Formulation Aspects and Potential Therapeutic Applications of Cannabidiol-Loaded Nano-formulations

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INTRODUCTION

Nanotechnology is one of the most promising technologies of the 21st century and offers opportunities in all areas of scientific research, such as medicine, pharmaceutical and cosmetic sciences, medicinal chemistry, bioengineering, genetic engineering and food technology. Nanocarriers and innovative pharmaceutical formulations play a significant role in improving the bioavailability of drugs or natural molecules, with a specific enrichment at the target site (Pires et al., 2022). Also, nanocarriers have been used as a potential platform for the targeted delivery of various phytocompounds including cannabidiol (CBD). Nano-delivery systems help in improving the stability of phytocompounds, enhance their absorption, protect them from early enzymatic deprivation or metabolism within the body, and extend their circulation time, thus limiting the various adverse effects (Assadpour et al., 2023). The modified nanocarriers improve the solubility and permeability, and assist in the sustained delivery of CBD to the targeted diseased sites, thus improving the bioavailability. The cannabidiol is a non-psychoactive cannabinoid isolated from *Cannabis sativa* L. and that has not been shown to have any intoxicating effects. CBD inhibits excitotoxicity and modifies cellular activity by binding to CB1, CB2, and 5HT1A receptors. Numerous illnesses, including neurological and metabolic disorders, have been linked to CBD's anti-inflammatory and antioxidant qualities. According to the Biopharmaceutics Classification System (BCS), pharmacologically active CBD intended for oral use is classified as Class II, due to their very low water solubility and high lipophilicity (12.6 mg/L, logP 6.3, pKa 9.29). CBD has a very poor oral bioavailability in plasma and tissues (around 6% and 1%, respectively) due to its high lipophilicity, sensitivity to light, and major breakdown in the duodenum (Barbara et al., 2021).

RESEARCH METHODOLOGY

For the purposes of our research, we used literature research of several original and review articles indexed in the databases: PubMed, SCOPUS and WoS. For the complete literature search in the indicated databases, we used the following keywords: nanocarriers AND cannabidiol; nano-formulations AND cannabinoids; niosomes AND cannabidiol; liposomes AND cannabidiol.

RESULTS AND DISCUSSION

Various lipid-based nanocarriers have been reported for the effective and site-specific delivery of CBD, including nanoliposomes, nanoemulsions, nanostructured lipid carriers (NLCs), and solid lipid nanoparticles (SLNPs). The advent of CBD-loaded in lipid-based nanocarriers presented greater therapeutic effects against different diseases and disorders.

Nanoemulsions

The ability to produce and transport weakly hydrophilic substances on a large scale is one of the benefits of nanoemulsions. CBD was added to oil-in-water nanoemulsions' oil phase by means of high-pressure homogenization and sonication. Taskar et al. (2019) observed that modified CBD-loaded nanoemulsions made by conjugating analogs of amino acids and dicarboxylic acids, CBD–divalinate–dihemisuccinate and CBD–divalinate, respectively, increased the bioavailability and permeability of CBD. In an *in vivo* study using a rabbit model, it was observed that the combination of both analogs greatly enhanced the ocular delivery of CBD. Furthermore, the analogues of CBD-dicarboxylic acids demonstrated improved CBD penetration across the ocular barriers. Particle size, surface charge, emulsifying agent type, pH, and other manufacturing parameters are important for the efficient delivery of CBD via nanoemulsions (Taskar et al., 2019). In a different study, castor oil-based nanoemulsions were created to distribute hydrophobic medications (such as fenofibrate or CBD) more efficiently while enhancing their stability and bioavailability. The stability of the nanoemulsions was largely controlled by the preparation process using a coaxial lamination mixer. Furthermore, the size, zeta potential, and polydispersity index of nanoemulsions were significantly impacted by the oil and surfactant (Polysorbate 80) concentrations (Erfle et al., 2021). To increase the solubility and oral bioavailability of CBD, CBD-loaded nanoemulsions made of ethanol, Tween-20, CBD oil, and vitamin E acetate were created. When given as CBD-loaded nanoemulsions (50 mg/kg), the results of pharmacokinetic tests conducted on a rat model demonstrated enhanced oral bioavailability of CBD.

Nanoliposomes

One or more phospholipid bilayers encircle the hydrophilic center of nanoliposomes. Verrico et al. (2020) developed dipole materials like phospholipids which combined with water using a variety of mechanical (such as high-pressure homogenization, ultrasonication, and microfluidization) and non-mechanical (such as reversed-phase evaporation) techniques to create nano-sized vesicles in order to prepare nanoliposomes. To increase the bioavailability of CBD, a

sunflower lecithin (phosphatidylcholine) basis was used to create a nanoliposome. About 100 nm in size, nanoliposomal CBD contained 10–20 mg/mL of CBD and shown excellent stability over three months at room temperature and in the refrigerator at pH 5–9. To increase its bioavailability for use in treating canine pain, liposomal CBD was created in a different study utilizing hydrogenated soy phosphatidylcholine with a median particle size of 5.6 µm and 50 mg/g of synthetic CBD. The transport of amphiphilic molecules with quick release, excellent targetability, and the potential for large-scale production are some of the benefits of nanoliposomes (Verrico et al., 2020).

Solid Lipid Nanoparticles (SLNPs)

Hot and cold homogenization are the two techniques used to produce SLNPs on a large scale. CBD dissolves in melting lipid during heat homogenization, and high-pressure homogenization yields oil-in-water emulsions. After the lipids in the emulsion cool and recrystallize, SLNPs will develop. CBD is dissolved in melted lipid via cold homogenization, and the resulting lipid microparticles are then crushed after cooling and solidifying. SLNPs are then obtained by dispersing the lipid microparticles in a cold surfactant solution and homogenizing them at room temperature (Balaga et al., 2022).

Nanostructured Lipid Carriers (NLCs)

The preparation process described for SLNs can be used to create NLCs by combining liquid and solid lipids. NLCs were created for the nasal delivery of CBD using cetylpyridinium chloride, Span 20, and stearic and oleic acids as solid and liquid lipids, respectively. Additionally, to create a CBD-NLC-gel, the CBD-NLC dispersion was mixed with the gelling polymers Pluronic F127 and Pluronic F68 (Matarazzo et al., 2021). For CBD, monodisperse lipid nanocapsules (LNCs) were created as biocompatible and degradable carriers. Caprylic-capric acid triglycerides, C18E15 polyethylene glycol (15) 12-hydroxystearate, soybean lecithin with 70% phosphatidylcholine, and NaCl were used to prepare LNCs using the energetically-efficient phase inversion temperature (PIT) technique. In addition to being biocompatible and decomposable, NLCs are more stable, have higher encapsulation loads, and release more quickly than SLNs (Verrico et al., 2020).

CONCLUSION

Although CBD and its derivatives have been found to be safe, their limited solubility and permeability raise concerns about their direct use. The use of other nanocarriers, such as polymers and lipid-based carriers, can get beyond these restrictions. By enhancing CBD's solubility and permeability across a range of biological barriers, these nanocarriers contribute to its increased bioavailability, targetability to sick areas, and minimal toxicity. Although therapeutic doses may differ between disease states, clinical trials examining the effectiveness of CBD for the treatment of pain, autoimmune diseases, mental disorders, substance use, and other ailments frequently rely on a single acute dose. Furthermore, a number of clinical trials should be conducted to investigate the effects of many dosages given often over an extended period of time before prescribing CBD to patients. As a result, it becomes essential to raise public knowledge of CBD usage and provide innovative delivery methods for its various applications, ranging from clinical to translational.

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