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The effect of Pro NanoLipospheres (PNL) formulation containing natural absorption enhancers on the oral bioavailability of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in a rat model

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Abstract

The lipophilic phytocannabinoids cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) show therapeutic efficacy in various medical conditions. Both molecules are poorly water soluble and subjected to extensive first pass metabolism in the gastrointestinal tract, leading to a limited oral bioavailability of approximately 9%. We have developed an advanced lipid based Self-Emulsifying Drug Delivery System termed Advanced Pro-NanoLiposphere (PNL) pre-concentrate. The PNL is composed of lipid and emulsifying excipients of GRAS status and are known to increase solubility and reduce Phase I metabolism of lipophilic active compounds. Advanced PNLs are PNLs with an incorporated natural absorption enhancers. These molecules are natural alkaloids and phenolic compounds which were reported to inhibit certain phase I and phase II metabolism processes. Here we use piperine, curcumin and resveratrol to formulate the Advanced-PNL formulations. Consequently, we have explored the utility of these Advanced-PNLs on CBD and THC oral bioavailability. Oral administration of CBD-piperine-PNL resulted in 6-fold increase in AUC compared to CBD solution, proving to be the most effective of the screened formulations. The same trend was found in pharmacokinetic experiments of THC-piperine-PNL which resulted in a 9.3-fold increase in AUC as compared to THC solution. Our Piperine-PNL can be used as a platform for synchronized delivery of piperine and CBD or THC to the enterocyte site. This co-localization provides an increase in CBD and THC bioavailability by its effect at the pre-enterocyte and the enterocyte levels of the absorption process. The extra augmentation in the absorption of CBD and THC by incorporating piperine into PNL is attributed to the inhibition of Phase I and phase II metabolism by piperine in addition to the Phase I metabolism and P-gp inhibition by PNL. These novel results pave the way to utilize piperine-PNL delivery system for other poorly soluble, highly metabolized compounds that currently cannot be administered orally.

Cannabinoids; First pass effect; Oral bioavailability; Piperine; SNEDDS.

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