Assessing Cannabinoid Permeability in a Mouse Dermal Administration Model

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Abstract

Cannabinoids are extremely lipophilic substances with LogP values >5. This makes cannabinoids amenable to formulation only with hydrophobic preparations for topical administration. We sought to evaluate various oil based preparations of 9-tetrahydrocannabinol (THC). The starting formulation (base) did not have permeation enhancers while other formulations did. Preparations were analyzed by liquid chromatography (LC)-mass spectrometry (MS) to confirm potency and chemical identity prior to study initiation.

Male CD-1 mice were used in the study following guidelines of humane animal use. Animals were anesthetized, dorsal regions were shaved and then tape stripped. A 2.00 mg sample of 0.1% THC preparation was applied to the skin of each animal. Mice were observed for signs of clinical toxicity and blood was collected by cardiac puncture 5 minutes to 4 hours post-dose under anesthesia. After blood collection, animals were humanely euthanized. Punch biopsies of the skin were then collected from each animal. Blood samples were processed to plasma and samples were treated with trifluoroacetic acid to prevent glucuronidation. Skin samples were homogenized and processed for tissue bioanalysis.

Plasma and tissue samples were analyzed for THC as well as the metabolites (±)-11-Hydroxy-Δ9-THC and (-)-11-nor-9-Carboxy-Δ9-THC by TOF LC-MS. Results of the analysis demonstrated the ability to separate THC from its metabolites in biological samples and individually quantify them from <1 ng/mL up to 500 ng/mL. The study enabled evaluation of both intradermal permeation and plasma concentrations of THC and its metabolites.

Study Methods

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Experimental Design

Topical formulations were prepared without permeation enhancers (NFB-A) or with permeation enhancers (NFB-B and NFB-C). On study day -1, CD-1 male mice (12-15/group) designated for topical treatments with NFB-A, NFB-B and NFB-C had the hair on their entire backs shaved and tape stripped. Animals with skin damage were moved to the IV dose group. On study day 0, animals were randomized into treatment groups based on body weight. Following randomization, either IV treatment with NFB-A or dermal treatment with NFB-A, -B or -C was initiated as indicated in TABLE 1. IV doses were administered based upon weight while dermal applications were the same for all mice. Blood collection time points are outlined in TABLE 2. At final time points, animals were anesthetized with isofluorane and blood for blood collection and dermal punch biopsies were collected. Blood was processed to plasma in trifluoroacetic acid to prevent glucuronidation. Tissues were homogenized and brought up in 200 µL PBS for analysis.

Overall Conclusions

- SIE extraction methods enabled isolation of THC and its metabolites
- Plasma and tissue THC, THC-OH and THC-COOH were analyzed by TOF LC-MS analysis with LOQs of 1, 5 and 5 ng/mL, respectively.
- Dermal administration of various topical preparations resulted in systemic exposure (<100 ng/mL) with substantial body surface area application.
- Permeation enhancers appear to improve dermal absorption of THC in mouse skin samples.

Relevant Literature

- We would like to thank Jed Pheneger for his technical expertise during the study