

Section A: Petitioner's Information			
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Section B: Delivery Method You Are Requesting Be Added
Please specify and provide a brief description of the proposed delivery method. Be as precise as possible in describing the delivery method you are requesting be added. <i>Attach additional pages as needed.</i>
SEE ATTACHED DOCUMENTS

Section C: Anticipated Benefits from the Proposed Delivery Method

Describe the anticipated benefits from the proposed delivery method and why it is better than currently approved delivery methods. Identify patient populations that do not benefit from current delivery methods
Attach additional pages if needed.

SEE ATTACHED DOCUMENTS

Section D: How Current Delivery Methods Are Inadequate

Provide information regarding the extent to which the currently approved delivery methods are unable to meet the needs of patients enrolled in the medical cannabis program. *Attach additional pages if needed.*

SEE ATTACHED DOCUMENTS

Section E (optional): Scientific Evidence of Support for the Delivery Method

It will strengthen your petition to include evidence generally accepted by the medical community and other experts that addresses the effectiveness of the proposed medical cannabis delivery method and discusses its potential risks and benefits. This includes but is not limited to full text, peer-reviewed published journals or other completed medical studies. Please attach complete copies of any article or reference, not abstracts.

I have attached relevant articles. (check box if you have attached scientific articles or studies)

Section F (optional): Letters in Support

Attach letters of support from persons knowledgeable about the use of the delivery method with medical cannabis.

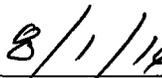
I have attached letters of support. (check box if you have attached letters of support)

Section I: Acknowledgement and Signature

Please Note: Any individually identifiable health information relating to any past, present, or future health condition or health care contained in this petition is classified as a health record under Minnesota Statutes §144.291, and is not subject to public disclosure.

I certify that the information provided in this petition is true and accurate to the best of my knowledge.

X 
SIGNATURE


DATE (mm/dd/yyyy)

To obtain this information in a different format, call:
(651) 201-5598 in the Metro area and (844) 879-3381 in the Non-metro.

Topical Formulations

Homogenized High Viscosity Liquid/Oil Matrices

Section B

Delivery method you are requesting be added:

This petition proposes that accurately dosed topical formulations of our oils extracted from medical cannabis, be approved as a permitted treatment method of medical cannabis. For effective topical application, this method would include various homogenized, high viscosity liquid oil matrices including, but not limited to creams, gels, and ointments. This document will outline and address the efficacy of topical treatments and evidence of their therapeutic effects, with a focus on the anti-inflammatory and analgesic effect of topical treatments through their action on peripheral CB1/CB2 receptors. Additionally, the safety and side effect profile of topical treatments, along with solutions for ensuring accurate dosing will be reviewed.

Literature

Topical cannabinoid enhances topical morphine antinociception

This study examined the effects of topically administered WIN 55, 212-2 on topical morphine antinociception by methods of the radiant tail-flick test in mice. AM 251, a CB1 receptor antagonist was found to antagonize the enhancement of antinociception of morphine by WIN 55, 212-2. Thus WIN 55, 212-1, a cannabinoid agonist with a lower potency than morphine, acts through a CB1 receptor to enhance the potency of morphine. Results showed that a combination of topical WIN 55, 212-2 with topical morphine increased analgesia compared to cases where topical morphine was used alone. In addition, spinally administered ineffective doses of WIN 55, 212-2 potentiated the antinociceptive effects of topical morphine. Thus, treatment with topical morphine antinociception and co-treatment with topical cannabinoids may offer a new remedy for pain management.¹

Topical cannabinoid antinociception: synergy with spinal sites

This study aimed to explore the antinociceptive actions of cannabinoids in the periphery. A receptor agonist known as WIN 55, 212-2, administered topically to the tails of mice, which examined the activity of topical cannabinoids. Study results demonstrated that the antinociceptive actions seen with topical WIN 55, 212-2 was limited to the region of tail exposed to drugs and were not seen in proximal areas, which was supported by the absence of motor

dysfunction in the CNS. Additionally, WIN 55, 212-2 was found to have nearly 30 times higher affinity for CB1 receptors compared to CB2 receptors. Conclusions were then drawn on the mechanism of action in topical application of cannabinoids, which is hypothesized to involve increased nociceptive threshold through inhibition of the cAMP second messengers in peripheral tissues, inhibition at primary afferent neurons, as well as hyperpolarization in neurons through open-gated potassium channels in Gi proteins.²

Comparative topical anti-inflammatory activity of cannabinoids and cannabivarinins

This study investigated the anti-inflammatory abilities of Δ^9 -THC, CBD, CBC and their cannabivarinins. Inflammation was stimulated by applying croton oil to the ear of mice. Control animals received no treatment while the remaining animals received the test substances. The results showed anti-inflammatory activity of CBD and THC is dose dependent with THC and its moieties showing stronger anti-inflammatory effects than the CBD group. Researchers concluded this is likely to the tricyclic nature of its structure.³

Anti-inflammatory activity of topical THC in DNFB-mediated mouse allergic contact dermatitis independent of CB1 and CB2 receptors

This study hypothesized that Δ^9 -Tetrahydrocannabinol (THC) had an anti-inflammatory effect that extended beyond its activation of CB1/CB2 receptors. This was examined by treating both wild-type mice and CB1/CB2 receptor deficient mice with allergic contact dermatitis with topical THC treatments. It was found that contact allergic ear swelling decreased in both mice populations, and additionally found evidence that this was due to THC inhibiting pro-inflammatory mediators, independent of the CB1/CB2 receptors.⁴

Mechanism of Action

Peripheral CB1 and CB2 receptors are GPCRs expressed in the periphery and CNS of the human body.⁵ There have been numerous studies investigating the effectiveness of topically administered cannabinoids as an analgesic and anti-inflammatory agent. Many of the studies have shown positive results, and have begun to elucidate the possible mechanisms of action.^{2,3,4}

Thus far, it has been hypothesized there is both an anti-inflammatory and neuropathic pathway for cannabinoid induction of analgesia. Cannabinoids combat inflammation primarily through the induction of apoptosis, inhibition of cell proliferation, suppression of cytokine production and the induction of T-reg cells.⁶ There are believed to be only a few possible mechanisms for how cannabinoids induce analgesia via the neuropathic pathway. The first, is CB1 receptor activation inhibits the release of substance P and CGRP from afferent neurons preventing the pain stimulus.⁷ The second, is CB1 receptor activation affects potassium and/or calcium channels leading to hyperpolarization and subsequent antinociception.^{7,8} In addition to the CB1 receptor, TRPV-1 and PPAR γ have also been shown to have cannabinoid anti-hyperalgesic activity.⁸ In a study done by *Costa et al*, researchers found that the analgesic effects were completely reversed only when all three of these receptors were inhibited.⁹

Although the exact mechanism of action for cannabinoid induced analgesic and anti-inflammatory activity is not completely understood, there are numerous studies providing strong preclinical evidence of these properties in both mice and humans.

Safety

Topical analgesic treatments for conditions such as chronic pain have increased as research has continued into pain physiology. There are a multitude of topical treatments including creams, gels, and ointments currently in use to treat painful conditions. Topical pain treatments have been developed and used for opioids, NSAIDs, antihistamines, anesthetics, and other analgesics over many years. As discussed elsewhere, for some patients, these treatments have a variety of advantages over the methods of delivery we currently offer, but a primary benefit is a strong safety profile with minimal side effects. The primary goal of developing topical phytocannabinoid formulations is "the improvement of patient compliance to medical treatment, by providing efficient pain relief with less central nervous system effects and minimal drug regimen burden."¹⁰ Topical cannabinoid oil applications such as creams, gels and ointments will provide local anti-inflammatory and analgesic effects, without the side effects that other cannabis modalities sometimes cause.

The safety of medical cannabis in the forms of administration currently permitted by the state have been well established. Topical formulations, in comparison, would possess an even greater safety profile for administering medical cannabis. Topical cannabis formulations are authorized for use in 24 out of 26 of the States and the District of Columbia where cannabis has been medically legalized. Preliminary clinical trials have shown that cannabinoid creams are well tolerated and safe.¹¹ Cannabinoids within the proposed topical formulations would act on local CB1, CB2, TRPV1, PPAR γ receptors to produce anti-inflammatory and analgesic effects.⁹ This will result in an anti-inflammatory and analgesic effect while likely minimizing or possibly eliminating the psychoactive effects sometimes experienced when taking oral, inhaled or centrally absorbed medical cannabis, as one of the primary goals of topical therapy is to minimize central effects.¹⁰ Topical cannabis will have an even lower side effect profile than other forms of medical cannabis that are already provided by primarily acting on peripheral CB receptors as opposed to central nervous system CB receptors. This would make topical creams, gels and ointments ideal treatment choices for certain categories of patients who do not tolerate common side effects associated with central use.

A potential concern regarding topically applied medication is the complexity in the dosing of these treatments. Topical patches infused with pre-measured amounts of active medication have been proposed as a solution to this complexity and are used for patient convenience elsewhere in the pharmaceutical industry. They offer one way to administer a controlled rate and amount of a drug under controlled conditions, however drug-infused patches have disadvantages for application of medical cannabis. They include multiple synthetic product components requiring separate safety and efficacy testing. There is an inevitable and variable retention of a portion of the medication in the solid patch matrix. Also, high product development complexity and cost, and potential high cost transfer to intended patients limit the practicality of drug-infused patches in Minnesota's medical cannabis program. Additionally, some patients

report skin irritation from patch components when using other drug-infused patch products.¹² Topical, high viscosity liquid/ oil matrices such as homogenized creams, gels, or ointments would be less costly to develop and consequently less cost prohibitive for patients. Additionally, these topical forms do not have any solid, synthetic portion such as adhesives, absorbent material or occlusive barriers which add to quality testing complexity, potentially harbor microbial contaminants, hold potential for adverse allergic reaction and absorb and retain some of the drug product.

Accurate dosing for topical oil formulations such as creams, gels and ointments is feasible using a range of solutions currently employed with multiple other pharmaceutical products. The first option includes providing the patient with clear instructions on how much high viscosity topical medication to apply based on a visual measurement tool or a specific length of medication extruded from a compressible packaging form with a defined opening size. This is similar to how multiple ointment and cream-form medications are presently prescribed. The following is a pharmaceutical example from *Facts and Comparisons*: Lidocaine 5% ointment: *Apply topically for adequate control of symptoms with a maximum dose of 5 g per single application (approximately 6 inches of ointment) per day.*¹³ Similar to this, a tool, such a dose measurement card can be utilized to aide a patient in quantifying the amount of medication applied. An example of this is seen with the NSAID cream Voltaren (Diclofenac): *Covering the marked area on the dose card will measure an approximately 2 gram dose.*¹⁴ A second dosing mechanism includes packaging topical medication with an applicator that controls how much product has been dispensed, similar to the current dosing protocol for prescribed Premarin vaginal cream.¹⁵ Likewise, it is possible to package topical formulations in individual dosing aliquots. This form of dosing control is utilized for various antibiotic ointments available on the market, which are sealed in small squeezable foil packs. A single pack contains a precisely measured full dose to be applied for each dose of the topical treatment. With medical cannabis oil topical formulations using this form of packaging and dosing, patients are instructed to apply the contents of one or more complete packets to the intended body area with intractable pain at scheduled intervals. These methods for applying precise doses of high viscosity oil based topical medications are all potentially applicable for our patients who currently use medical cannabis. These methods would allow dosing of topical medical cannabis with precision comparable to current inhaled and oral forms of medication.

Section C

Anticipated Benefits from the Proposed Delivery Method

Transdermal application provides a route of cannabinoid exposure that avoids the first-pass metabolism in the liver and increases the bioavailability of THC.¹⁶ This increased bioavailability is more suitable for treating multidimensional ailments such as chronic or intractable pain, which require ongoing treatment and continual management.¹⁰ Transdermal or topical application allows for local analgesia without the complications of systemic absorption and without limiting the desired effect.¹⁰ Topical application of cannabinoid based medication additionally allows for efficient pain relief with low risk for adverse effects including sedation and respiratory depression - side effects common in other medications currently available to treat chronic pain such as opiates.¹⁰

Another benefit in using transdermal application addresses the pain perception in individuals. Patients are motivated to use topical medications as they provide a rationale of direct application to the site of their pain.¹⁰ Many patients also perceive oral medications to carry a heavier burden on their health and believe them to have a greater risk of side effects.¹⁰ Topical administration has been shown to reduce the number of subjectively reported side effects including nausea and rated pain level.¹⁰ Furthermore, patient compliance is high with transdermal application due to its non-invasive nature and the fact that it is easy to use with long time intervals between each application.¹⁷

Section D

How Current Delivery Methods Are Inadequate

For some patients with intractable pain, the area or pain in question can be located in the musculoskeletal tissue, the skin, or the underlying connective soft tissue. These locations are easily accessible to the patient. In these cases, dermal or topical application may surpass currently available routes of administration because of the localized and targeted medication effect provided by direct contact with the location of the pain and without significant systemic absorption. By limiting a drug's exposure to the peripheral system, central side effects can be reduced.² Though pain perception is believed to be primarily controlled by neurotransmitters in the CNS, antinociceptive mechanisms also occur in the peripheral system. In a study conducted by *Calignano et al* it was concluded that endogenous cannabinoids may play a role in buffering emerging pain signals in soft tissue sites of the periphery.¹⁸ Subsequently, peripherally administered CB1-like and CB2-like agents may reduce pain without the common side effects and perceived abuse potential of opiates.¹⁸

Transdermal application allows for a mechanism to avoid dose-related side effects that may occur with other modes of transmission. This is the case with oral administration, which can cause severe nausea, gastric disturbances, and variable serum concentrations in a low bioavailability setting.^{10,19} Furthermore, physiological variability such as intestinal absorption and rates of metabolism and excretion will influence drug concentrations.¹⁶

Inhalation, another mode of administration, currently serves as a primary route of medical cannabis administration. This method results in a rapid and sometimes intense effect on the central nervous system as medication is delivered quickly from the lungs to the blood, to the brain. For various conditions, this absorption mechanism is useful but the psychoactive side

effects from rapid THC absorption may be undesirable for some patients. The psychoactive side effects associated with THC are otherwise avoided with topical administration routes.¹⁴ Inhaled administration methods also have a large variability in bioavailability in smoked cannabis studies, ranging anywhere from 2%-56%, resulting from varied inhalation techniques across patients.¹⁶ This variability may be reduced with topical application of cannabinoids to ensure precise dosing, which is critical in chronic pain patients who may also be supplementing with oral narcotics in order to manage their pain.

Section E

Scientific Evidence

The following literature citations help support this petition for the addition of topical forms of medical cannabis. Many of these studies are cited or summarized above in our petition. Please see attached full text versions for reference.

Cited Sources

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14. Voltaren (diclofenac sodium) [prescribing information]. Malvern, PA: Endo Pharmaceuticals, Inc; May 2016.
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