FORMULATION AND EVALUATION OF MAGISTRAL TOPICAL CREAM AND LOTION CONTAINING CANNABIDIOL FOR USE IN RHEUMATOID ARTHRITIS

Katerina Bozhinova
Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia, aptekialtea@gmail.com
Bistra Angelovska
Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
bistra.angelovska@ugd.edu.mk

Abstract: When proprietary medicinal products are no longer available in pharmacies, the compounding of topical individual formulations may represent an effective alternative solution. Specific circumstances, such as rare indications, pediatric use, or intolerance to certain ingredients, often create challenges related to the availability, dosage, and selection of appropriate pharmaceutical formulations. In such cases, magistral preparations provide flexibility and enable personalized therapy tailored to individual patient needs. Prepared magistral formulations can be as effective as proprietary or generic medicinal products while maintaining comparable quality standards. In addition, they allow adaptation of the formulation composition and are often more economically accessible. In many situations, magistral preparations remain the only viable therapeutic option when a medicinal product is unavailable on the market. Cannabis has been used as a medicinal plant for millennia; however, systematic scientific investigations of its main components began in the 1960s. Since then, extensive research has been conducted on cannabinoids and their biological activity. In countries where medicinal cannabis use is approved, strict regulations govern its clinical application. One method of administration is through magistral preparations prescribed by a physician and prepared in facilities that meet quality standards, ensuring controlled levels of tetrahydrocannabinol (THC) and cannabidiol (CBD). The aim of this study was the characterization and evaluation of two topical formulations, a cream and a lotion, containing cannabis oil at a concentration of 10%. The primary objective was the selection of suitable bases according to the solubility of the active substance in order to ensure successful formulation. The prepared formulations were evaluated based on appearance, color, identification, pH value, spreadability, cannabidiol content, viscosity, relative density, and microbiological purity. The obtained results demonstrated satisfactory physicochemical characteristics and compliance with pharmacopoeial requirements, indicating appropriate quality and stability of the formulations. Furthermore, the topical dosage forms showed favorable technological properties relevant for routine pharmaceutical compounding and patient use. The study highlights the importance of appropriate excipient selection and formulation design for achieving consistent quality in magistral preparations. Overall, the findings support the potential role of magistral topical cannabis-based preparations as a complementary therapeutic option in pharmaceutical practice and warrant further investigation of their clinical applicability.
Keywords: cannabidiol, magistral preparation, topical formulation, rheumatoid arthritis

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by persistent synovial inflammation, progressive joint destruction, pain, and functional disability, leading to significant impairment in quality of life (Philpott et al., 2017). Although systemic pharmacotherapy remains the mainstay of treatment, many patients continue to experience localized joint pain and inflammation that negatively affect daily functioning and may persist despite adequate systemic control (Arthritis Foundation, 2021). Furthermore, current international recommendations emphasize a treat-to-target strategy and recognize the need for individualized approaches in patients with difficult-to-treat rheumatoid arthritis (EULAR points to consider; Nagy et al., 2022).

Topical pharmaceutical preparations represent an effective approach for localized drug delivery at or near the site of inflammation, potentially reducing systemic exposure and minimizing adverse effects. For this reason, topical therapy is commonly used as an adjunct to systemic treatment in inflammatory and musculoskeletal disorders, especially when local symptom control is required (Benson et al., 2019; Roberts et al., 2002).

Cannabidiol (CBD) is a major non-psychoactive phytocannabinoid derived from Cannabis sativa. Unlike Δ^9-tetrahydrocannabinol (THC), CBD does not induce psychotropic effects and has demonstrated a favorable safety profile in preclinical and clinical settings (Mechoulam et al., 2007; Pisanti et al., 2017). Pharmacological evidence suggests that CBD exhibits anti-inflammatory, analgesic, antioxidant, and immunomodulatory activity through interaction with multiple molecular targets, including CB1/CB2 receptor-related pathways, modulation of the endocannabinoid system, transient receptor potential (TRP) channels, and additional signaling pathways involved in nociception and inflammation (Pertwee, 2008; Pisanti et al., 2017). Importantly, experimental investigations have

shown that transdermal administration of CBD may reduce inflammation and pain-related behaviors in animal models of arthritis and osteoarthritis, supporting its potential for localized symptom management (Hammell et al., 2016; Lodzki et al., 2003; Philpott et al., 2017).

Magistral pharmaceutical preparations enable individualized therapy and represent an important alternative when commercial products are unavailable, unsuitable, or insufficiently adapted to patient needs. In dermatological and transdermal therapy, formulation design plays a critical role, as skin barrier properties strongly influence drug permeation and overall therapeutic performance (Roberts et al., 2002). The development of topical CBD dosage forms requires careful selection of excipients and suitable emulsion bases to ensure adequate stability, skin compatibility, preservation effectiveness, and patient acceptability (Jurka et al., 2020). In addition, the formulation should maintain appropriate physicochemical characteristics (e.g., viscosity, spreadability, and pH) to support consistent dosing and appropriate dermal application (Alkilani et al., 2015; Benson et al., 2019).

The objective of this study was to formulate and evaluate two magistral topical dosage forms—a cream and a lotion—containing 10% cannabidiol oil, intended for topical use in patients with rheumatoid arthritis. Recent pharmaceutical research has also emphasized the importance of topical cannabidiol formulation design in order to achieve effective cutaneous delivery and appropriate local biodistribution. (Lapteva et al., 2024). In addition, contemporary systematic evidence confirms increasing interest in topical and transdermal CBD dosage forms, while highlighting the need for further standardized evaluation and clinical investigation. (Scholfield et al., 2023)

2. MATERIALS AND METHODS

Materials

The active substance used in this study was cannabidiol oil (Canabigal CBD 10%, Galapharm, Skopje, North Macedonia), containing cannabidiol as the primary cannabinoid and tetrahydrocannabinol below the legally permitted limit.

The excipients used for formulation included Emulgade® 1000 NI (non-ionic emulsifier), Cetiol® LC (emollient), shea butter (emollient and consistency agent), glycerol (humectant), Phenonip® (preservative), and purified water (*Aqua purificata*) compliant with the European Pharmacopoeia.

Formulation of the lotion

The lotion was prepared as an oil-in-water (O/W) emulsion. The oil phase, consisting of cannabidiol oil, Emulgade® 1000 NI, and Cetiol® LC, was heated to 70 ± 2 °C under continuous stirring until complete melting and homogenization.

The aqueous phase, composed of purified water and glycerol, was heated separately to the same temperature. The aqueous phase was gradually added to the oil phase under controlled homogenization (600–800 rpm) until a stable emulsion was formed. After emulsification, the formulation was cooled below 40 °C and the preservative was incorporated. The lotion was allowed to stabilize at room temperature for 24 hours prior to evaluation.

Formulation of the cream

The cream was formulated using a similar O/W emulsification process. The oil phase, consisting of cannabidiol oil, Emulgade® 1000 NI, shea butter, and Cetiol® LC, was heated to 70 °C until a homogeneous mixture was obtained.

The aqueous phase containing purified water and glycerol was heated separately to the same temperature and gradually incorporated into the oil phase under continuous mixing. After emulsification, the formulation was cooled and the preservative was added. The cream was allowed to stabilize before further evaluation.

Evaluation of the formulations

Both formulations were evaluated for appearance, color, homogeneity, and organoleptic properties. Physicochemical characterization included determination of pH, viscosity, spreadability, and relative density. Cannabidiol content was assessed using appropriate analytical methods, while microbiological purity testing was performed in accordance with pharmacopoeial requirements for topical preparations.

3. RESULTS

Both the cream and lotion formulations exhibited smooth, homogeneous appearance without visible phase separation. The pH values of the formulations were within the acceptable range for dermal application, indicating good skin compatibility.

Viscosity measurements demonstrated appropriate consistency for topical administration, with the cream showing higher viscosity than the lotion, as expected due to its higher lipid content. Spreadability testing indicated good application properties for both dosage forms, enabling uniform distribution on the skin surface.

Cannabidiol content remained within acceptable limits, confirming adequate incorporation of the active substance and formulation stability. Microbiological testing demonstrated compliance with pharmacopoeial standards, confirming microbiological safety of both preparations.

4. DISCUSSION

The findings of this study demonstrate the feasibility of preparing stable magistral topical formulations containing 10% cannabidiol oil under controlled galenic laboratory conditions. The successful development of both a cream and a lotion dosage form highlights the importance of excipient selection and emulsification parameters in achieving desirable stability, homogeneity, and suitable application characteristics. These outcomes are consistent with established principles of topical and transdermal formulation development, where viscosity profile, spreadability, and organoleptic properties influence patient acceptability and dosing reliability (Benson et al., 2019; Jurka et al., 2020).

Topical administration of CBD may provide advantages for localized management of inflammatory symptoms in rheumatoid arthritis due to its targeted action at affected sites and reduced risk of systemic adverse effects. Preclinical evidence supports the anti-inflammatory and analgesic potential of CBD in joint-related inflammatory conditions. In particular, transdermal CBD has been shown to reduce inflammation and pain-related behaviors in animal arthritis models, suggesting that topical delivery can be a relevant approach for local symptom relief (Hammell et al., 2016; Lodzki et al., 2003). Moreover, CBD-related modulation of inflammatory mediators and pain pathways is supported by pharmacological literature describing its interaction with multiple receptor systems and signaling targets involved in immune regulation and nociception (Pertwee, 2008; Pisanti et al., 2017).

The evaluated formulations demonstrated physicochemical properties appropriate for dermal application, including acceptable pH, adequate consistency, and suitable spread ability. These parameters are relevant from a pharmaceutical perspective because they influence product performance, stability, and user compliance during topical therapy (Benson et al., 2019; Roberts et al., 2002). Compliance with pharmacopoeial microbiological quality requirements further supports the safety of magisterial preparations when manufactured under controlled conditions and with appropriate preservation systems (European Pharmacopoeia Commission, 2023).

In addition to quality and stability considerations, the clinical implementation of CBD-based topical preparations should also take into account broader scientific and regulatory aspects. International regulatory bodies emphasize the importance of product quality control, consistent cannabinoid content, and evidence-based evaluation of cannabidiol-containing products, particularly due to variation in market products and heterogeneity in therapeutic claims (EMA, 2019; FDA, 2020). Therefore, while the current study confirms the feasibility of preparing stable magistral CBD topical dosage forms, further clinical evaluation is required to confirm therapeutic efficacy, optimize dosing regimens, and establish standardized use in patients with rheumatoid arthritis (Arthritis Foundation, 2021). Recent clinical data further support the potential applicability of transdermal/topical cannabidiol formulations in arthritic conditions, including improvements in pain-related outcomes, reinforcing the rationale for additional controlled clinical trials and standardized dosing strategies. (Bawa et al., 2024)

5. CONCLUSION

This study confirms that stable magistral topical cream and lotion formulations containing 10% cannabidiol can be successfully prepared and evaluated in a pharmaceutical laboratory setting. Both formulations demonstrated acceptable physicochemical characteristics, stable cannabidiol content, and microbiological safety.

Magistral topical CBD preparations may represent a valuable complementary approach for localized symptom management in patients with rheumatoid arthritis. Further clinical evaluation is recommended to confirm therapeutic efficacy.

ACKNOWLEDGEMENTS

The author expresses sincere gratitude to the mentor for professional guidance and constructive feedback. Special thanks are extended to the author's family for their continuous support and encouragement.

REFERENCES

Alkilani, A. Z., McCrudden, M. T. C., & Donnelly, R. F. (2015). Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics, 7(4), 438–470.

Arthritis Foundation. (2021). Cannabidiol (CBD) and arthritis pain. Arthritis Foundation Scientific Report.

Benson, H. A. E., Watkinson, A. C., & Roberts, M. S. (2019). Topical and transdermal drug delivery: Principles and practice. Wiley-Blackwell.

Bawa, Z., et al. (2024). An open-label feasibility trial of transdermal cannabidiol for hand osteoarthritis. Scientific Reports.

EMA. (2019). Cannabis for medical use: Scientific considerations. European Medicines Agency.

European Pharmacopoeia Commission. (2023). European Pharmacopoeia (11th ed.). Strasbourg: Council of Europe.

FDA. (2020). Cannabidiol (CBD): What we know and what we don't. U.S. Food and Drug Administration.

Hammell, D. C., Zhang, L. P., Ma, F., Abshire, S. M., McIlwrath, S. L., Stinchcomb, A. L., … Lichtman, A. H. (2016). Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. European Journal of Pain, 20(6), 936–948.

Jurka, T., et al. (2020). Selection of excipients for dermal and transdermal drug delivery systems. International Journal of Pharmaceutics, 586, 119580.

Lapteva, M., Mignani, S., Malyukin, A., & Majoral, J. P. (2024). Cutaneous delivery and biodistribution of cannabidiol in aqueous formulations developed for targeted local treatment of dermatological conditions. Pharmaceutics, 16(2), 202.

Lodzki, M., Godin, B., Rakou, L., Mechoulam, R., Gallily, R., & Touitou, E. (2003). Cannabidiol—transdermal delivery and anti-inflammatory effect in a murine model. Journal of Controlled Release, 93(3), 377–387.

Mechoulam, R., Peters, M., Murillo-Rodriguez, E., & Hanus, L. O. (2007). Cannabidiol—recent advances. Chemistry & Biodiversity, 4(8), 1678–1692.

Nagy, G., Roodenrijs, N. M. T., Welsing, P. M. J., Kedves, M., Hamar, A., van der Goes, M. C., Rauch, A., & van Laar, J. M. (2022). EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Annals of the Rheumatic Diseases, 81(1), 20–33.

Perucca, E., & Bialer, M. (2020). Critical aspects affecting cannabidiol oral bioavailability and metabolic elimination. Epilepsia, 61(6), 1045–1058.

Pertwee, R. G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin. British Journal of Pharmacology, 153(2), 199–215.

Philpott, H. T., O'Brien, M., & McDougall, J. J. (2017). Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. Pain, 158(12), 2442–2451.

Pisanti, S., Malfitano, A. M., Ciaglia, E., Lamberti, A., Ranieri, R., Cuomo, G., … Bifulco, M. (2017). Cannabidiol: State of the art and new challenges for therapeutic applications. Pharmacology & Therapeutics, 175, 133–150.

Roberts, M. S., Cross, S. E., & Pellett, M. A. (2002). Skin transport. In Dermatological and transdermal formulations. Marcel Dekker.

Scholfield, C. N., et al. (2023). Systematic review on transdermal/topical cannabidiol: Efficacy and safety for skin-applied formulations containing CBD. Cannabis and Cannabinoid Research.