# Selective cannabinoid nanoparticles for Atherosclerosis treatment

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Abstract

Atherosclerosis is the major cause of cardiovascular disease death in the developed world, for which there is no specific treatment(1). Currently, the inflammatory process in atherosclerosis is related with the endocannabinoid system. Cannabinoid receptor type 2 (CB2) is expressed in immune cells and is characterized for its anti-inflammatory properties, introducing CB2 agonists as a potential treatment(2,3). Our research group has been exploring a platform of biodegradable, biocompatible and polymeric nanoparticles (NPs) as selective CB2 agonist delivery systems for the treatment of atherosclerosis. For this purpose, we selected JWH-133, a synthetic, selective and potent CB2 agonist. Moreover, since cell adhesion molecule VCAM-1 was highly expressed in the vascular endothelium of the atheroma plaque(4), NPs were functionalized with a VCAM-1 binding peptide (VCAM-1 BP) to target nanosystems in the atherosclerotic region. Polymeric NPs were produced by nanoprecipitation method(5) using a mixture of three types of poly(lactide-co-glycolic): (i) PLGA; (ii) poly(lactide-co-glycolide)-b-poly (ethylene glycol) (PLGA-PEG) and (iii) poly(lactide-co-glycolide)-b-poly (ethylene glycol)-maleimide (PLGA-PEG-Mal) polymers at different ratios. NPs prepared using 85:5:10 w/w ratio of PLGA:PLGA-PEG:PLGA-PEG-Mal, were functionalized with VCAM-1 BP. The NPs were in 150-200nm of diameter, showed spherical morphology, negative surface charge and, high encapsulation efficiency of JWH-133. After conjugation, functionalized NPs maintained their shape and size. Cell viability assays on human umbilical vein endothelial cells (HUVEC) indicated low or non-toxicity for both blank and loaded-JWH-133 NPs. In contrast, cell viability was compromised when free CB2 agonist was incubated at high concentrations, indicating the positive impact of drug nanoencapsulation. Cell NP uptake was studied using fluorescently labeled NPs by confocal microscopy in tumor necrosis factor alpha (TNFα) stimulated cells. TNFα stimulation resulted in a pro-inflammatory profile that mimicked the pathogenic condition. In vitro stimulated HUVEC expressed high levels of VCAM-1, resulting in increased recruitment and cell uptake of functionalised NPs in comparison of non-stimulated cells. These preliminary results highlight the potential of formulated and functionalized NPs loaded with CB2 agonist for the treatment of atherosclerosis.

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