บทความวิจัย

แบบจำลองเภสัชจลนศาสตร์แบบแบ่งช่องที่มีการกำจัดแบบเชิงเส้นและแบบไม่เชิงเส้นสำหรับน้ำมันแคนนาบิไดออลทางการแพทย์

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บทคัดย่อ

การศึกษานี้นำเสนอการพัฒนาแบบจำลองแบบแบ่งช่อง เพื่ออธิบายเภสัชจลนศาสตร์ของแคนนาบิไดออล (CBD) ในน้ำมันกัญชาทางการแพทย์ภายหลังการให้ยา โดยแบบจำลองได้รวมทั้งการกำจัดยาแบบเชิงเส้นและแบบไม่เชิงเส้นตามสมการจลนศาสตร์ของไมเคิลลิส–เมนเทน (Michaelis–Menten kinetics) เพื่ออธิบายการขับออกของยาทางปัสสาวะและการเปลี่ยนแปลงทางเมตาบอลิซึมของยา สมการเชิงอนุพันธ์สามัญถูกสร้างขึ้นโดยอาศัยกฎการกระทำของมวล เพื่อจำลองความสัมพันธ์ระหว่างความเข้มข้นและเวลาในแต่ละช่อง และแก้สมการเชิงตัวเลขด้วยโปรแกรม MATLAB โดยใช้ฟังก์ชัน ode45 พร้อมทั้งประมาณค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ผ่านการปรับเส้นโค้งให้สอดคล้องกับข้อมูลทางคลินิก ผลการจำลองแสดงให้เห็นว่าค่าความเข้มข้นของแคนนาบิไดออลในพลาสมาที่ได้จากแบบจำลองมีความสอดคล้องใกล้เคียงกับข้อมูลทางคลินิก โดยมีค่าความเข้มข้นสูงสุดประมาณ 1.45 นาโนกรัมต่อมิลลิลิตร ที่เวลาประมาณ 120 นาที นอกจากนี้ค่าพารามิเตอร์ที่ได้จากการปรับแบบจำลองยังสามารถนำไปใช้จำลองความเข้มข้นของยาในช่องอื่น ๆ ได้อีกด้วย งานวิจัยนี้มีความสำคัญเนื่องจากช่วยเชื่อมโยงความเข้าใจเชิงกลไกเกี่ยวกับการกระจายและการกำจัดของแคนนาบิไดออลเข้ากับการประยุกต์ใช้ทางคลินิกอย่างเป็นระบบ โดยแบบจำลองที่พัฒนาขึ้นสามารถใช้เป็นเครื่องมือสนับสนุนการกำหนดขนาดยาและการวางแผนการใช้น้ำมันแคนนาบิไดออลทางการแพทย์ในคลินิกอย่างปลอดภัยและมีประสิทธิผล

คำสำคัญ: แบบจำลองแบบแบ่งช่อง น้ำมันแคนนาบิไดออลทางการแพทย์ จลนศาสตร์ของไมเคิลลิส–เมนเทน เภสัชจลนศาสตร์

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Research Article

A Compartmental Pharmacokinetic Model with Linear and Nonlinear Elimination for Medical Cannabidiol Oil

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Abstract

This study presents the development of a compartmental model to describe the pharmacokinetics of cannabidiol (CBD) in medical cannabis oil following drug administration. The model incorporates both linear and nonlinear elimination based on Michaelis–Menten kinetics to represent urinary excretion and metabolic transformation of the drug. Ordinary differential equations were formulated based on the law of mass action to simulate the concentration–time relationships in each compartment and were solved numerically using MATLAB with the ode45 function. Pharmacokinetic parameters were estimated through curve fitting to clinical data. Simulation results demonstrate that the model-predicted plasma CBD concentrations are in close agreement with clinical data, with a peak concentration of approximately 1.45 ng/mL occurring at around 120 minutes. In addition, the estimated parameters can be applied to simulate drug concentrations in other compartments. This study is significant because it systematically links mechanistic understanding of CBD distribution and elimination with clinical applications. The developed model can serve as a supportive tool for dose determination and treatment planning, enabling the safe and effective clinical use of medical CBD oil.

Keywords: Compartmental Model, Cannabidiol Oil, Michaelis-Menten Kinetics, Pharmacokinetics

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1. Introduction

The therapeutic application of medical cannabis, particularly cannabidiol (CBD), has expanded significantly in recent years, with growing evidence supporting its efficacy in managing conditions such as epilepsy, chronic pain, anxiety, and sleep disorders. For example, Devinsky *et al.* [1] demonstrated the effectiveness of CBD in reducing seizure frequency in patients with Dravet syndrome. In clinical studies by Cuñetti *et al.* [2], CBD provided pain relief in the majority of kidney transplant patients with chronic pain. Furthermore, Gundugurti *et al.* [3] have demonstrated that a nanodispersible oral cannabidiol solution is effective and well tolerated in reducing anxiety symptoms. Similarly, in Thailand, the legalization of medical cannabis in 2019 has enabled the supervised use of CBD, positioning CBD oil as a promising therapeutic option alongside conventional treatments. Among the available formulations, medical-grade CBD oil has been most widely adopted, including products manufactured by the Government Pharmaceutical Organization (GPO) of Thailand and formulations developed by Chao Phraya Abhaibhubejhr Hospital. Owing to its non-psychoactive properties, favorable safety profile, and broad therapeutic potential, CBD oil has attracted considerable clinical interest. Several clinical studies conducted in Thailand have provided evidence supporting the safety and therapeutic potential of CBD oil. For instance, Lusawat *et al.* [4] reported that medical-grade CBD oil is safe and well tolerated when used as an adjunct therapy in patients with epilepsy. Additionally, Aiewtrakoon *et al.* [5] reported that four weeks of CBD administration significantly improved insomnia symptoms compared with placebo, leading to increased total sleep time and improvements in overall sleep quality and quality of life. Furthermore, Monton *et al.* [6] investigated the development and optimization of cannabis extract formulations, including CBD oil, highlighting their clinical relevance and emphasizing the importance of understanding pharmacokinetic behavior to support appropriate dosing strategies and ensure safe clinical use.

Given the expanding clinical use of CBD oil and the incomplete understanding of its pharmacokinetic behavior, significant challenges remain in optimizing appropriate dosing strategies. In this context, mathematical modeling has emerged as a valuable tool for systematically characterizing the pharmacokinetics of CBD and supporting rational dose selection. Several previous studies have developed compartmental pharmacokinetic models for CBD; however, these models are generally simplified and predominantly rely on linear elimination assumptions, without fully accounting for nonlinear elimination processes. For example, in 2021, Schultz *et al.* [7] investigated the pharmacokinetics of CBD in healthy adults using a population pharmacokinetic modeling approach. Data from a phase I, randomized, four-way crossover study were analyzed using a three-compartment model to describe CBD absorption and elimination. Similarly, in 2025, Kolli and Hoeng [8] examined CBD pharmacokinetics using a four-compartment model that incorporated Weibull-based oral absorption and evaluated nonlinear oral bioavailability via the Cedergreen–Ritz–Streibig model. Despite these advances, such relatively

simplified models may not fully capture the complexity of CBD pharmacokinetics, potentially resulting in suboptimal dose selection and reduced therapeutic efficacy.

To address these gaps in existing models, this study aims to develop a more mechanistically detailed compartmental pharmacokinetic model of CBD oil that incorporates both linear elimination and nonlinear Michaelis–Menten kinetics [9]. The proposed model consists of interconnected compartments representing key physiological systems, including an absorption compartment (mouth and sublingual regions leading to the gastrointestinal tract), a central compartment (plasma and rapidly equilibrating tissues such as the heart, liver, lungs, and kidneys), a peripheral compartment (slowly equilibrating tissues), and an effect-site compartment. This structure captures the fundamental processes of absorption, distribution, and elimination, which occur through both urinary excretion and metabolic conversion. Ordinary Differential Equations (ODEs) are formulated based on the law of mass action to describe the concentration–time dynamics within and between compartments. Numerical simulations are conducted using MATLAB's ode45 solver, and kinetic parameters are estimated by curve fitting to clinical concentration–time data.

2. Methods

The work began with the construction of a mechanistic compartmental model to describe the concentration–time profiles of CBD. The model structure realistically represents the processes of absorption, distribution, and elimination of CBD

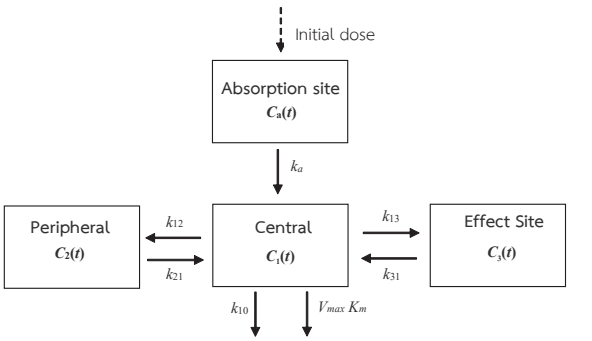

Figure 1 A compartmental pharmacokinetic model of CBD after administration of medical CBD oil.

within the body. It is organized into four main compartments. The CBD concentration in each compartment is denoted as $C_a(t)$ for the absorption compartment (sublingual into the gastrointestinal tract); $C_1(t)$ for the central compartment (plasma and rapidly equilibrating tissues such as the heart, liver, lungs, and kidneys); $C_2(t)$ for the peripheral compartment (slowly equilibrating tissues such as fat and bone); and $C_3(t)$ for the effect site at time t.

k_a denotes the first-order absorption rate constant, describing absorption from the absorption site into the central compartment, k_{12} and k_{13} represent the distribution rate constants from the central compartment to the peripheral compartment and the effect site, respectively. Conversely, k_{21} and k_{31} denote the redistribution rate constants from the peripheral compartment and the effect site back to the central compartment. For elimination, k_{10} represents urinary excretion, while V_{max} and K_m denote metabolic elimination following Michaelis–Menten kinetics. The compartmental structure is illustrated in Figure 1.

After developing the compartmental model, we applied the law of mass action to formulate a set of ordinary differential equations that quantitatively describe the dynamic changes in drug concentrations over time within each compartment. The equations governing these processes are presented below:

$$\frac{dC_a(t)}{dt} = -k_a C_a(t),\ C_a(t) = C_0 \quad (1)$$

$$\frac{dC_1(t)}{dt} = k_a C_a(t) - (k_{10} + k_{12} + k_{13})C_1(t) - \frac{V_{\max} C_1(t)}{K_m + C_1(t)} + k_{21}C_2(t) + k_{31}C_3(t),\ C_1(0) = 0 \quad (2)$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t) - k_{21}C_2(t),\ \ C_2(0) = 0 \quad (3)$$

$$\frac{dC_3(t)}{dt} = k_{13}C_1(t) - k_{31}C_3(t),\ \ C_3(0) = 0 \quad (4)$$

where C_0 is the initial concentration.

Based on Equations (1)–(4), numerical simulations of the system of ordinary differential equations were conducted using MATLAB's ode45 solver. Model parameters were estimated via nonlinear least-squares curve fitting implemented in MATLAB, with convergence determined by predefined tolerance criteria on the objective function and parameter updates. The experimental data used for comparison were obtained from the study by Guy and Robson [10]. Initial parameter values were specified as k_a, k_{12}, k_{13}, k_{21}, k_{31}, k_{10}, V_{max} are 0.05 and K_m is 1 based on commonly reported orders of magnitude for first-order absorption, distribution, and elimination rate constants in pharmacokinetic models, and were used solely as reasonable starting points to ensure numerical stability and convergence during the curve-fitting procedure. The study framework is shown in Figure 2.

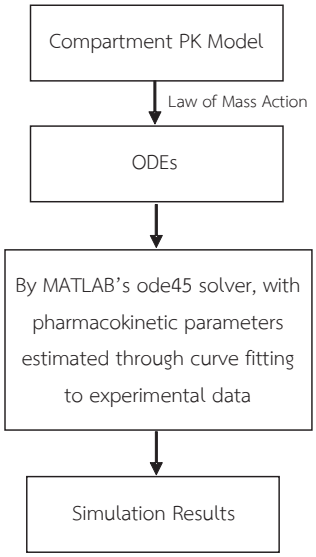

Figure 2 Framework.

3. Result and Discussion

In the simulation, CBD oil was assumed to have an initial concentration (C_0) of 5,000 ng/mL in the absorption compartment. This value was calculated based on an initial dose of 2.5 mg CBD, as reported in the study by Guy and Robson [10], and a volume of distribution in the absorption compartment (mouth and gastrointestinal tract) of approximately 0.5 L. The optimal rate constants were obtained by curve fitting the model to actual CBD plasma concentration data, as shown in Table 1. It can be observed that the estimated Michaelis–Menten parameters, V_{max} and K_m, fall within physiologically plausible ranges. The relatively low Km value indicates a high affinity of CBD for the elimination pathway, supporting the appropriateness of incorporating nonlinear

metabolic processes into the model. Meanwhile, the magnitude of Vmax reflects a capacity-limited elimination process, which is consistent with the hepatic metabolism of CBD.

Table 1 Optimal parameters of the rate constants

Rate Constants	Values
k_a	0.00066407 1/min
k_{12}	0.2935 1/min
k_{13}	3.3565 1/min
k_{10}	0.0485 1/min
k_{21}	0.3376 1/min
k_{31}	0.2042 1/min
V_{max}	3.1053 ng/mL/min
K_m	0.0613 ng/mL

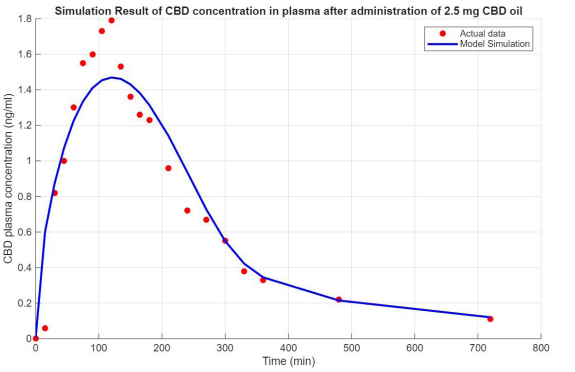

Figure 3 Simulated plasma concentration–time profile of CBD following sublingual administration of 2.5 mg CBD oil. The solid line represents the model simulation, while the symbols denote experimental plasma CBD concentrations reported by Guy and Robson [10].

The simulated plasma CBD concentration–time profile, $C_1(t)$, is show in Figure 3. In addition, the parameters obtained from curve fitting (Table 1) to the plasma CBD concentration were subsequently used to simulate the concentration–time profiles of CBD in the peripheral tissues, $C_2(t)$, and at the effect site, $C_3(t)$, as presented in Figures 4 and 5, respectively.

In Figure 3, the simulated plasma concentration–time profile of CBD following administration of 2.5 mg CBD oil demonstrates rapid absorption during the early phase (0–120 min), with the plasma concentration gradually increasing and reaching a peak (C_{max}) of approximately 1.45 ng/mL at around 120 min. This behavior reflects efficient uptake via the sublingual route and partial avoidance of first-pass hepatic metabolism. Following the peak, the plasma concentration exhibits a gradual decline over the intermediate phase (approximately 120–360 min), which can be attributed to extensive distribution of CBD into peripheral tissues, consistent with its high lipophilicity, together with systemic elimination through metabolic conversion governed by Michaelis–Menten kinetics and linear renal excretion. At later time points (beyond 360 min), the plasma concentration decreases more slowly and approaches a low, relatively stable level, indicating that elimination processes become dominant after distribution equilibrium is achieved. Overall, the model adequately captures the temporal trend of plasma CBD concentrations, with most predicted values lying within the mean ± standard deviation of the experimental data. Minor quantitative discrepancies, particularly around the peak concentration and during the post-peak decline phase, are observed and likely reflect inter-individual variability

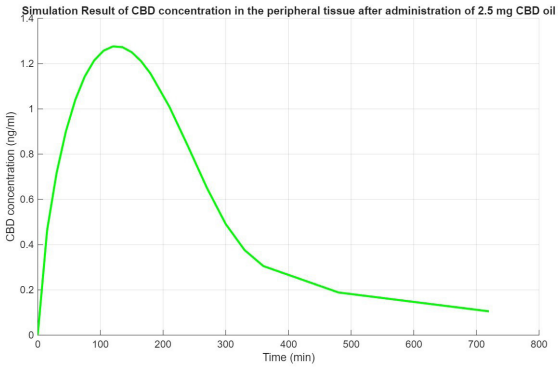

Figure 4 Simulated concentration–time profile of CBD in the peripheral tissue following sublingual administration of 2.5 mg CBD oil, illustrating distribution and gradual elimination from peripheral tissues.

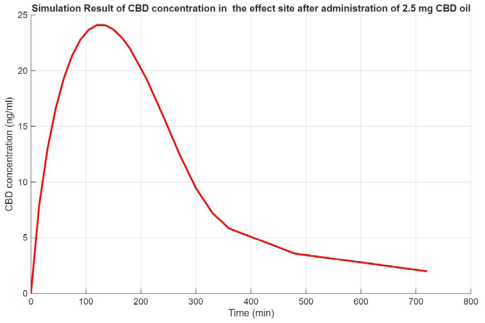

Figure 5 Simulated concentration–time profile of CBD at the effect site following sublingual administration of 2.5 mg CBD oil, representing the compartment associated with pharmacological action.

or structural simplifications inherent in the model.

In Figure 4, the CBD concentration in the peripheral tissue is shown. This graph illustrates the time course of CBD concentration in the peripheral tissue after administration of 2.5 mg CBD oil. The concentration rises rapidly during the initial phase (0–100 min), reaching a maximum of approximately 1.2–1.3 ng/mL around 100 min. This reflects the absorption and subsequent distribution of CBD from plasma into peripheral tissues. After reaching the peak, the concentration gradually declines, with a noticeable reduction between 200 and 400 min, and eventually stabilizes at a low level (~0.1–0.2 ng/mL) around 600–700 min. This represents a secondary distribution site where CBD accumulates moderately but is eliminated more slowly compared with plasma.

Building on the analysis of the peripheral tissue, Figure 5 illustrates the CBD concentration at the effect site, which represents the compartment corresponding to the target of pharmacological action. The simulated CBD concentration at the effect site increases rapidly during the initial phase, similar to that observed in the peripheral tissue. However, the predicted magnitude is substantially higher, reaching approximately 25 ng/mL at around 100–120 min. This pronounced accumulation can be partly explained by the structure and parameterization of the model, particularly the transfer rate constants and assumptions regarding the volume of distribution of the effect-site compartment, which were introduced to represent delayed pharmacodynamic responses rather than directly measurable tissue concentrations. From a physiological perspective, such high concentrations may be qualitatively consistent with the high lipophilicity of CBD and its tendency to accumulate in lipid-rich or receptor-dense tissues; however, quantitative experimental evidence supporting effect-site concentrations of this magnitude remain limited. After reaching the peak, the

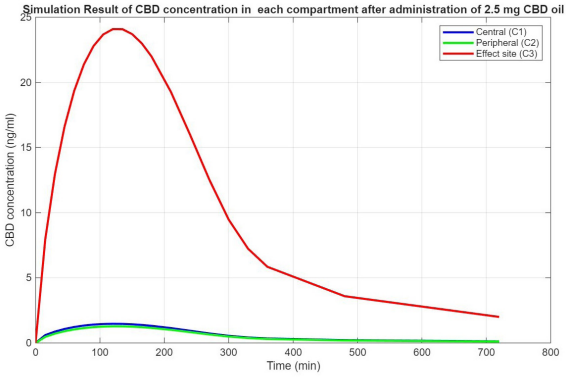

Figure 6 Comparison of simulated CBD concentration–time profiles across the central (plasma), peripheral, and effect-site compartments following sublingual administration of 2.5 mg CBD oil, highlighting distinct distribution patterns among compartments.

concentration gradually declines but remains relatively elevated at later time points, indicating prolonged retention of CBD at the effect site, which may contribute to the persistence of pharmacological effects.

Based on the simulation results of the proposed mechanistic compartmental model, CBD exhibits distinct distribution patterns across different compartments, as shown in Figure 6, reflecting its pharmacokinetic behavior. The model demonstrates close agreement with experimental data, indicating its effectiveness in capturing the pharmacokinetics of CBD in the central compartment. In contrast, the peripheral and effect-site compartments exhibit markedly different concentration–time profiles, with the effect site showing substantially higher and more sustained CBD exposure.

From a clinical perspective, these findings have important implications for dose optimization of medical CBD oil. The sustained concentrations predicted at the effect site suggest that therapeutic effects may persist even when plasma concentrations are relatively low, indicating that plasma levels alone may not fully reflect pharmacological activity. Moreover, the inclusion of nonlinear Michaelis–Menten elimination underscores the risk of disproportionate increases in CBD exposure at higher doses due to metabolic saturation, which may promote drug accumulation and adverse effects, particularly during repeated dosing or dose escalation.

Compared with existing pharmacokinetic models of cannabidiol, the present model provides a more mechanistic description of CBD disposition. Previous models, such as those by Schultz *et al.* [7] and Kolli and Hoeng [8], as well as earlier clinical pharmacokinetic investigations by Millar *et al.* [11] and Taylor *et al.* [12], successfully characterized plasma concentrations and absorption behavior but placed limited emphasis on nonlinear elimination and effect-site exposure. In contrast, the current model explicitly incorporates nonlinear Michaelis–Menten elimination together with an effect-site compartment, enabling a more physiologically meaningful interpretation of sustained CBD exposure. This enhanced structure increases the model's relevance for dose optimization and translational clinical applications.

4. Conclusion

This study successfully developed a mechanistic compartmental model to describe the pharmacokinetics of medical CBD oil in humans. By integrating both linear elimination and nonlinear Michaelis–Menten kinetics, the model effectively captures

the dual pathways of CBD elimination via urinary excretion and metabolic conversion. The four-compartment structure, encompassing the absorption, central, peripheral, and effect site compartments, allows for comprehensive simulation of CBD distribution and action throughout the body. The model's predictions of plasma CBD concentrations closely align with experimental data, while also enabling the estimation of concentrations in less accessible tissues. Overall, this modeling framework provides a reliable and practical tool to support dose optimization, therapeutic planning, and further pharmacokinetic–pharmacodynamic studies of medical CBD oil in clinical applications.

Despite the encouraging results, several limitations should be acknowledged. The model was developed using secondary clinical data with a limited dataset, which may affect parameter uncertainty and generalizability. Inter-individual variability and heterogeneous tissue distribution were not considered, as the model represents average pharmacokinetic behavior. Although an effect-site compartment was included, the model has not yet been explicitly linked to a pharmacodynamic (PK–PD) framework due to the lack of clinical response data. Future work will focus on incorporating population variability, nonlinear absorption kinetics, and further validation using larger clinical datasets.

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