. Nasal toxicity study was performed on goat nasal mucosa to evaluated nasal epithelium cell necrosis. Stability study was performed at accelerated condition. Drug-excipients were found to be compatible to each other which were confirmed by FTIR study. The solubility of cyclosporine-A was found to be 99.13±0.41 mg/ml and 59.32±0.11 mg/ml in olive oil and tween-80 respectively. Globule size, poly dispersity index and zeta potential were found to be 131.9±0.54 nm, 0.11±0.0009 and -10.2±0.14 mV respectively for optimized batch. Emulsification time and drug content of optimized batch was found to be 0.8±0.001 second and 96.1±0.15% respectively. Carr's index, hausner's ratio and angle of repose were found to be 18.38±0.11%, 1.097±0.001 and 31.21±0.09° respectively, which indicates good flow property of freeze dried powder. *In vitro* drug release of self-emulsified freeze dried powder and plain drug were found to be 96.93±0.81% and 41.43±0.56% in 4 hours respectively. Absence of nasal cell necrosis and removal of epithelium cell of mucosa was confirmed by histopathological examination of nasal mucosa. Stability study was carried out of freeze-dried powder containing Cyclosporine-A was stable at accelerated condition. The present study demonstrated that, self-emulsified freeze dried nasal powder of cyclosporine-A is promising dosage form for intranasal delivery with improved peptide absorption and patient compliance for treatment of lung transplantation.

Keywords: Cyclosporine-A; Bronchiolitis obliterans; self-emulsifying system; freeze dried powder; Box Behnken Design.