ScienceDirect

International Journal of Pharmaceutics

Volume 617, 5 April 2022, 121627

The dose-dependent effect of a stabilized cannabidiol nanoemulsion on ocular surface inflammation and intraocular pressure

Leslie Rebibo [a], Marina Frušić-Zlotkin [a], Ron Ofri [b], Taher Nassar [a 1], Simon Benita [a 1]

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https://doi.org/10.1016/j.ijpharm.2022.121627

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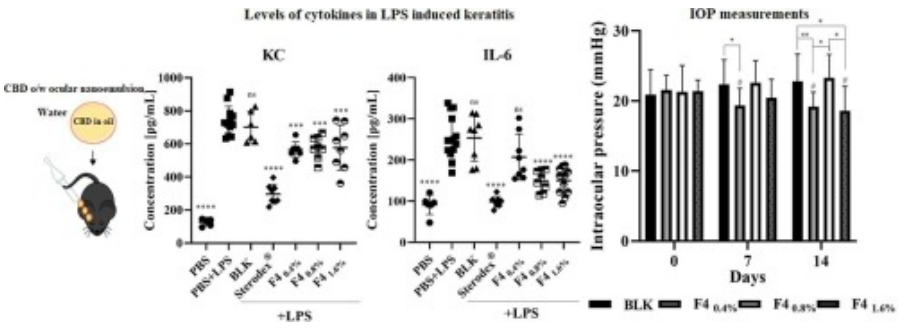
Highlights

- Cannabidiol ocular nanoemulsions were designed and characterized.
- Antioxidant was mandatory to obtain a long-term stabilized formulation.
- From 0.4 %w/v, cannabidiol reduced cytokines' levels in LPS induced keratitis.
- Efficient concentrations lowered or did not affect the mice intraocular pressure.
- Cannabidiol nanoemulsions could potentially treat ocular inflammations in humans.

Abstract

Cannabidiol (CBD) is a phytocannabinoid that has a great clinical therapeutic potential. Few studies have been published on its efficacy in ocular inflammations while its impact on intraocular pressure (IOP), a major risk factor for glaucoma, remains unclear. Moreover, due to its lability and high lipophilicity, its formulation within a prolonged stable topical ophthalmic solution or emulsion able to penetrate the highly selective corneal barrier is challenging. Therefore, various CBD nanoemulsions (NEs) were designed and evaluated for stability in accelerated conditions. Further, the optimal formulation was tested on a murine LPS-induced keratitis inflammation model. Lastly, increasing CBD concentrations were topically applied, for two weeks, on mice eyes, for IOP measurement. CBD NEs exhibited optimal physicochemical characteristics for ocular delivery. A specific antioxidant was required to obtain the stable, final, formulation. *In vivo*, 0.4 to 1.6% CBD w/v reduced the levels of key inflammatory cytokines, depending on the concentration applied. These concentrations decreased or did not affect the IOP. Our results showed that a well-designed CBD ocular dosage form can be stabilized for an extended shelf life. Furthermore, the significant decrease in inflammatory cytokines levels could be exploited, provided that an adequate therapeutic dosage regimen is identified in humans.

Graphical abstract



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Introduction

Inflammation is a hallmark of many prevalent ocular surface diseases such as keratitis (Torrecilla et al., 2018), dry eye (Yu et al., 2021) and allergic conjunctivitis (Erdinest et al., 2020). In nonpathological states, the cornea, the limbus, and the conjunctiva in the anterior segment, protect the eye by providing the first line of physical and immunological defense against harmful materials (Lim et al., 2015). However, recurrent erosions, corneal dystrophies, stem cell deficiency, infection by microorganisms, and autoimmune mediated diseases all disrupt the ocular surface and can lead to severe inflammation with immune cells recruitment, loss of corneal clarity, scarring and eventually blindness if not properly treated (Stepp and Menko, 2021).

During the last three decades, many studies have focused on the anti-inflammatory effects of purified cannabidiol (CBD), the major non psychoactive ingredient of Cannabis, in various animal disease models, including rheumatoid arthritis (Malfait et al., 2000), diabetes type 1 (Weiss et al., 2008) and multiple sclerosis (Kozela et al., 2011). Nevertheless, reports on its efficacy in ocular surface inflammations are limited to a single study, in a corneal injury model, that evaluated the antinociceptive and anti-inflammatory effects of a topically administered 5% CBD solution in soybean oil (Thapa et al., 2018). Thus, the pharmacodynamical effects of CBD on other ocular inflammation models, as well as lower CBD concentrations, should be investigated. Furthermore, assuming that CBD is efficacious in inflammatory ocular disorders, its impact on intraocular pressure (IOP) must be determined before considering it as a potential therapeutic option. Indeed, reports on the subject are conflicting, as some indicate that CBD does not affect IOP (Elsohly et al., 1984, Green et al., 1982, Liu and Dacus, 1987, Waller et al., 1984), others show that CBD reduces IOP (Colasanti et al., 1984, Green et al., 1978) while two studies reveal an increase in IOP due to topical CBD instillation (Miller et al., 2018, Tomida et al., 2006). This potential side-effect is critical, as elevated IOP is the main risk factor in the pathogenesis of glaucoma (Sit and Liu, 2009), a leading cause of blindness in developed countries (Sun et al., 2022).

Effective topical ocular drug delivery remains challenging due to the various, dynamic, anatomical and physiological barriers that protect the eye from noxious insults (Gote et al., 2019). Indeed, in the anterior part of the globe, tear film turn-over, nasolacrimal and conjunctival drainage, along with blinking lead to a precorneal drug half-time of 1–3 min (López-Machado et al., 2021), thereby decreasing considerably the formulation corneal contact time (Lakhani et al., 2018). Furthermore, these mechanisms divert the molecules to the systemic circulation, engendering adverse reactions and further reducing the ocular drug bioavailability to less than 5% of the dose applied (Agrahari et al., 2016).

To overcome these barriers, various nano delivery systems were investigated. Amongst them, nanoemulsions (NEs) which are colloidal dispersions of, generally, two immiscible liquids stabilized by surfactants, have several advantages (Gawin-Mikołajewicz et al., 2021). In addition of being kinetically stable, their small droplets size provides a large contact area with the eyeball. Besides, the presence of surface-active ingredients in the NEs enables enhanced mixing of the nanodroplets with the precorneal constituents and consequently a greater dispersion of the drug over the cornea. Altogether, this results in a prolonged contact time of the drug with the corneal epithelium, improve its absorption and leads to a localized therapeutic effect with a rapid onset of action (Navarro-Partida et al., 2021). Additionally, these carriers can include both hydrophilic and hydrophobic compounds (Kaur and Kakkar, 2014, Shah et al., 2019).

CBD is a phytocannabinoid that is practically insoluble in water (Ladha et al., 2020), exhibiting a log P of 6.3 (Odi et al., 2020). Thus, its formulation into simple aqueous ophthalmic solutions is not feasible. In addition, this intrinsic characteristic eases the drug's penetration through capillary walls, resulting in unwanted systemic absorption of the drug that reduces the topical effect (Abdul Nasir et al., 2016). To the best of our knowledge, few studies reported the CBD loading in colloidal lipid emulsions (Francke et al., 2021),

nanoemulsions (Banerjee et al., 2021), and self-nanoemulsifying drug delivery systems (De Prá et al., 2021, Kok et al., 2022). Nevertheless, in all these reports, the CBD formulations aimed to oral (Banerjee et al., 2021, De Prá et al., 2021, Kok et al., 2022) or parenteral (Francke et al., 2021) delivery but no report was found on ocular application. Current commercially available CBD preparations include oil- and alcohol-based solutions of various concentrations that are not adapted to the ocular physiologic requirements and can even lead to irritation. Moreover, CBD undergoes oxidation and degradation, particularly when exposed to light and elevated temperatures (Millar et al., 2020). Consequently, there is an unmet need for a stable CBD delivery system, suitable for topical ophthalmic application, and able to effectively circumvent the ocular barriers to achieve a local anti-inflammatory therapeutic effect without raising IOP.

Section snippets

Materials

Cannabidiol (CBD, 99.9% purity) was purchased from Symrise AG (Holzminden, Germany). Castor oil and medium-chain triglyceride (MCT) were obtained from TAMAR Industries (Rishon LeTsiyon, Israel). Polysorbate 80 (Tween® 80), propyl gallate, butylhydroxytoluene (BHT), *Pseudomonas aeruginosa* Lipopolysaccharides (LPS) and Bovine Serum Albumin (BSA) were acquired from Sigma-Aldrich (St. Louis, USA). Macrogol 15 hydroxystearate (Solutol® HS15) was kindly donated by BASF (Ludwigshafen, Germany).…

Physicochemical characterization of the NEs

To find the optimal formulation, numerous nanoemulsions were prepared by varying mainly the oil, antioxidant, and glycerin contents. All the selected preparations (Table 1) exhibited appropriate physicochemical characteristics with a mean droplet diameter under 200 nm and a narrow size distribution (PDI < 0.2), enhancing the drug's ocular absorption through the corneal epithelial cells via endocytosis (Danaei et al., 2018, Gawin-Mikołajewicz et al., 2021). Furthermore, the zeta potential (ZP)…

Conclusions

In our study, we successfully designed and optimized a CBD nanoemulsion exhibiting appropriate physicochemical characteristics for ocular physiologic requirements. This formulation at high drug concentrations, starting from 0.4%, reduced key inflammatory markers of LPS induced keratitis, an ocular surface inflammation. Furthermore, we showed that at 0.4% and 1.6%, the IOP was decreased while it was not affected at 0.8%. These results indicate that patients could benefit from a well-designed CBD …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Acknowledgments

We would like to thank Dr. Yoram Soroka for his technical assistance.…

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.…

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