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Polymeric Nanocarriers for Intranasal Delivery of Cannabidiol in Neurodevelopmental Disorders

Authors : Rania Awad, Avi Avital, Alejandro Sosnik

Abstract : Neurodevelopmental disorders, including autism spectrum disorder (ASD), affect 5.9% of the global population. Recently, research indicated the potential therapeutic use of cannabidiol (CBD) to treat different neurodevelopmental disorders, including ASD. Intranasal drug delivery (IN) is a non-invasive and painless administration route that enhances drug bioavailability in the brain by bypassing the blood-brain barrier. However, IN has limited bioavailability due to the low nasal mucosa permeability. Various polymeric nanoparticles (NPs) have been investigated for IN delivery with different successes. In this study, we investigate the nanoencapsulation of CBD within self-assembled polymeric NPs for nose-to-brain delivery in ASD to increase the bioavailability of CBD in the brain. The nanoencapsulation of CBD within self-assembled polymeric NPs, namely poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (PEO-PPO-PEO) polymeric micelles, was assessed. The CBD-loaded system was characterized by different methods. The compatibility was assessed in the nasal septum epithelium cell line Rpmi 2650. In vitro, permeability studies were conducted using Rpmi2650 cell monolayers cultured in semipermeable membranes 2650. The accumulation of CBD-loaded NPs labeled with near-infra-red fluorescent dye in the brain was measured after IN and oral administration after 20 and 45 min using IVIS spectrum CT imaging (IVIS-CT). Pharmacokinetic (PK) studies were conducted to assess the CBD concentration in rat plasma and brain tissues at different time points, PK parameters were measured and analyzed. Then, the effect of IN and oral administration of CBD-loaded NPs on a social cooperation test, which is a relevant behavioral test in the ASD model in rats, was investigated. Initially, we produced Pluronic® F127 polymeric micelles loaded with 25% w/w of CBD, with a size of 23 ± 1 nm, with suitable physical properties for IN administration. Then, Pluronic® F127 nanoparticles (F127 NPs) in the medium showed good compatibility and permeability in Rpmi 2650 cells. In the IVIS-CT study, the accumulation of IN administration of CBD-loaded F127 in the rat's brains was higher than the oral. Pharmacokinetic analysis of rat brain tissues revealed that, 20 minutes after administration, the concentration of CBD was higher following a 5 mg/kg nasal administration compared to a 15 mg/kg oral administration of CBD-loaded F127. Followed by IN administration of CBD-loaded F127 improved the social cooperation performance of the ASD model in rats as compared to oral and control groups.

Keywords : drug delivery to the brain, Intranasal drug delivery, nanoencapsulation, neurodevelopmental disorders, polymeric nanoparticles.
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