The Role of 4-24 Micron Far Infrared Heat & Ultrasound Waves in the Topical Absorption of Cannabinoid-Based Drugs

Jeremy Madvin, Madiha Khalid, and Ali Anique

ABSTRACT

The best way to deliver a drug in pursuit of maximum potential is to deliver it with maximal bioavailability. There are many options in delivering a drug, but each way reduces the drug's bioavailability differently. For treating localized discomfort, the transdermal approach or the topical approach is considered to be an advantageous one mainly because of its rapid localized action and the fewest side effects associated with this route. Drug delivery through topicals is an easy-to-reach approach and, in most cases, bypasses the first-pass metabolism. However, under certain conditions, the drug either needs to be delivered in its unaffected, concentrated form or needs to be delivered deeper into the dermal layers of the skin with immediate effect. This paper will review and suggest all those possible ways through which topical drug delivery can be universally enhanced in rate, effectiveness, and efficiency. Specialized ultrasound waves and sub-spectrum far-infrared heat help accelerate and deliver topical ingredients to the site of action. Making this the basis of our argument, we shall see in detail why they help achieve the desired results and why both these methods should be adapted in a combined approach to deliver the drug to the precise site of action through the topical or transdermal approach. Furthermore, Cannabidiol (CBD) is a model drug in this paper due to its faster absorption rate and outnumbered measurable benefits.

Keywords: Cannabis, heat, infrared radiation, topical drug delivery, ultrasound.

I. INTRODUCTION

Cannabis is one of the most famous and historically used drugs of abuse; however, until recently, the cannabis plant has not been adequately studied. At least 144 different cannabinoids are isolated from cannabis, exhibiting varied effects. Many cannabinoids exert numerous effects on the body once it has been administered, but the main effects that remain the subjects of interest are the behavioral, pathological, neurological, and muscular effects [1]. THC (Delta9-THC or Delta8-THC) is the primary psychoactive compound in cannabis, while Cannabidiol (CBD) is an example of another major constituent of the plant that is commonly used for treating discomfort [2].

To understand the mechanism by which cannabinoids cause such effects in the body and to control such effects, it is very important that we first understand the dynamics of the mechanism of action and pharmacodynamics of cannabis so that it can be made useful [3]. Its therapeutic effects can be utilized to the fullest while at the same time minimizing and nullifying the potential negative, toxic effects.

For the purposed of this paper, we will focus on cannabidiol (CBD) used for the pursuit of treating discomfort.

A. Administration of Cannabinoids

There are various routes for the administration and introduction of cannabis in the human body. It must be remembered that the route by which the drug is administered and the form of the drug when it is being administered speaks greatly about the absorption and bioavailability of the drug in the system[4].

The major routes used for the administration of Cannabis (CBD) in the human body include:

- Smoking
- Oral
- Oromucosal
- Transcutaneous (Transdermal/Topical)
- Rectal
- Intravenous

All these routes have an entirely different mechanism for absorption of cannabis, absorption, and utilization rates, and each of them takes a different time period for complete absorption to start affecting the body [5].

B. The Route of Choice for the Best Therapeutic Results

Out of all the routes mentioned above, if we discuss the
safe and the most preferred way for the localized delivery of drugs based on Cannabinoids in relation to their associated properties, it is undoubtedly going to be the Transdermal Route that offers the best cost-benefit ratio (at least, medicinally) [6].

The reason for this choice is simple:
1. The topical approach bypasses first-pass metabolism, which does not alter with (a) affects the body as a whole, (b) will not target a specific point of discomfort, and (c) increases the chances of abuse and damage to the throat, lungs or other tissue.
2. This route also increases the bioavailability of the drug. The bioavailability is greatest with the inhalation route, but the drug has been demonstrated to change into a substance of greater potential abuse and is not necessarily effective for localized applications.
3. The rate of delivery to the brain is slow when applied topically, which is good because it automatically reduces the potential for drug abuse.
4. A maintained, balanced, and continuous drug dosage can be effectively administered without fearing adverse effects [7].

C. Disadvantages of the Topical Administration Route

With many benefits, there are some obvious disadvantages associated with the topical or transdermal approach for the administration of Cannabinoids.

These disadvantages, in increasing order of their severity, include:
1. Local irritation due to the sensitive nature of the skin.
2. Lower levels of skin penetration, mainly due to the hydrophilic structure of Cannabinoids.
3. Lower levels of drug efficiency due to insufficient concentration in the dermis and non-uniform rates of pick-up by the capillaries.

As evident, the second reason is the most common reason why the topical administration of Cannabinoids is still frowned upon by many.

Cannabinoids are highly hydrophobic, making their necessary absorption deeper inside the skin hinder their optimal performance. Their hydrophobic nature prevents them from crossing the aqueous membrane of the skin, that is, the Corneum stratum, which reduces its efficacy, and allows a lower, altered concentration to reach the site of action, that is, if it manages to arrive in the first place [8].

It is believed that if somehow, there is a way to assure the fast and proper delivery of the drug into the system without these barriers, then scientists and researchers would be able to introduce an entirely new and unique way of treating medical conditions like those of neuropathic pain, localized inflammation, arthritis, muscular discomfort, certain dermatological conditions, and many other related symptoms using topical elements of cannabis effectively.

II. INCREASING THE TOPICAL ABSORPTION OF CANNABIDIOL (CBD) USING SPECIALIZED ULTRASOUND AND FAR INFRARED RADIATION

Despite the barriers and constraints discussed above, research has revealed a shortcut that could help the Cannabinoids effectively reach their site of action through the topical/transdermal route.

These methods involve employing specific ultrasound and sub-spectrum far-infrared heat (4-25 micron) to increase the absorption of cannabinoids into the skin, thus bypassing all the hindrances and impermeable membranes encountered by it.

A. The Role of Ultrasound

Since the skin layers prove to be a barrier restricting the entry of certain hydrophobic drug molecules from entering the deeper tissues, ultrasound is employed to solve the problem. Ultrasound works to permeabilize these barriers without invasion of the skin tissues reversibly. This way, the drug gets effectively transported across the layers and reaches its desired site of action to act upon [9].

Ultrasound waves can be divided into three different frequency ranges, all of which are said to increase skin permeability, but through different mechanisms:
- Low-Frequency Sonophoresis (20 - 100 kHz)
- Therapeutic (0.7 - 3 kHz)
- High-Frequency Sonophoresis (More than 3 MHz)

It is also believed that the frequency of the ultrasound waves is inversely proportional to the degree of skin penetration it causes. Ultrasound-mediated drug delivery also shortens the time required for the drug to reach and act on its site of action.

The main mechanisms by which ultrasound waves enhance the permeability of the skin for the delivery of the drugs are:

1) Acoustic Cavitation

It is the most important mechanism [10]. In this method, bubbles are caused to be created in a fluid by exerting excessive force on it, that is, through passing ultrasound waves of low frequency through it. These bubbles can increase in size due to the pressure wave impacting them (Fig. 1), and they can also collapse when brought in proximity of a solid-liquid interface while generating a shockwave [11]. It is called an “Inertial” or “Transient Cavitation,” which is basically what mediates the ultrasound-enhanced delivery of the topically applied drug.

Low-frequency ultrasound waves and the therapeutic range of ultrasound waves are preferred for acoustic cavitation. High-frequency ultrasound waves are seen to erode and cause invasive effects on the skin, which is destructive, hence the preference for the former two.
2) Other Mechanisms

The other mechanisms for ultrasound-mediated drug delivery are heat-related and include convection, acoustic radiation, and thermal effects [12]. All these methods involve their radiation towards the barrier placed ahead of them and thus cause it to be permeabilized for a limited time.

Therefore, by using specialized ultrasound waves for the increased absorption of cannabinol, we are doing the CBD drug a favor and allowing it to reach its desired site to produce the desired results effortlessly. Ultrasound waves will also allow us to control better the amount of the Cannabinoid being delivered, which means that we can also control the outcome associated with the drug.

Based on an ultrasound frequency of 1 MHz, 10 Watts, and 4-24 micron far infrared output, the CBD WAND falls under the therapeutic category and is deemed perfect for delivering the cannabinoids deeper inside the skin tissues.

B. Role of Far Infrared Emission

Far-infrared heat radiation is yet another modality that is used for the delivery of Cannabinoids into the skin. The relevant spectrum of far-infrared heat has a wavelength ranging from 4 to 25 microns which is invisible to the eyes.

It acts on the skin and causes it to be heated up through vascular dilation. This heat is felt as a gentle heating sensation on the skin where it is applied, and there is typically no other pain or discomfort associated with it [13].

The use of far-infrared radiation (FIR) for the delivery into the skin is associated with the fact that the application of heat on the surface of the skin raises the temperature (up to 43 degrees), and then this helps to efficiently and rapidly allow the drug to be absorbed into the skin. A cannabinoid-based drug must be delivered unchanged into the system, without modifications made to work according to its full potential.

Far infrared radiation does this favor for Cannabinoids and helps them to be absorbed into the skin easily.

In addition, 4-25-micron FIR increases the capillaries' size, speed, and health for accelerated delivery of oxygen, nutrients, and active ingredients (CBD) to the localized target.

Many appliances and materials are designed for delivering Far Infrared radiation into the skin, such as skin patches, heat-emitting fabrics, heat lamps, heat-radiating ceramics, devices, and saunas. Once these products increase the temperature of that part of the body where the CBD-based drug has to be applied, the skin becomes open to receiving the CBD drug with open arms. The plasma drug concentration of CBD gets significantly increased, and the time for the delivery of the CBD drug to its destination is considerably shortened. These factors contribute to the effective and unharmed concentration of the CBD drug inside the body and its various systems within.

III. INCREASING THE TOPICAL ABSORPTION OF CANNABINOIDs THROUGH SPECIALIZED ULTRASOUND AND FAR INFRARED RADIATION MEDIATED VASCULAR DILATION

A. Role of Ultrasound

Focused ultrasound waves within the therapeutic range are preferred for this purpose. The ultrasound waves, when focused on the point of interest, stimulate the endothelium of the focused blood vessel to release nitric oxide, a potent vasodilator. It also relaxes the blood vessels, and thus, the blood is allowed to flow freely [14]. This vasodilation is limited for the entire duration the ultrasound waves focus on the blood vessel of choice. As soon as the ultrasound waves are removed, the blood vessel/s return to their original forms. Employing this method for delivering a CBD-based drug can be an efficient means of transport as it does not cause damage of any kind, and in this way, the blood vessels are caused to be dilated in a non-invasive manner, and the CBD drug can very easily enter the system and reach its desired site of action rapidly with the rapid blood flow. This way, the first-pass metabolism gets bypassed easily, and the drug reaches its target in its original form (Fig. 2).

![Fig. 2. Mechanism of ultrasound in causing vasodilation.](image)
interaction of electromagnetic radiation with living cells can be framed in terms of altered cell membrane potentials and altered mitochondrial metabolism. FIR energy (photons with quantum energy levels of 12.4 meV – 1.7 eV) is absorbed by vibrational levels of bonds in molecules. Six vibrational modes cover symmetric and antisymmetric stretching, scissoring, rocking, wagging, and twisting. Considering the high concentration of water in biological systems, an association of water molecules with ions (solvation effect), the dielectric properties of the water, and the large dipole moment that this effect generates, this will be a dominant factor in biological solutions. At lower frequencies, water molecules can rotate freely in an oscillating electric field with little or almost no energy loss. However, if the frequency of the electric field reaches 108 Hz levels, the rotational mode becomes hindered (due to the "dielectric friction" effect), and the absorbed energy starts dissipating by collision or nearest-neighbor interactions in the media [2]. The dielectric relaxation of water at 310 K is around 25 GHz, where the rotational response of the dipoles to the electromagnetic field is spread over a broad frequency range.

In living systems, in addition to the water molecules associated with the electromagnetic field and its effects, one has to consider the "mesostructure" effect, where proteins and charged groups (located at specific sites on the proteins) are crucial to the overall biological activity. These specifically located charged groups associate with the water molecules and, by doing this, influence the whole molecular assembly's dielectric behavior, affecting its biologic functioning. Thus, the dielectric properties of tissues (even at the cellular level) depend on and vary with the water content. In addition, the relaxation of these molecular "mesostructures" can show variations with frequency. For these reasons, water content is critical in interacting with FIR and living organisms.

In this regard, the dynamics of water clusters have attracted considerable interest since there is a noticeable difference concerning the dynamics of bulk-liquid water, and this may have significant implications in biological environments. Local changes in the molecular environment (caused by solvation or confinement) are shown to substantially affect the translational and vibrational modes in the FIR frequency range. It is found that water cluster size and temperature affect the FIR absorption spectrum significantly.

FIR wavelength is too long to be perceived by the eyes; however, the body experiences its energy as a gentle radiant heat that can penetrate up to 1.5 inches (almost 4 cm) beneath the skin. FIR energy is sufficient to exert rotational and vibrational modes of motion in bonds forming the molecules (including the water molecules) and resonate with cellular frequencies. The resulting epidermal temperature is higher when the skin is irradiated with FIR than if similar thermal loads from shorter wavelengths are used. The prolonged erythemal response due to FIR exposure has been proposed to be due to increased epidermal temperatures associated with it, but levels of FIR that do not produce any detectable skin heating can also have biological effects.

When FIR in the 4-25 micron range is used to focus on a particular point on the skin, they are shown to increase blood flow through increased vasodilation [16]. All of this occurs because this particular wavelength range causes cellular resonance with a byproduct of heat. The vasodilator effect seems to stimulate the endothelium, and thus, it also starts producing Nitric Oxide (Fig. 3). This particular application of far-infrared radiation is extremely helpful; the vasodilation-mediated delivery of the CBD drug can help reduce potential life-threatening conditions like stroke, heart disease, etc. For this purpose, the usage of FIR for CBD drug delivery within the safe limits should be normalized.

IV. INCREASING THE HEALING & RECOVERY PROCESSES ALONG WITH REDUCING DISCOMFORT THROUGH THE APPLICATION OF SPECIALIZED ULTRASOUND AND FAR INFRARED RADIATIONS

Lastly, when it comes to decreasing discomfort, speeding up healing and recovery, and getting back to one's normal life, ultrasound waves and FIR has proven themselves to be useful.

Both of these modalities can be very safely used for accelerating the healing and recovery processes, along with easing the discomfort experienced by the person. Let's investigate the mechanisms causing these effects.

A. Role of Ultrasound

Ultrasound waves, when used as a handheld device with wavelengths measuring in the therapeutic range, can greatly help provide comfort, stress relief, and relaxation. The particular effect of ultrasound combined with the additional beneficial effects of properly administered CBD generate an outcome far more helpful than the beneficial effects of the CBD drug alone.

Ultrasound waves, when penetrating the skin tissues, cause a warm sensation radiating deep into the tissues, providing a relaxing feeling. This effect catalyzes the body's natural healing process and can help accelerate recovery [17].

In the same way, ultrasound-mediated therapy can increase circulation towards a particular area (vasodilation), which further helps reduce inflammation and relieve pain.

B. Role of Far Infrared Radiation:

FIR is a safe-for-use modality without any side effects that helps in wound healing and recovery and alleviates pain,
reducing the discomfort experienced by a person. FIR does so through vasodilation, fibroblast proliferation, and collagen generation, all of which are important factors in promoting healing [18].

The use of FIR has not been widely introduced for relieving pain. However, the heat the FIR radiates over the skin surface has shown to improve microcirculation over the area of focus, which contributes to the reduction of discomfort, and widely increases the absorption of CBD across the surface.

V. DISCUSSION

The topical drug delivery system is gaining popularity due to its advantages over oral drug delivery, and studies continue to assess TDD as a topical drug delivery approach for improving percutaneous drug absorption. Significant investigations into ultrasound processes and absorption pathways and the medicines employed in sonophoresis have confirmed the efficacy of ultrasound in improving transdermal transport during the past few decades.

A multiphysics problem including acoustic wave propagation, bioheat transfer, and drug transport is ultrasound-assisted drug transport.

Enhancement of sonophoresis cavitation activity has recently been undertaken because cavitation is the primary mechanism in ultrasound due to the development of intercellular lipid channels and the disordering of lipid bilayers. MI, created to express the chance of cavitation, rises as the center frequency decreases and the peak rarefaction pressure rises. One technique to augment existing cavitation bubbles is to use low-frequency sonophoresis.

However, because the FIR wavelength is too long, the body feels its energy as a gentle radiant heat that can penetrate up to 1.5 inches (almost 4 cm) into the skin. FIR radiation is powerful enough to cause rotational and vibrational motion in the bonds that hold molecules together and resonate with cellular frequencies. The resulting epidermal temperature is higher when the skin is irradiated with FIR.

It was difficult to determine if these findings resulted from electromagnetic radiation or a heat-activated systemic effect, such as improved microcirculation. As a result, for future animal or clinical trials, non-electronically generated FIR sources (non-heating devices) should be used. More research is needed to assess the efficacy of FIR in clinical settings, such as improving microcirculation and uncovering the underlying mechanism experimentally to put the final piece of the puzzle into the overall picture.

VI. CONCLUSION

Combined ultrasound-mediated and far-infrared radiation-based therapies are the most underestimated treatment enhancement regimens for topical cannabidiol (CBD) products.

(a) 1MHz, 10W Ultrasound has therapeutic effects,
(b) Far infrared in the range of 4-25 micron has therapeutic effects,
(c) Cannabinoids, such as cannabidiol, have therapeutic effects. If the beneficial effects of either Ultrasound, Far-infrared, or CBD are compiled together, they exceed the benefits that anyone has independently.

Cannabinoids, if used within certain limits, and administered properly as a topical, offer extremely beneficial therapeutic effects. Unfortunately, it is not accepted and absorbed by the body easily. Ultrasound therapy and FIR therapy can be used according to their required protocols to increase the absorption of CBD through the skin and help deliver the drug in unchanged form to the target tissue.

Specific ultrasound opens the pores and helps dilate the capillaries; far-infrared contributes to the greater opening of the pores and dilation of the capillaries. Cannabinol can penetrate in larger, concentrated amounts deeper into the dermis, which is received by stronger localized blood flow. This stronger localized blood flow delivers more cannabinol to the targeted site faster.

REFERENCES