Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Cannabidiol: Pharmaceutical formulations and biomedical applications

Ali Fadavi Eslam [1], Leila Mohtashami [1], Parvin Moghimi [2], Mehrdad Iranshahi [2*]

[1] Department of Pharmacognosy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article type:
Review

Article history:
Received: Aug 29, 2025
Accepted: Dec 2, 2025

Keywords:
Cannabidiol
Cannabis sativa
Intranasal delivery
Nanotechnology
Oral delivery
Pulmonary delivery
Transmucosal delivery

ABSTRACT

Cannabidiol (CBD) is a phytocannabinoid compound that can be utilized in different pharmaceutical industries. However, high lipophilicity and extensive first-pass metabolism limit its further applications. Therefore, the development of delivery approaches to overcome these obstacles has been of great interest. Herein, a comprehensive review of CBD, the receptors it targets, pharmacokinetic studies, and pharmaceutical formulations for effective delivery is presented. A comprehensive search was conducted in the Scopus, Web of Science, PubMed, and Google Scholar databases from 2016 to 2025. Different *in vitro*, *in vivo*, and clinical studies were included, whereas dissertations and conference abstracts were excluded.The results showed that CBD can target 5-HT1A, TRPV1-4, and PPAR-γ with minimal CB1/CB2 agonistic effects. This is consistent with the fact that CBD is effective in the treatment of epilepsy, pain, inflammation, neuropsychiatric disorders, and cancer without expressing psychoactive effects. Additionally, it was indicated that oral delivery formulations, such as long-chain triglyceride vehicles, self-nanoemulsifying systems, and polymeric/microencapsulated carriers, can improve CBD solubility and accelerate its absorption. Pulmonary delivery provides rapid absorption and is suitable for rapid symptom control, whereas intranasal formulations are suitable for nose-to-brain delivery. Transdermal systems elicit localized anti-inflammatory and neuroprotective effects, whereas transmucosal systems can bypass first-pass metabolism. CBD shows promising therapeutic potential; however, its effects across organs depend primarily on the route of administration. All formulations can be effective, but long-term safety evaluations are necessary.

▶ Please cite this article as:
Fadavi Eslam A, Mohtashami L, Moghimi P, Iranshahi M. Cannabidiol: Pharmaceutical formulations and biomedical applications. Iran J Basic Med Sci 2026; 29:

Introduction

Cannabidiol (CBD) (Figure 1) is a phytocannabinoid compound with a wide commercial market. CBD is extracted from *Cannabis sativa* L. (Cannabaceae) and was first obtained from Mexican marijuana and Indian charas, both in 1940, by Roger Adams and Alexander Todd, respectively (1). *C. sativa* grows in different geographical regions. Its cultivation dates back to 5000-6000 years ago, when it was first used in Egypt and Western Asia as a textile fiber. *Cannabis* application was expanded to Europe around 2000 to 1000 B.C., and to Chile in 1545 AD. In 1606, hemp cultivation was started in North America; however, it is currently illegal in the United States due to federal laws (2). These strict and inconsistent laws have led to reduced research about the therapeutic potential of *C. sativa*. As a result, the market of CBD-based products has been without regulatory approval. It seems essential to establish more precise and consistent regulations, along with better public and professional understanding of how CBD formulations should be used safely and effectively (3). Despite these limitations, CBD marketing was estimated at $4.6 billion in 2018 and is projected to exceed $20 billion in the United States in 2024 (4, 5). Cosmetics, textile fiber and clothing, beverages and food, and pharmaceuticals are different industries that use CBD (5). CBD has potential applications for treating schizophrenia (6), anxiety, graft-versus-host disease (GvHD) (7), inflammatory bowel disease (IBD) (8), and cancer (9). Pure CBD is permissible to be used only in drug-resistant epilepsy of children (10, 11). Generally, CBD is well-tolerated, but different side effects may occur when administered along with other drugs. The therapeutic window of CBD may be affected by other medications, necessitating consideration of alternative therapies (12, 13). Another big obstacle in CBD administration is its low water solubility and insufficient bioavailability. To overcome these limitations, various pharmaceutical and nanosized pulmonary, intranasal, oral, transdermal, and transmucosal formulations have been developed. They offer advantages such as increased solubility and absorption, improved bioavailability, bypass of first-pass metabolism, and controlled delivery of CBD (14, 15). In this paper, we have reviewed recent studies about therapeutic applications of CBD, various pharmaceutical formulations of this compound, and the pharmacodynamics and pharmacokinetics of the formulations.

***Corresponding author:** Mehrdad Iranshahi. Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran. Tel:+98-51-31801256, Fax: +98-51-38823251, Email: iranshahim@mums.ac.ir

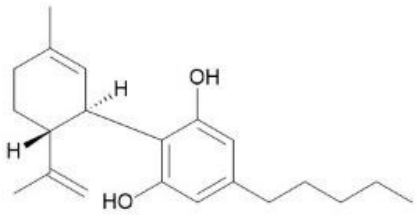

Figure 1. Structure of cannabidiol

Materials and Methods

A comprehensive literature search was conducted in the Scopus, Web of Science, PubMed, and Google Scholar databases from 2016 to 2025 using the following keywords: ("Cannabidiol" OR "CBD" OR "*Cannabis sativa*" OR "tetrahydrocannabinol" OR "THC" OR "phytocannabinoid" OR "*Cannabis* plant") AND ("pharmaceutical formulations" OR "drug delivery" OR "self-nanoemulsifying drug delivery system" OR "SNEDDS" OR "Epidiolex" OR "Oral formulation" OR "intranasal delivery" OR "transdermal delivery" OR "inhalation" OR "pulmonary delivery" OR "dry powder inhaler" OR "DPI" OR "metered dose inhaler" OR "MDI" OR "transmucosal delivery" OR "sesame oil vehicle" OR "olive oil" OR "anti-nociceptive" OR "anti-inflammatory" OR "neuroprotection" OR "oxidative stress" OR "anti-cancer" OR "CB1 receptor" OR "CB2 receptor" OR "5-HT1A"). *In vitro*, *in vivo*, and clinical studies were included, while dissertations and conference abstracts were excluded.

Results

Biological effects of cannabidiol

As an important phytocannabinoid, CBD has demonstrated therapeutic effects in psychiatric and neurological disorders, cancer, inflammation, oxidative stress, and pain. THC has been found to be effective in altering mood, slowing cognitive processes and reducing general performance through its effect on the nervous system (16). But CBD has not shown the same effects and could protect the nervous system against THC. Different receptors such as serotonin 1A (5-HT1A), peroxisome proliferator-activated receptor gamma (PPAR-γ), transient receptor potential cation channel subfamily V member 1 (TRPV1), and multiple orphan G protein-coupled receptors (GPCRs) have been introduced as CBD targets; besides, this compound shows no psychoactive side effects (17, 18). The anti-psychotic effect of CBD was initially observed in the 1970s, when experiments evidenced the reduction of THC-induced psychosis, reduction of anxiety, and the possible effects against panic attacks, post-traumatic stress disorder (PTSD), and obsessive–compulsive disorder (OCD). CBD could abolish symptoms of schizophrenia without side effects, which might be due to the non-dopaminergic mechanisms of this compound (19-21). CBD is effective in the modulation of epilepsy, particularly treatment-resistant forms like Dravet and Lennox-Gastaut syndromes (22). This compound is analgesic and has been introduced as an alternative to opioids since the risk of addiction to CBD is low (23). CBD could show anti-cancer effects, especially through inhibition of G-coupled protein receptor (GPR) 55 signaling pathways in pancreatic cancer (24). Additionally, it was effective in reducing myocardial apoptosis, oxidative stress, and inflammation in diabetes (25). CBD can be considered as a potential therapeutic molecule, and additional experiments to validate its clinical applications are crucial.

Cannabidiol receptors

here are two kinds of cannabinoid receptors, cannabinoid 1 (CB1) and cannabinoid 2 (CB2). CB1 is found primarily in the central nervous system (CNS); however, the cardiac and immune systems, the small intestine, liver, lungs, and kidneys also express this receptor (26, 27). CB2 is substantially found in the immune cells, but is also present in the gastrointestinal tract and CNS. Studies have proved the limited effectiveness of CBD on both CB1 and CB2 receptors (26, 28).

Pharmaceutical formulations of CBD

When administered orally, CBD undergoes high first-pass metabolism, with bioavailability of less than 10% (12). To overcome these problems, different pharmaceutical formulations, including pulmonary, intranasal, oral, transdermal, and transmucosal dosage forms, have been developed.

Inhalation and pulmonary delivery

The lungs are an ideal target for drug delivery due to bypassing first-pass metabolism and possessing a large surface area, a thin alveolar membrane, and a controlled enzymatic environment. The lungs are suitable for both local treatment of respiratory diseases and systemic therapies (29, 30). Factors such as the intrinsic defense system of the lungs and formulation properties, including particle size and dispersity, can affect safety and efficacy and limit proper drug delivery (30). Different pulmonary drug delivery devices have been introduced, including metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers (31, 32). This route has different advantages, such as simple, rapid, efficient, precise, and non-invasive administration that can minimize systemic side effects (33).

Improved pharmacokinetic parameters

In a study by Hložek *et al.* CBD, THC, and a combination of these two were administered to Wistar rats through inhalation, oral, and subcutaneous delivery. For pulmonary administration, THC, CBD, and their combination were vaporized and inhaled by rats for 5 minutes. Based on the results, pulmonary delivery showed the fastest cannabinoid absorption and elimination (34). These results have been shown in another *in vivo* research as well. It was indicated that the inhalation group showed faster absorption, higher peak concentrations, faster elimination, and more detectable metabolites by LC-MS/MS (35).

The pharmacokinetic parameters of CBD and THC between oral and vaporized formulations have also been compared in clinical trials. Pre- and post-dose blood samplings indicated higher and earlier peak concentrations in vaporized administration in comparison to the oral route (36). In an open-label phase-1 clinical trial, THC and CBD were administered to 11 healthy subjects through either a pressurized MDI or intravenous (iv) route. Peak concentrations of THC and CBD were reached extremely rapidly after administration within 5 minutes, and much shorter half-lives were observed with the inhaled formulation in comparison to the IV route. Inhaled products were well-tolerated with minimal adverse effects, whereas iv administration resulted in more severe side effects (37).

Another phase 1 clinical study has compared the DPI formulation of CBD with Epidiolex®. Epidiolex® is a lipid-based solution in sesame oil for treating seizures linked to tuberous sclerosis complex (TSC) in patients aged one year and older. Authorized for managing seizures in Lennox-Gastaut syndrome and Dravet syndrome, Epidiolex® is the only FDA-approved medication from CBD (38). Higher bioavailability and faster C_{max} were observed in the DPI administered group, and the participants reported safety and tolerability of both formulations (39).

In a within-subjects, crossover, double-blind, double-dummy study, 18 participants completed 4 experimental sessions, separated by a one-week washout. The 4 sessions were100 mg oral CBD, 100 mg vaporized CBD, 100 mg CBD along with 3.7 mg THC in vaporized CBD-dominant cannabis, and placebo. Minimal effects and the lowest blood concentration of CBD were observed with oral CBD. Vaporized CBD produced a higher CBD peak, and vaporized CBD-dominant cannabis led to the highest CBD and THC levels (40).

Improved pharmacological effects

An MDI formulation of CBD was prepared to directly target lung inflammation triggered by SARS-CoV-2 antigens, bacterial lipopolysaccharides, and pollutants like silica particles, nicotine, and coal tar. MDI formulation was prepared in absolute ethanol, and HFA-134a was used as propellant. The formulation was found to be safe for respiratory cells at concentrations below 44 µg/mL. The results confirmed that MDI formulation has a comparable effect to budesonide in reducing cytokines (41). In a pilot, randomized clinical trial, CBD was evaluated for potential impact on smokers who are trying to quit cigarette consumption. Twenty-four participants were randomly divided into two groups; whenever the participants felt the desire to smoke, one group received CBD by pressurized MDI containing 400 µg CBD per dose, and the other received a placebo. After one week, an approximate 40% reduction in the number of cigarettes smoked was observed in the CBD-treated group, whereas the placebo group showed no change. These findings indicate the impact of CBD on the reduction of cigarettes smoked, which might be due to the modulation of the endocannabinoid system (42).

Intranasal delivery

EThe endothelial membrane of the nasal canal is an appropriate route for drug delivery due to the presence of abundant vessels in its epithelium. This drug delivery method can lead to elimination of first-pass metabolism, faster absorption, and lower side effects (43, 44). It is also desirable for drug delivery to the CNS since it can overcome the blood-brain barrier (BBB) (45). CBD can also be administered intranasally (46, 47). Studies about intranasal delivery of CBD are reviewed in this section.

Improved pharmacokinetic parameters

Ahmed *et al.* investigated a nose-to-brain delivery of CBD using a nanoemulsion. The formulation was prepared using capryol 90, Tween 80, and Transcutol P. The results indicated increased *in vitro* drug release and enhanced nasal permeability *ex vivo*. A drug targeting efficiency of 419.64%, direct transport of 76.17%, and higher brain concentration of CBD were also observed, which confirmed the potential of this nanoemulsion for CBD delivery (48). In another study, the pharmacokinetic parameters of intranasal (20 mg), intrarectal (100 mg), and oral (100 mg) CBD were evaluated in six healthy Beagle dogs. It was revealed that intrarectal administration had plasma concentrations below the quantification limit, and the intranasal route resulted in faster tmax in comparison to the oral route. Oral delivery showed higher AUC and C_{max} (49).

Upadhyay *et al.* introduced a hydrophilic water-in-oil nanoemulsion of CBD (oil phase: Croda GTCC oil+CBD+polysorbate-80; aqueous phase: β-cyclodextrin in Milli-Q water) for direct nose-to-brain delivery. Male C57BL/6 mice received intranasal CBD, and CBD and its metabolite, 7-COOH-CBD, were quantified by LC–MS/MS after 2, 4, and 8 h post administration. The results showed a CBD peak in the brain and plasma at 4 h, while 7-COOH-CBD peaked at 2 h. These results indicated rapid metabolism of CBD and limited penetration of CBD to the brain via this formulation (50).

Improved pharmacological effects

A mucoadhesive nanostructured lipid carrier (NLC) has been used to evaluate the effect of nasal CBD on neuropathic pain. The carrier was prepared by stearic acid, oleic acid, span 20, and cetylpyridinium chloride. An *in vivo* investigation was performed on Swiss male mice that were suffering chemotherapy-induced neuropathic pain. Mice were divided into four groups, each receiving a different formulation including oral CBD solution, nasal CBD solution, nasal CBD-NLC, or nasal CBD-NLC-gel. The anti-nociceptive effect of nasal CBD-NLC was determined to be higher in comparison to oral or nasal CBD solution. CBD was not released properly from the hydrogel matrix of CBD-NLC-gel, which led to the failure of pain alleviation (51). Besides, an intranasal temperature-sensitive hydrogel containing a CBD inclusion complex (CBD TSGs) was assessed for the treatment of post-traumatic stress disorder (PTSD). *In vivo* experiments were conducted using a PTSD mouse model. The results confirmed that CBD TSGs formulation led to a significant reduction in anxiety, fear-related behaviors, and neuroinflammation. Moreover, neuroplasticity was improved as evidenced by an increase in brain-derived neurotrophic factor (BDNF) and expression of 5-HT1A receptor. Based on the pharmacokinetic analysis, the formulation was found to be more effective in brain targeting, and improved bioavailability was confirmed in comparison to oral delivery. These results suggested CBD TSGs as promising therapeutic agents for PTSD (52).

Another nasal spray of CBD was prepared using a β-cyclodextrin–complexed polymeric micelle (CBD-β-CDPM) to treat cytokine storm induced by COVID-19. CBD was released in under a minute, and the formulation showed high mucosal permeability and no cytotoxicity. Both *in vitro* and *ex vivo* experiments resulted in a significant inhibition of TNF-α, IL-1β, and IL-6 production that confirmed the anti-inflammatory effect of this formulation (53).

Oral delivery

Improved pharmacokinetic parameters

Lipid-based formulations

Lipid excipients can have a great impact on the systemic exposure of cannabinoids, specifically THC and CBD. It has been indicated that lipid-based oral formulation of CBD with sesame oil as a long-chain triglyceride (LCT) can lead to enhanced intestinal lymphatic transport. Following in vitro

lipolysis, more than 30% of the administered cannabinoids were incorporated into micelles that facilitate absorption (54). In another study, male Sprague-Dawley rats were treated with different oral samples of CBD, formulated with either natural sesame oil or glycerol trioleate, linoleic acid, oleic acid, oleic acid plus 2-oleoylglycerol, and oleic acid plus glycerol. A CBD formulation with sesame oil showed better lymphatic transport and bioavailability than other groups (55). Also, formulation with pure sesame oil has resulted in superior CBD levels in serum, lymph, and mesenteric lymph nodes of rats in comparison to formulations that used a combination of sesame oil with medium-chain triglycerides (MCT) or surfactants (56). Further, among CBD oral samples formulated by either sesame oil or olive, sunflower, coconut, soybean, and peanut oils, olive and sesame oils have the best results in terms of the intestinal lymphatic transport and systemic bioavailability. Olive oil formulation was found to be the best for CBD absorption (57).

To evaluate how well CBD is absorbed from the oral route, 8 healthy horses were given IV CBD (1 mg/kg) or oral CBD (10 mg/kg, prepared in sesame oil or micellar formulation). Blood samples were then collected and analyzed using LC-MS/MS, and the results revealed that CBD had a half-life of 24–34 hr, large volume of distribution (36 L/kg), and systemic clearance rate of 1.46 L/h/kg. Both oral formulations showed bioavailability of approximately 14%. The micellar formulation was absorbed more quickly, whereas the oil formulation maintained CBD levels for longer (58). An advanced Pro Nano-Liposphere (PNL) drug delivery system was developed for THC and CBD, utilizing a lipid core and piperine, curcumin, or resveratrol as natural absorption enhancers. Piperine-PNL formulation was observed to be the smallest and the most stable one in the particle evaluations. Male Wistar rats that received CBD-Piperine-PNL had a 6- and 2-fold increase in AUC compared to rats that received CBD-PNL and CBD solution, respectively. Among these advanced systems, the piperine-formulated preparation was the most effective when administered orally (59).

In another study, the self-nanoemulsifying drug delivery system of CBD (CBD-SNEDDS) was compared with the MCT oil formulation of CBD (MCT-CBD) and Epidiolex®. Oral administration of formulations (20 mg/kg of CBD) to female Sprague-Dawley rats showed a faster absorption of SNEDDS and better systemic exposure to CBD when compared to MCT. Additionally, one of the SNEDDS formulations showed better absorption than Epidiolex® (60). The impact of LCT and MCT lipids on the oral absorption and bioavailability of THC-SNEDDS and CBD-SNEDDS was also explored. First formulation (type I) was based on liquid lipids, including sesame oil as LCT and MIGLYOL® 812N as MCT, while the second (type II) was based on solid lipids, including cocoa butter as LCT and tricaprin as MCT. An *in vivo* evaluation was performed on male Wistar rats. The results showed primarily systemic absorption with limited lymphatic contribution for the type I formulation. In contrast, enhanced lymphatic absorption and reduced first-pass metabolism were observed in the type II formulation. Systemic absorption and minimal lymphatic absorption were not significantly different between LCT and MCT in type I. Meanwhile, bioavailability was higher for LCT than for MCT in type II (61). Wang *et al.* have evaluated how MCT, LCT, or their combination could affect the carrier ability for CBD delivery. The formulations were stabilized using whey protein-maltodextrin. The highest bioavailability was observed when CBD was emulsified by LCT (62).

Non-lipid-based formulations

The effect of propylene glycol as a lipid-free vehicle, and coconut oil, rapeseed oil, and sesame oil as lipid vehicles in oral formulations of CBD was evaluated by Brookes *et al.* After administration of formulations to male Sprague-Dawley rats, CBD distribution in various brain regions was investigated. The results showed the highest CBD levels in the entire brain by the propylene glycol formulation. But after individual brain parts were analyzed, the LCT-rich rapeseed oil formulation was found to be the best one among all to deliver CBD to specific areas of the brain (63). Additionally, CBD encapsulated in the poly(ethylene glycol)-b-poly(epsilon-caprolactone) block copolymer has been administered to rats, and the results revealed a 20-fold increase in Cmax, a decrease in tmax, and a 14-fold increase in AUC compared with the free CBD suspension (64). Another method used to increase the stability and bioavailability of CBD in oral administration was to encapsulate CBD in zein-whey protein composite. The water solubility of CBD was increased significantly after encapsulation. *In vivo* investigations on Sprague-Dawley rats showed better absorption of encapsulated CBD in comparison to free CBD. Encapsulated CBD achieved twice the C_{max}, 1.75-fold increase in AUC, faster t_{max} (2h), and longer circulation time (65). Sodium alginate microencapsulation can have an impact on the oral bioavailability of CBD as well, particularly when co-administered with deoxycholic acid (DCA). The microencapsulated CBD, microencapsulated CBD with DCA, and naked CBD oil were administered to C57BL/6J mice, and plasma and brain CBD concentrations were measured at multiple time points thereafter. The bioavailability and brain levels were found to be increased significantly in the DCA-formulated group compared to the naked CBD oil group (66).

A recent study has compared PTL101, a gelatin-based acid-resistant formulation of CBD, with Sativex® spray (a prescribed medicine that contains equal proportions of THC and CBD to treat muscle spasticity in multiple sclerosis patients) (67). Fifteen healthy male volunteers were enrolled in the trial; each received either a 10 mg PTL101 capsule, a 100 mg PTL101 capsule, or a 10 mg dose of CBD via Sativex® spray, with a 7-day washout between treatments. PTL101 (10 mg) led to a 1.7- and 1.3-fold higher C_{max} and AUC, respectively, compared to the spray. PTL101 (100 mg) led to a 15-fold increase in both C_{max} and AUC compared to the spray. PTL101 absorption was delayed relative to Sativex®, but its bioavailability was 134% of the spray. This formulation was well-tolerated and had mild side effects. PTL101 was found to be more effective for CBD delivery, which could improve patient adherence in long-term applications (68).

Topical and transdermal delivery

Topical and transdermal delivery systems offer advantages such as eliminating bioavailability limitations and enabling direct delivery of CBD to the skin for localized or systemic effects (69, 70). The central and peripheral nervous systems are where CB1 and CB2 receptors are located (71). Afferent nerve fibers, skin adnexa, and inflammatory cells have

been identified to possess these receptors, suggesting the skin as a potential target for CBD (72). Several studies have investigated the transdermal and topical effects of CBD formulations, which are mentioned in the following.

Improved pharmacokinetic parameters

Pickering emulsions are considered as emulsions in which two immiscible phases are stabilized by adsorption of organic or inorganic solid particles between water and oil phases (73). In a study by Sharkawy *et al.*, Pickering emulsions were prepared by chitosan/collagen peptides nanoparticles and used for the topical delivery of CBD. Olive oil was the oil of choice for preparing a gel-like Pickering emulsion. The skin absorption tests showed little permeation and high retention of CBD on the stratum corneum, which makes the emulsion suitable for topical applications (74).

Microemulgels can be advantageous carriers for hydrophobic drugs. They are made of oil-in-water microemulsions, presented in a gel base. These formulations present the characteristics of both microemulsions and gels (75, 76). Vanti *et al.* developed a CBD-loaded microemulgel for localized dermatological applications. It showed good stability and a controlled release pattern. Permeability evaluation confirmed that this formulation is proper for localized skin delivery of CBD with minimal systemic side effects (77).

Improved pharmacological effects

Addiction and neurodegeneration

Gonzalez-Cuevas *et al.* have studied the potential of a transdermal CBD preparation in reducing relapse of drug seeking, anxiety, and impulsivity by *in vitro* and *in vivo* models. *In vitro* evaluations confirmed that CBD interacts with CB1, CB2, 5-HT1A, and opioid receptors, thereby modulating the endocannabinoid system and reducing oxidative stress and inflammation. Reductions in context- and stress-induced drug-seeking, anxiety, and impulsivity were seen in male Wistar rats with histories of alcohol or cocaine self-administration. There was no tolerance, sedation, or naturally motivated behaviors. These effects were observed up to 138 days post-treatment, suggesting a lasting neurobiological impact. The findings suggested transdermal_CBD as a promising candidate for addiction treatment (78).

nother study conducted by Liput *et al.* has focused on the use of transdermal CBD in alcohol-induced neurodegeneration. *In vitro*, the transdermal permeability of CBD increased significantly with ethosomal transdermal formulations. For *in vivo* assessment, male Sprague-Dawley rats were administered alcohol and received CBD gels at 1%, 2.5%, and 5% concentrations. The 5% formulation showed the most promising neuroprotective effects in the entorhinal cortex. In later phases of the study, the neuroprotective effects of an optimized 2.5% gel were compared with intraperitoneal (IP) CBD injection (40 mg/kg/day). After alcohol exposure, the rats were given different CBD formulations. A reduction of 56.1% and 50.6% in neurodegeneration was observed in the transdermal CBD gel group and the intraperitoneal CBD group, respectively (79).

Arthritis

The effects of CBD gel for the treatment of knee arthritis have been investigated in male Sprague-Dawley rats. The results indicated a dose-dependent reduction of joint swelling, spontaneous pain behaviors, and nociceptive sensitization. Also, paw withdrawal latency was normalized. Investigations at the molecular level revealed a reduction in pro-inflammatory biomarkers as well (80).

Cancer

Momekova *et al.* investigated β-cyclodextrin (β-CD) and 2-hydroxyethyl cellulose (HEC) cryogels as topical delivery systems for CBD. *In vitro* evaluation demonstrated burst release in the first 3 hours, followed by a sustained release profile. This can indicate an effective system for topical formulations. Cytotoxicity evaluations were conducted on MJ and HUT-78 cutaneous T lymphoblast lymphoma cell lines using formulations with 100:0, 50:50, 40:60, and 20:80 ratios of HEC/β-CD. The results revealed concentration-dependent cytostatic activity for the formulations, with free CBD exhibiting greater cytotoxicity (81).

A nanocomposite cryogel of CBD-loaded HEC network was also developed as a sustained transdermal delivery system. *In vitro* evaluations on mouse fibroblast cells (CCL-1) showed that blank cryogel carriers have no cytotoxicity. CBD-loaded cryogels had a sustained release pattern and showed dose-dependent anti-cancer effects on MJ (cutaneous T lymphoblast lymphoma) and T-24 (urinary bladder carcinoma) cells. These results suggest cryogels as localized CBD delivery systems that can be beneficial for treating cutaneous and bladder cancers (82).

Epidermolysis bullosa

In a case report study, three patients with different subtypes of epidermolysis bullosa (EB) were assessed after they were given topical CBD. Treatments consisted of CBD spray, oil, or cream, applied to affected areas multiple times daily. Reduced blistering and pain, and faster wound healing were observed in all cases. Two patients even discontinued oral analgesics, and one had improved mobility. None of them showed side effects. Although these results indicate therapeutic benefits, the authors emphasized the necessity of randomized, double-blind, controlled trials to determine the safety and efficacy of topical CBD in the treatment of EB (83).

Epilepsy

A stimuli-responsive transdermal delivery system for CBD was developed to be used in the treatment of conventional epilepsy. This nanoparticulate system was synthesized using chitosan and ZnO. *In vitro* evaluations confirmed the biocompatibility, enhanced drug loading capacity of NPs, and controlled CBD release. Investigations on L929 mouse fibroblasts confirmed mechanical durability, high porosity, and sustained drug release with minimal cytotoxic effects. Therefore, this transdermal system can be a promising alternative for CBD delivery in epilepsy treatment (84).

Pain and inflammation

The anti-nociceptive and anti-inflammatory effects of a transdermal CBD cream were investigated on two opioid-naive patients. They have applied the cream twice daily for 12 weeks, and the findings suggested a promising analgesic effect (85). Besides, CBD ointment has shown a significant improvement in different symptoms of psoriasis, atopic dermatitis, and scars in patients when applied for three

months. No irritation and allergic reactions occurred (86).

Transmucosal delivery

Transmucosal drug delivery has shown different advantages, including good patient compliance, bypassing first-pass metabolism, and prevention of drug elimination in the gastrointestinal tract (87). In this regard, CBD oil users are usually told to take it sublingually to enable CBD absorption through the oral mucosal membranes. In a clinical study, healthy volunteers were given oil solution and sublingual wafers of *C. sativa* extract, standardized to CBD content. The safety, tolerability, and pharmacokinetics of these forms were compared with nabiximol's oromucosal spray. The oil solution and sublingual wafers were well tolerated and had equivalent concentrations of CBD compared to the nabiximol spray (88).

Advantages and disadvantages of different delivery methods have been summarized in Table 1.

Discussion

CBD is a non-psychoactive phytocannabinoid that needs further clinical evaluations. This compound can affect multiple receptor pathways, including 5-HT1A, TRPV1-4, and PPAR-γ, rather than just directly targeting CB1 and CB2 receptors. These multi-target effects can explain its broad therapeutic profile (17-22, 26).

When being used orally, CBD encounters a high first-pass metabolism and low bioavailability (12). To address this issue, pulmonary, intranasal, oral, transdermal, and transmucosal formulations of CBD have been introduced.

Pulmonary delivery systems, namely MDIs, DPIs, and nebulizers, can lead to rapid absorption, higher bioavailability, and minimal systemic side effects (34-37, 39, 40). Further, the safety, efficacy, and tolerability of CBD inhalation have been improved (37, 39, 40). Thus, it is an ideal administration route for CBD in both respiratory and systemic treatments.

Intranasal delivery can result in the elimination of first-pass metabolism, faster absorption, and lower side effects; therefore, it can be considered as a promising CNS delivery method (43-45). Intranasal CBD has demonstrated faster systemic absorption compared to the oral route (49), highlighting its importance as an effective delivery method for neurotherapeutics. Using nano-formulations of CBD can improve the therapeutic efficacy of intranasal delivery (51). Besides, improved bioavailability in comparison to the oral route and improved neuroplasticity were obtained using a temperature-sensitive intranasal hydrogel (52).

According to several studies, oral formulations of CBD are among the most convenient and widely accepted administration routes. However, the oral route has low bioavailability and limited absorption. To overcome these challenges, researchers have developed various formulation strategies to enhance CBD solubility, absorption, and systemic exposure. Among them, lipid-based formulations, particularly those containing LCTs like sesame oil and olive oil, have demonstrated promising intestinal lymphatic transport, reduced metabolism, and improved overall bioavailability (54-57, 61, 62). It has been reported that LCTs are more efficient than MCTs (54, 57, 61, 62). Moreover, the addition of absorption enhancers such as piperine to the lipid-based formulations can boost CBD bioavailability (59). In addition to lipid-based formulations, advanced nanoformulations such as SNEDDS have also been developed to enhance CBD solubility and systemic exposure. These nano-sized carriers have faster and sometimes better absorption in comparison to traditional oils (60). Other encapsulation techniques, including polymeric nanoparticles and sodium alginate microencapsulation, can improve CBD stability and bioavailability and enable targeted delivery (64-66). Altogether, the combination of LCT-based lipid carriers and nano-delivery technologies may be considered as one of the most effective approaches for enhancing the oral bioavailability of CBD.

Transdermal CBD could reduce drug-seeking behaviors, anxiety, and impulsivity *in vivo* (78) and has shown neuroprotective effects against alcohol-induced neurodegeneration (79). Formulations like Pickering emulsions (74), microemulgels (77), ethosomal gels (79), nanocomposite cryogels (81, 82), and stimuli-responsive nanoparticulate systems were prepared for CBD. Some of them have led to local CBD retention and delivery, and some could release CBD in a controlled pattern. In contrast, transmucosal drug delivery still has challenges in significantly improving bioavailability (88) and requires further optimization in future work.

Table 1. Advantages and disadvantages of different Cannabidiol (CBD) delivery methods

Delivery method	Advantages	Disadvantages	Ref.
Pulmonary	Rapid and efficient delivery Simple administration Minimizing systemic side effects Improvement of bioavailability	Limitations imposed by pulmonary defense mechanisms Higher dependence of efficacy on formulation properties	29, 30, 33-37, 39, 40
Intranasal	Avoidance of first-pass metabolism Faster absorption Lower side effects Desirable method for CNS delivery	Challenging optimization	43-45, 48-53
Oral	Enhancement of patient compliance Ideal for long-term therapy Optimization by different formulations	Low bioavailability First-pass metabolism Poor gastrointestinal absorption Slow onset of action	54-68
Topical and transdermal	Improvement of bioavailability Avoidance of gastrointestinal degradation Direct delivery to the skin	Limited skin permeability Lack of systemic delivery	69, 70, 74, 77-80, 82, 83
Transmucosal	Enhancement of patient compliance Avoidance of first-pass metabolism Avoidance of gastrointestinal degradation	Accidentally swallowing and unpredictable absorption Variable bioavailability	87, 88

Conclusion

This review aimed to summarize historical and regulatory background, biological mechanisms, and receptor interactions, and particularly recent advances in the pharmaceutical formulations of CBD. Based on the results, CBD was found effective on multiple targets like 5-HT1A, TRPV1-4, and PPAR-γ besides CB-1 and CB-2. This gives it the potential to be used in different situations such as epilepsy, pain, inflammation, mental disorders, and cancer. However, insufficient bioavailability of oral CBD has led to the development of different pharmaceutical formulations. Lipid-based oral systems, especially LCT vehicles and SNEDDS, are some oral formulations that are capable of improving solubility and absorption. Pulmonary delivery provides rapid absorption that is suitable for rapid symptom control, whereas intranasal formulations are suitable for nose-to-brain delivery. Transdermal systems demonstrated promising anti-inflammatory and neuroprotective effects, and transmucosal systems could bypass first-pass metabolism. The findings of this study highlighted the importance of developing appropriate CBD formulations to achieve the desired effects. However, there is still a need for careful dosing, clear labeling, and designing studies for the assessment of CBD's long-term safety. *In vitro*-to-*in vivo* and *in vivo*-to-clinical dose translation seems crucial for future work.

Acknowledgment

The authors would like to thank Mashhad University of Medical Sciences Research Council for funding this study. The results presented in this paper were part of a PharmD dissertation.

Authors' Contributions

A F provided conceptualization, investigation, and original draft writing. L M performed data curation, critical revision, and writing original draft. P M contributed to review and editing of the writing. M I managed data curation, project administration, review, editing, and visualization.

Conflicts of Interest

The authors have no conflicts of interest.

Declaration

We have not used any AI tools or technologies to write this manuscript.

References

1. Mechoulam R, Hanuš L. Cannabidiol: An overview of some chemical and pharmacological aspects. Part I: chemical aspects. Chem Phys Lipids 2002; 121: 35-43.
2. Small E, Marcus D. Hemp: A new crop with new uses for North America. In: Trends in New Crops and New Uses (Edited by: J Janick and A Whipkey). ASHS Press. Proceedings of the Fifth National Symposium. 2001. p. 284-326.
3. Jardim C, Delgado-Charro MB. The regulatory environment surrounding *Cannabis* medicines in the EU, the USA, and Australia. Pharmaceutics 2025; 17: 635.
4. Dorbian I. CBD market could reach $20 billion by 2024, Says new study. Forbes 2019.
5. Nelson KM, Bisson J, Singh G, Graham JG, Chen SN, Friesen JB, *et al.* The essential medicinal chemistry of cannabidiol (CBD). J Med Chem 2020; 63: 12137-12155.
6. Johnson K, Weldon AJ, Burmeister MA. Differential effects of *Cannabis* constituents on schizophrenia-related psychosis: A rationale for incorporating cannabidiol into a schizophrenia therapeutic regimen. Front Psychiatry 2024; 15: 1386263.
7. Yeshurun M, Shpilberg O, Herscovici C, Shargian L, Dreyer J, Peck A, *et al.* Cannabidiol for the prevention of graft-versus-host-disease after allogeneic hematopoietic cell transplantation: Results of a phase II study. Biol Blood Marrow Transplant 2015; 21: 1770-1775.
8.Portman A, Bukovich E, Bissex J, Flanagan M, Pojednic R. The perceived effectiveness of cannabidiol on adult women with inflammatory bowel disease. Medicina 2024; 60: 2059.
9. Esmaeli M, Dehabadi MD, Khaleghi AA. Cannabidiol as a novel therapeutic agent in breast cancer: Evidence from literature. BMC Cancer 2025; 25: 772.
10. Mitelpunkt A, Kramer U, Hausman Kedem M, Zilbershot Fink E, Orbach R, Chernuha V, *et al.* The safety, tolerability, and effectiveness of PTL-101, an oral cannabidiol formulation, in pediatric intractable epilepsy: A phase II, open-label, single-center study. Epilepsy Behav 2019; 98: 233-237.
11. Millar SA, Maguire RF, Yates AS, O'Sullivan SE. Towards better delivery of cannabidiol (CBD). Pharmaceuticals 2020; 13: 219.
12. Millar SA, Stone NL, Yates AS, O'Sullivan SE. A systematic review on the pharmacokinetics of cannabidiol in humans. Front Pharmacol 2018; 9: 1365.
13. Mlost J, Bryk M, Starowicz K. Cannabidiol for pain treatment: Focus on pharmacology and mechanism of action. Int J Mol Sci 2020; 21: 8870.
14. Hossain KR, Alghazwini A, Valenzuela SM. Current challenges and opportunities for improved cannabidiol solubility. Int J Mol Sci 2023; 24: 14414.
15. Sholmore LH, Willmer AR, Capparelli EV, Rosania GR. Food effects on the formulation, dosing, and administration of cannabidiol (CBD) in humans: A systematic review of clinical studies. Pharmacotherapy 2021; 41: 405-420.
16. Pesta DH, Angadi SS, Burtscher M, Roberts CK. The effects of caffeine, nicotine, ethanol, and tetrahydrocannabinol on exercise performance. Nutr Metab (Lond) 2013; 10: 71.
17. Wang X, Zhang H, Liu Y, Xu Y, Yang B, Li H, *et al.* An overview on synthetic and biological activities of cannabidiol (CBD) and its derivatives. Bioorg Chem 2023; 140: 106810.
18. Lee S, Lee Y, Kim Y, Kim H, Rhyu H, Yoon K, *et al.* Beneficial effects of cannabidiol from *Cannabis*. Appl Biol Chem 2024; 67: 32.
19. Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics 2015; 12: 825-836.
20. Lowe DJE, Sasiadek JD, Coles AS, George TP. *Cannabis* and mental illness: A review. Eur Arch Psychiatry Clin Neurosci 2019; 269: 107-120.
21. McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, *et al.* Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. Am J Psychiatry 2018; 175: 225-231.
22. Silvestro S, Mammana S, Cavalli E, Bramanti P, Mazzon E. Use of cannabidiol in the treatment of epilepsy: Efficacy and security in clinical trials. Molecules 2019; 24: 1459.
23. Hurd YL, Yoon M, Manini AF, Hernandez S, Olmedo R, Ostman M, *et al.* Early phase in the development of cannabidiol as a treatment for addiction: Opioid relapse takes initial center stage. Neurotherapeutics 2015; 12: 807-815.
24. Ferro R, Adamska A, Lattanzio R, Mavrommati I, Edling CE, Arifin SA, *et al.* GPR55 signalling promotes proliferation of pancreatic cancer cells and tumour growth in mice, and its inhibition increases effects of gemcitabine. Oncogene 2018; 37: 6368-6382.
25. El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai NT, Caldwell RB, Liou GI. Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. Am J Pathol 2006; 168: 235-244.
26. Britch SC, Babalonis S, Walsh SL. Cannabidiol: Pharmacology and therapeutic targets. Psychopharmacology 2021; 238: 9-28.

27. Buchholz H, Uebbing K, Maus S, Pektor S, Afahaene N, Weyer-Elberich V, *et al.* Whole-body biodistribution of the cannabinoid type 1 receptor ligand [^{18}F] MK-9470 in the rat. Nucl Med Biol 2017; 52: 63-69.
28. Núñez E, Benito C, Pazos MR, Barbachano A, Fajardo O, González S, *et al.* Cannabinoid CB2 receptors are expressed by perivascular microglial cells in the human brain: An immunohistochemical study. Synapse 2004; 53: 208-213.
29. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol 2003; 56: 588-599.
30. He S, Gui J, Xiong K, Chen M, Gao H, Fu Y. A roadmap to pulmonary delivery strategies for the treatment of infectious lung diseases. J Nanobiotechnol 2022; 20: 101.
31. Ramírez-Rigo MV, Guzmán ML, Olivera ME. Pulmonary drug delivery. In: The ADME Encyclopedia: A Comprehensive Guide on Biopharmacy and Pharmacokinetics (Edited by A Talevi). Springer Cham. 2022. p. 1029-1040.
32. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications. Br J Clin Pharmacol 2003; 56: 600-612.
33. Wang B, Wang L, Yang Q, Zhang Y, Qinglai T, Yang X, *et al.* Pulmonary inhalation for disease treatment: Basic research and clinical translations. Mater Today Bio 2024; 25: 100966.
34. Hložek T, Uttl L, Kadeřábek L, Balíková M, Lhotková E, Horsley RR, *et al.* Pharmacokinetic and behavioural profile of THC, CBD, and THC+CBD combination after pulmonary, oral, and subcutaneous administration in rats and confirmation of conversion in vivo of CBD to THC. Eur Neuropsychopharmacol 2017; 27: 1223-1237.
35. Schwotzer D, Kulpa J, Trexler K, Dye W, Jantzi J, Irshad H, *et al.* Pharmacokinetics of cannabidiol in Sprague-Dawley rats after oral and pulmonary administration. Cannabis Cannabinoid Res 2023; 8: 360-373.
36. Bergeria CL, Spindle TR, Cone EJ, Sholler D, Goffi E, Mitchell JM, *et al.* Pharmacokinetic profile of Δ^9-tetrahydrocannabinol, cannabidiol and metabolites in blood following vaporization and oral ingestion of cannabidiol products. J Anal Toxicol 2022; 46: 583-591.
37. Meyer P, Langos M, Brenneisen R. Human pharmacokinetics and adverse effects of pulmonary and intravenous THC-CBD formulations. Med Cannabis Cannabinoids 2018; 1: 36-43.
38. FDA approves new indication for drug containing an active ingredient derived from *Cannabis* to treat seizures in rare genetic disease. Available from https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd.
39. Devinsky O, Kraft K, Rusch L, Fein M, Leone-Bay A. Improved bioavailability with dry powder cannabidiol inhalation: A phase 1 clinical study. J Pharm Sci 2021; 110: 3946-3952.
40. Spindle TR, Cone EJ, Goffi E, Weerts EM, Mitchell JM, Winecker RE, *et al.* Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. Drug Alcohol Depend 2020; 211: 107937.
41. Srichana T, Chunhachaichana C, Suedee R, Sawatdee S, Changsan N. Oral inhalation of cannabidiol delivered from a metered dose inhaler to alleviate cytokine production induced by SARS-CoV-2 and pollutants. J Drug Deliv Sci Technol 2022; 76: 103805.
42. Morgan CJA, Das RK, Joye A, Curran HV, Kamboj SK. Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. Addict Behav 2013; 38: 2433-2436.
43. Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol 2001; 53: 3-21.
44. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today 2002; 7: 967-975.
45. Pagar SA, Shinkar DM, Saudagar RB. A review on intranasal drug delivery system. J Adv Pharm Edu & Res 2013; 3: 333-346.
46. Chung S, Peters JM, Detyniecki K, Tatum W, Rabinowicz AL, Carrazana E. The nose has it: Opportunities and challenges for intranasal drug administration for neurologic conditions including seizure clusters. Epilepsy Behav Rep 2023; 21: 100581.
47. O'Sullivan SE, Jensen SS, Nikolajsen GN, Ziegler Bruun H, Bhuller R, Hoeng J. The therapeutic potential of purified cannabidiol. J Cannabis Res 2023; 5: 21.
48. Ahmed B, Rizwanullah M, Mir SR, Akhtar MS, Amin S. Development of cannabidiol nanoemulsion for direct nose to brain delivery: Statistical optimization, *in vitro* and *in vivo* evaluation. Biomed Mater 2022; 17: 065009.
49. Polidoro D, Temmerman R, Devreese M, Charalambous M, Van Ham L, Cornelis I, *et al.* Pharmacokinetics of cannabidiol following intranasal, intrarectal, and oral administration in healthy dogs. Front Vet Sci 2022; 9: 899940.
50. Upadhyay G, Fihurka O, Patel P, Sanchez-Ramos J. Quantitation of cannabidiol (CBD) in brain regions and plasma following intranasal administration of a CBD nanoformulation. J Cannabis Res 2025; 7: 63.
51. Matarazzo AP, Elisei LMS, Caryalho FC, Bonfílio R, Ruela ALM, Galdino G, *et al.* Mucoadhesive nanostructured lipid carriers as a cannabidiol nasal delivery system for the treatment of neuropathic pain. Eur J Pharm Sci 2021; 159: 105698.
52. Pang L, Zhu L, Ma L, Zhu L, Liu Y, Ou G, *et al.* Intranasal temperature-sensitive hydrogels of cannabidiol inclusion complex for the treatment of post-traumatic stress disorder. Acta Pharm Sin B 2021; 11: 2031-2047.
53. Changsan N, Sawatdee S, Suedee R, Chunhachaichana C, Srichana T. Aqueous cannabidiol β-cyclodextrin complexed polymeric micelle nasal spray to attenuate *in vitro* and *ex vivo* SARS CoV-2-induced cytokine storms. Int J Pharm 2023; 640: 123035.
54. Zgair A, Wong JCM, Lee JB, Mistry J, Sivak O, Wasan KM, *et al.* Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. Am J Transl Res 2016; 8: 3448-3459.
55. Feng W, Qin C, Chu Y, Berton M, Lee JB, Zgair A, *et al.* Natural sesame oil is superior to pre-digested lipid formulations and purified triglycerides in promoting the intestinal lymphatic transport and systemic bioavailability of cannabidiol. Eur J Pharm Biopharm 2021; 162: 43-49.
56. Feng W, Qin C, Cipolla E, Lee JB, Zgair A, Chu Y, *et al.* Inclusion of medium-chain triglyceride in lipid-based formulation of cannabidiol facilitates micellar solubilization *in vitro*, but *in vivo* performance remains superior with pure sesame oil vehicle. Pharmaceutics 2021; 13: 1349.
57. Feng W, Qin C, Abdelrazig S, Bai Z, Raji M, Darwish R, *et al.* Vegetable oils composition affects the intestinal lymphatic transport and systemic bioavailability of co-administered lipophilic drug cannabidiol. Int J Pharm 2022; 624: 121947.
58. Sánchez de Medina A, Serrano-Rodríguez JM, Díez de Castro E, García-Valverde MT, Saitua A, Becero M, *et al.* Pharmacokinetics and oral bioavailability of cannabidiol in horses after intravenous and oral administration with oil and micellar formulations. Equine Vet J 2023; 55: 1094-1103.
59. Cherniakov I, Izgelov D, Domb AJ, Hoffman A. 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. Eur J Pharm Sci 2017; 109: 21-30.
60. Kok LY, Bannigan P, Sanaee F, Evans JC, Dunne M, Regenold M, *et al.* Development and pharmacokinetic evaluation of a self-nanoemulsifying drug delivery system for the oral delivery of cannabidiol. Eur J Pharm Sci 2022; 168: 106058.
61. Izgelov D, Shmoeli E, Domb AJ, Hoffman A. The effect of medium chain and long chain triglycerides incorporated in self-nano emulsifying drug delivery systems on oral absorption of cannabinoids in rats. Int J Pharm 2020; 580: 119201.
62. Wang C, Dong C, Lu Y, Freeman K, Wang C, Guo M. Digestion

behavior, *in vitro* and *in vivo* bioavailability of cannabidiol in emulsions stabilized by whey protein-maltodextrin conjugate: Impact of carrier oil. Colloids Surf B Biointerfaces 2023; 223: 113154.
63. Brookes A, Jewell A, Feng W, Bradshaw TD, Butler J, Gershkovich P. Oral lipid-based formulations alter delivery of cannabidiol to different anatomical regions in the brain. Int J Pharm 2023; 635: 122651.
64. Shreiber-Livne I, Sulimani L, Shapira A, Procaccia S, Meiri D, Sosnik A. Poly(ethylene glycol)-b-poly(epsilon-caprolactone) nanoparticles as a platform for the improved oral delivery of cannabidiol. Drug Deliv Transl Res 2023; 13: 3192-3203.
65. Wang C, Wang J, Sun Y, Freeman K, Mchenry MA, Wang C, *et al.* Enhanced stability and oral bioavailability of cannabidiol in zein and whey protein composite nanoparticles by a modified anti-solvent approach. Foods 2022; 11: 376.
66. Majimbi M, Brook E, Galettis P, Eden E, Al-Salami H, Mooranian A, *et al.* Sodium alginate microencapsulation improves the short-term oral bioavailability of cannabidiol when administered with deoxycholic acid. PLoS One 2021; 16: e0243858.
67. O'Sullivan SE, Jensen SS, Kolli AR, Nikolajsen GN, Bruun HZ, Hoeng J. Strategies to improve cannabidiol bioavailability and drug delivery. Pharmaceuticals 2024; 17: 244.
68. Atsmon J, Heffetz D, Deutsch L, Deutsch F, Sacks H. Single-dose pharmacokinetics of oral cannabidiol following administration of PTL101: A new formulation based on gelatin matrix pellets technology. Clin Pharmacol Drug Dev 2018; 7: 751-758.
69. Mahmoudinoodezh H, Telukutla SR, Bhangu SK, Bachari A, Cavalieri F, Mantri N. The transdermal delivery of therapeutic cannabinoids. Pharmaceutics 2022; 14: 438.
70. Varadi G, Zhu Z, Crowley HD, Moulin M, Dey R, Lewis ED, *et al.* Examining the systemic bioavailability of cannabidiol and tetrahydrocannabinol from a novel transdermal delivery system in healthy adults: A single-arm, open-label, exploratory study. Adv Ther 2023; 40: 282-293.
71. Makhakhe L. Topical cannabidiol (CBD) in skin pathology–A comprehensive review and prospects for new therapeutic opportunities. S Afr Fam Pract 2022; 64: a5493.
72. Hashim PW, Cohen JL, Pompei DT, Goldenberg G. Topical cannabinoids in dermatology. Cutis 2017; 100: 50-52.
73. de Carvalho-Guimarães FB, Correa KJ, de Souza TP, Rodriguez Amado JR, Ribeiro-Costa RM, Silva-Júnior JOC. A review of pickering emulsions: Perspectives and applications. Pharmaceuticals 2022; 15: 1413.
74. Sharkawy A, Silva AM, Rodrigues F, Barreiro F, Rodrigues A. Pickering emulsions stabilized with chitosan/collagen peptides nanoparticles as green topical delivery vehicles for cannabidiol (CBD). Colloids Surf A Physicochem Eng Asp 2021; 631: 127677.
75. Ashara KC, Paun JS, Soniwala MM, Chavda JR, Mendapara VP, Mori NM. Microemulgel: An overwhelming approach to improve therapeutic action of drug moiety. Saudi Pharm J 2016; 24: 452-457.
76. Kushwah P, Sharma PK, Koka SS, Gupta A, Sharma R, Darwhekar GN. Microemulgel: A novel approach for topical drug delivery. J Appl Pharm Res 2021; 9: 14-20.
77. Vanti G, Grifoni L, Bergonzi MC, Antiga E, Montefusco F, Caproni M, *et al.* Development and optimisation of biopharmaceutical properties of a new microemulgel of cannabidiol for locally-acting dermatological delivery. Int J Pharm 2021; 607: 121036.
78. Gonzalez-Cuevas G, Martin-Fardon R, Kerr TM, Stouffer DG, Parsons LH, Hammell DC, *et al.* Unique treatment potential of cannabidiol for the prevention of relapse to drug use: Preclinical proof of principle. Neuropsychopharmacol 2018; 43: 2036-2045.
79. Liput DJ, Hammell DC, Stinchcomb AL, Nixon K. Transdermal delivery of cannabidiol attenuates binge alcohol-induced neurodegeneration in a rodent model of an alcohol use disorder. Pharmacol Biochem Behav 2013; 111: 120-127.
80. Hammell DC, Zhang LP, Ma F, Abshire SM, McIlwrath SL, Stinchcomb AL, *et al.* Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. Eur J Pain 2016; 20: 936-948.
81. Momekova D, Danov Y, Momekov G, Ivanov E, Petrov P. Polysaccharide cryogels containing β-cyclodextrin for the delivery of cannabidiol. Pharmaceutics 2021; 13: 1774.
82. Momekova D, Ivanov Y, Konstantinov S, Ublekov F, Petrov PD. Nanocomposite cryogel carriers from 2-hydroxyethyl cellulose network and cannabidiol-loaded polymeric micelles for sustained topical delivery. Polymers 2020; 12: 1172.
83. Cheliah MP, Zinn Z, Khuu P, Teng JMC. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. Pediatr Dermatol 2018; 35: e224-e227.
84. Kaczan-Pragłowska J, Janus L, Piątkowski M, Sierakowska A, Szajna E, Matýsek D, *et al.* Development of stimuli-responsive chitosan/ZnO NPs transdermal systems for controlled cannabidiol delivery. Polymers 2021; 13: 211.
85. Eskander JP, Spall J, Spall A, Shah RV, Kaye AD. Cannabidiol (CBD) as a treatment of acute and chronic back pain: A case series and literature review. J Opioid Manag 2020; 16: 215-218.
86. Palmieri B, Laurino C, Vadalà M. A therapeutic effect of cbd-enriched ointment in inflammatory skin diseases and cutaneous scars. Clin Ter 2019; 170: e93-e99.
87. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. J Control Release 2011; 153: 106-116.
88. Hosseini A, McLachlan AJ, Lickliter JD. A phase I trial of the safety, tolerability and pharmacokinetics of cannabidiol administered as single-dose oil solution and single and multiple doses of a sublingual wafer in healthy volunteers. Br J Clin Pharmacol 2021; 87: 2070-2077.