DEVELOPMENT OF INJECTABLE INTRATHECAL CANNABIDIOL FORMULATIONS

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Background: Neuropathic pain leads to decline in normal functioning and quality of life. Cannabidiol (CBD) has been reported to have a therapeutic action manifesting as pain relief, however, the main drawbacks are extensive first-pass metabolism, low oral bioavailability (logP 6.33) and poor penetration into the central nervous system (CNS). Recent developments in intrathecal drug delivery allow for this technique to administer drugs directly to the site of action in the spine. The aim of this project is to develop solid polymer coated CBD nanoparticles (NPs) and a lipid CBD nanoemulsion for intrathecal delivery to treat neuropathic pain.

Methods: CBD NPs were produced by a double nanoprecipitation method using a 3 armPEG_{1014}-$(LA)_{100}$ polymer. Free drug was removed by size exclusion chromatography and NPs were freeze-dried to allow quantification of CBD by HPLC. Particle size and zeta-potential were characterised using dynamic light scattering (DLS). Microfluidizer technology was used to manufacture oil-in-water nanoemulsions (composed of soybean oil, lecithin and glycerol). Density gradient ultracentrifugation using various densities of saline solutions was used to load CBD into the lipid droplets and then separate out unbound drug. These formulations were injected intrathecally after exposure of the spinal cord via a laminectomy in rats. Following mechanical stimulation, electrophysiology of pain pathways was recorded. The biodistribution of formulations in the CNS was then measured by HPLC.

Results: Polymer coated CBD NPs displayed a monodisperse population, 110.7 nm with 0.1 PDI, zeta-potential of -62.9 and were stable for 7 days at 4 ^{o}C. High encapsulation efficiency of 90.68% and drug loading of 30.2% were achieved. Incubation followed by density gradient ultracentrifugation approach was successful (65.1% and 90.95% association with commercial and microfluidized nanoemulsion respectively). The addition of CBD did not affect particle size < 300 nm or zeta-potential -55 mV which remained stable for 70 days post incorporation. Both nanoemulsions exhibited a PDI of < 0.2. Following intrathecal injection in rats, CBD nanoemulsion was preferentially retained within the lumbar segment of the spinal cord (2545 µg/g) with minimal concentrations reaching the brain (129.6 µg/g). The formulation lead to the inhibition of electrophysiology activity to noxious stimuli within 10 minutes of injection.

Conclusions: These findings pose critical considerations for the development of formulations for small lipophilic molecules for IT delivery, by allowing optimisation of nanoparticle properties to attain widespread distribution within the CNS.