

DEVELOPMENT OF FAST-DISINTEGRATING CANNABIDIOL ORODISPERSIBLE TABLETS: A 2³ FACTORIAL DESIGN APPROACH

Gupta N.^{1,2}, Maan P.S.^{1,3}, Sen D.⁴, Shrivastava J.^{1*}

¹Department of Pharmacy, School of Healthcare and Allied Sciences, GD Goenka University, Sohna, Gurugram, 122103, India.

²School of Pharmacy, Noida International University, Greater Noida, Yamuna Expressway, Uttar Pradesh, 201312 India.

³Lloyd Institute of Management and Technology, Plot No-11, Knowledge Park, Greater Noida, Uttar Pradesh, 201306, India.

⁴Department of Pharmaceutical Chemistry, BCDA College of Pharmacy and Technology, 78 Jessore Road, Hridaypur, Kolkata -127, West Bengal, India.

*Corresponding Author: [jyotishrivastavapharmacy@gmail.com](mailto: jyotishrivastavapharmacy@gmail.com)

Abstract:

Cannabidiol (CBD), an antiepileptic phyto-cannabinoid approved by the FDA as Epidiolex® for Dravet and Lennox–Gastaut syndromes, suffers from poor aqueous solubility, high lipophilicity, and low oral bioavailability (~6%) due to extensive first-pass hepatic metabolism. Oro-dispersible tablets (ODTs) dosage forms that disintegrate within 30 seconds on the tongue without water offer a clinically attractive platform for CBD by improving patient compliance and enabling pre-gastric buccal absorption that can partially circumvent first-pass elimination. This study developed and optimized CBD-ODTs by direct compression, selected as the manufacturing method using the Analytic Hierarchy Process (AHP). A 2³ full factorial design varied three independent factors: co-processed excipient concentration, super-disintegrant type and Kyron T-314® (polacrillin potassium) concentration (0–15mg/tablet). ANOVA-backed regression analysis and Response Surface Methodology (RSM) were applied; UV spectrophotometric method validation was performed per ICH Q2(R1). Twelve formulations (OD1–OD12) were evaluated for flowability, mechanical strength, disintegration time (DT), wetting time, drug content, and dissolution. All formulations met pharmacopeial specifications: friability 0.25–0.61%, weight variation 198–204 mg, drug content 93.9–101.4%. The optimized formulation OD12 achieved DT of 12 s, wetting time 15 s, hardness 3.8 kg/cm², friability 0.25%, and cumulative CBD release of 99.8% at 30 min in phosphate buffer pH 6.8. Factorial design Kyron T-314® concentration identified as the most significant factor ($p < 0.001$); the X2×X3 interaction was highly significant ($p = 0.003$). Accelerated (40°C/75% RH) and long-term (25°C/60% RH) stability studies over 6 months confirmed formulation integrity with no degradation products detected. OD12 represents a potentially promising formulation strategy for improved CBD delivery in epilepsy.

Keywords: Cannabidiol; orodispersible tablets; epilepsy; factorial design; Kyron T-314®; disintegration; bioavailability

How to cite this article: Gupta N.1 2 Maan P.S.13 Sen D.4 Shrivastava J.1. DEVELOPMENT OF FAST-DISINTEGRATING CANNABIDIOL ORODISPERSIBLE TABLETS: A 2³ FACTORIAL DESIGN APPROACH. Int J Drug Deliv Technol. 2026;16(84s):903-915.

DOI: 10.25258/ijddt.16.84s.98.

1. Introduction

Epilepsy is one of the most prevalent chronic neurological disorders worldwide, affecting over 50 million people across all age groups and socioeconomic strata. Despite the availability of more than 30 licensed antiepileptic drugs (AEDs), approximately 30% of patients remain refractory to conventional pharmacotherapy¹. Moreover, widely prescribed synthetic AEDs are associated with severe adverse effects

including sedation, cognitive impairment, teratogenicity, and hepatotoxicity; addiction liabilities; and the requirement for continuous therapeutic drug monitoring — and up to 40% of treatment failures are directly attributed to adverse drug reactions¹. The neuroinflammatory mechanisms underpinning epilepsy involve excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), pathological NF-κB activation, and kainate

receptor-mediated excitotoxicity, which collectively drive neuronal hyperexcitability and seizure propagation². This therapeutic gap has motivated renewed interest in phytocannabinoids, particularly cannabidiol (CBD), as a mechanistically differentiated antiepileptic agent.

CBD is a non-psychoactive phytocannabinoid derived from *Cannabis sativa* (PubChem CID: 644019; $C_{21}H_{30}O_2$) with a broad pharmacological profile encompassing neuroprotective, cardioprotective, anti-inflammatory, anxiolytic, antiemetic, anti-ischemic, antibacterial, immunosuppressive, bone-stimulant, and antiepileptic activities^{3,4}. As a multi-target drug with potent antioxidant properties, CBD exerts its antiepileptic effect primarily through modulation of targets within the endocannabinoid system, inhibiting neuronal excitability by regulating astrocyte and microglia activity and thereby reducing seizure occurrence and frequency⁵. The clinical legitimacy of CBD was formally established by US FDA approval of Epidiolex® (cannabidiol oral solution, 100 mg/mL) in 2018 for Dravet syndrome and Lennox–Gastaut syndrome, with subsequent EMA authorization as Epidyolex®. Multiple ongoing Phase 2–4 clinical trials continue to evaluate CBD in diverse refractory epilepsy populations^{6,7}, further cementing its translational relevance.

Despite this therapeutic promise, CBD presents substantial formulation challenges. It is a highly lipophilic compound (iLOGP = 3.9; log P $\approx$ 6.3) with poor aqueous solubility (approximately 0.4 μ g/mL), an approximate half-life of 24 hours, and notoriously low oral bioavailability of approximately 6%, primarily attributable to incomplete gastrointestinal absorption and extensive first-pass hepatic metabolism^{8,9}. *In silico* Swiss ADME analysis corroborates these challenges: while CBD demonstrates high predicted GI absorption and blood-brain barrier permeability, it presents one Lipinski rule-of-five violation, a bioavailability score of only 0.55, and a synthetic accessibility score of 4.05⁸. These properties collectively necessitate advanced delivery strategies that can meaningfully improve the therapeutic utility of CBD beyond what the existing oral solution achieves.

Orodispersible tablets (ODTs) represent a particularly attractive delivery platform in this context. Defined by the US FDA as uncoated tablets that disintegrate within 30 seconds upon

contact with saliva — forming a solution or suspension prior to swallowing — ODTs eliminate the need for water, reduce the risk of choking and aspiration, and substantially improve patient compliance in pediatric, geriatric, and neurologically impaired populations⁹. Beyond these practical advantages, ODTs offer a pharmacokinetic benefit: rapid disintegration in the oral cavity enables pre-gastric buccal and sublingual mucosal absorption, which can partially bypass first-pass hepatic metabolism and accelerate therapeutic onset. This advantage is especially significant for CBD, given the extent of its first-pass elimination¹⁰. Tabboon et al. (2022) experimentally demonstrated measurable CBD permeation across buccal mucosa from rapidly disintegrating formulations, providing direct evidence that this route can reduce first-pass metabolism relative to conventional swallowed oral dosage forms¹¹. Paudel et al. (2010) further confirmed that the oral mucosa presents viable permeation pathways specifically for lipophilic cannabinoids, establishing the mechanistic plausibility of the ODT strategy for CBD delivery¹².

Formulating CBD as an ODT, however, introduces its own technical challenge: the inverse relationship between tablet mechanical strength and disintegration time is well-recognized in ODT development, and achieving both adequate hardness and ultra-rapid disintegration simultaneously requires careful optimization of the superdisintegrant system. Kyron T-314® (polacrillin potassium), a strongly acidic cation exchange resin with high water uptake capacity, has demonstrated superior disintegrant performance in lipophilic drug ODTs compared to conventional superdisintegrants such as croscarmellose sodium and crospovidone¹³; however, its performance in CBD-ODTs has not been systematically evaluated within a statistically rigorous optimization framework.

The Analytic Hierarchy Process (AHP), developed by Saaty (1984), is a structured multi-criteria decision-making methodology that enables systematic pairwise comparison of alternatives across qualitative and quantitative criteria, with built-in consistency verification¹⁴. Applied prior to formulation development, AHP provides a transparent and reproducible rationale for manufacturing method selection — an upstream decision that profoundly influences downstream formulation outcomes

yet is rarely approached with formal rigor in the pharmaceutical literature. A 2^3 full factorial design, augmented with Response Surface Methodology (RSM) and desirability function optimization, was employed to quantify the effects of excipient type and concentration on critical quality attributes (CQAs) and identify the optimal formulation in a statistically principled manner¹⁵.

While CBD ODT formulations have been previously reported — notably who developed CBD-ODTs using a 2^3 factorial design¹⁶ the present study offers several distinct and practically meaningful contributions: (i) the a priori use of AHP for rational, quantified manufacturing method selection, providing a reproducible decision framework that is absent from prior reports; (ii) systematic evaluation of Kyron T-314® as the superdisintegrant in CBD-ODTs, with its effects quantified through ANOVA-based regression modelling and interaction analysis; (iii) comprehensive ICH Q2(R1)-compliant validation of the UV spectrophotometric analytical method; and (iv) a full 6-month dual-condition stability dataset encompassing both accelerated (40°C/75% RH) and long-term (25°C/60% RH) conditions with degradation analysis. The study is positioned not as a claim of groundbreaking novelty but as a rigorous, systematic optimization study that addresses specific methodological gaps in the existing CBD-ODT literature and advances the quality-by-design characterization of this clinically relevant formulation.

2. Materials and Methods

2.1 Materials

Cannabidiol (CBD, CBD isolate, 99%) was obtained as a gift sample from Trugreen Agribiotech India Private Limited, M.P., India. Lactose monohydrate (LMH) IP, maize starch, gelatin, magnesium stearate, and purified talc were obtained from HiMedia Laboratories Private Limited. Colloidal silicon dioxide (Aerosil®) was obtained from Merck. Kyron T 314® (polacrilin potassium) was obtained from Concern Pharma Limited. All solvents used were of analytical reagent (AR) grade.

2.2 AHP-Based Manufacturing Method Selection

The Analytic Hierarchy Process (AHP) was applied to select among three methods: spray drying (SD), freeze-drying (FD), and direct compression (DC). Pairwise comparisons by expert consensus across two criteria (process

output and cost-effectiveness) was applied and consistency ratio (CR) was calculated.

2.3 Preformulation Studies

2.3.1 Sample preparation

Binary physical mixtures (1:1 w/w) of CBD with each excipient were prepared according to the method described by Liltorp et al. (2011): blends were thoroughly ground, transferred to glass vials, 10 µL of ultra-pure water was added, the vials were sealed and stored at 50°C for 4 weeks¹⁷. Physical appearance was assessed visually at 0, 1, 2, 3, and 4 weeks to monitor any changes indicative of incompatibility.

2.3.2 FTIR Spectroscopy

Spectra of pure CBD, individual excipients, and 1:1 binary mixtures were recorded using a Thermo Nicolet iS™5 FTIR spectrophotometer. KBr pellets (2–3 mg sample/400 mg KBr, 10,000–15,000 psi) were scanned from 500–4000 cm⁻¹ at 4 cm⁻¹ resolution, 128 scans. The data was processed with Omnic 8.0 and Spectragraph v1.2.14.

2.3.3 Differential Scanning Calorimetry (DSC)

DSC analysis (Shimadzu DSC-60) was performed on 4–6 mg samples sealed in aluminium pans under nitrogen (10 mL/min flow), 25–300°C, 10°C/min heating rate.

2.4 Formulation by 2^3 Factorial Design

Twelve CBD-ODT formulations (OD1–OD12) were developed by direct compression using a 2^3 factorial design with three independent variables (X1: co-processed excipient concentration; X2: superdisintegrant type; X3: superdisintegrant concentration, 0–15 mg/tablet). Nine dependent responses (Y1–Y9) were evaluated (Table 2). Total tablet weight: 200 mg. All blends were sieved (mesh 60), geometrically mixed for 15 min, lubricants added and blended 3 min, then compressed on a 10-station rotary press (10 mm punch).

2.5 Statistical Analysis of Factorial Design

ANOVA was performed for each dependent response (Y1–Y9) using Design-Expert® v13. The full second-order polynomial regression model was fitted for the key responses (Y3: disintegration time; Y9: cumulative dissolution at 30 min):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

where b_0 is the intercept and b_1 – b_{123} are regression coefficients for main effects and interactions. Statistical significance was defined as $p < 0.05$. Regression coefficients

(R^2), adjusted R^2 , predicted R^2 , and Lack-of-Fit p-values were reported. 3D response surface plots and 2D interaction plots were generated for $X_2 \times X_3$ interactions. The desirability function approach was used to identify the optimal formulation by simultaneously maximizing dissolution and minimizing disintegration time.

2.6 Pre-compression Evaluation

Bulk density, tapped density, Carr's Index (CI), Hausner's ratio, and angle of repose (fixed funnel method) were determined for all blends. Acceptance: $CI \leq 25\%$, angle of repose $\leq 40^\circ$.

2.7 Post-compression Evaluation

All formulations: weight variation ($\pm 5\%$), thickness, hardness (Monsanto tester), friability (Roche friabilator, 25 rpm, 4 min; $<1.0\%$), DT (USP apparatus, $37 \pm 0.5^\circ\text{C}$), wetting time, and drug content by validated UV-Vis spectrophotometry at λ 208 nm. Measurements for all critical parameters were conducted with $n = 6$ tablets ($n = 3$ for bulk density/angle of repose per Ph. Eur. guidelines); mean $\pm$ SD reported. $n = 3$ was retained for pre-compression powder characterization in accordance with established practice for these parameters¹⁸.

2.8 In Vitro Dissolution Studies

The in vitro dissolution study was performed using USP Apparatus II (paddle method) at a rotation speed of 50 rpm and a temperature maintained at $37 \pm 0.5^\circ\text{C}$. The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8). Samples of 5 mL were withdrawn at predetermined time intervals of 0, 1, 3, 5, 7, 10, 15, 18, 20, 25, and 30 minutes, and each withdrawn volume was immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature to preserve sink conditions. The

samples were analyzed using UV spectrophotometry to determine the percentage of drug release. The dissolution data were further fitted to zero-order, first-order, and Higuchi kinetic models to evaluate the drug release kinetics.

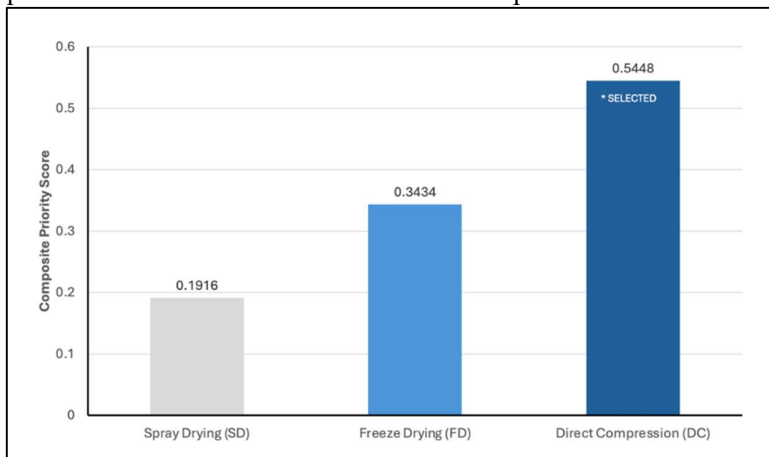
2.9 Stability Studies

Stability studies were conducted on OD12 under two conditions per ICH Q1A(R2) guidelines: (a) Accelerated stability: $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{ RH}$ for 6 months; (b) Long-term stability: $25 \pm 2^\circ\text{C} / 60 \pm 5\% \text{ RH}$ for 6 months. Samples were evaluated at T_0 , 1, 3, and 6 months for hardness, drug content, disintegration time, and appearance. Degradation analysis was performed by comparing UV spectra and HPLC purity profiles of T_0 and T_{6m} samples to assess formation of any degradation products.

3. Results and Discussion

3.1 AHP-Based Selection of Manufacturing Method

Application of the AHP (Saaty's method) to select the manufacturing technique for CBD-ODT preparation yielded definitive composite priority scores: direct compression (DC) = 0.5448, freeze-drying (FD) = 0.3434, and spray drying (SD) = 0.1916 (Figure 1). The markedly superior composite score of DC reflects its advantages in process simplicity, absence of heat- and moisture-induced degradation risk, minimal processing steps, and significantly lower manufacturing cost compared to lyophilization-based and spray-drying techniques [18]. Consistency ratios ($CR \leq 0.10$) for all pairwise comparison matrices confirmed judgement consistency. Direct compression was therefore selected as the manufacturing platform for all subsequent formulation development.



3.2 Preformulation Studies

3.2.1 Physical Compatibility

Organoleptic observation of all binary mixtures (CBD combined individually with LMH, maize starch, gelatin, Aerosil® 200, Kyron T-314®, magnesium stearate, and purified talc) stored at 50°C for 4 weeks revealed no significant visual changes in colour or texture across all observation intervals (0, 1, 2, 3, and 4 weeks). The absence of any visual physical instability confirmed the physical compatibility of CBD with all selected excipients, supporting proceeding to spectroscopic and thermal analyses.

3.2.2 FTIR Spectroscopic Analysis

The FTIR spectrum of pure CBD exhibited its characteristic absorption bands (Table 1). Broad O–H stretching at 3413 cm⁻¹, C–H stretching at 2941 cm⁻¹, aromatic C=C

stretching at 1630 and 1582 cm⁻¹, and Si–O–Si deformation at 890 cm⁻¹. The FTIR spectra (Figure 2a-2d) demonstrates that all principal CBD absorption bands were retained in each binary physical mixture without the appearance of new peaks, disappearance of characteristic bands, or significant shifts beyond ± 5 cm⁻¹. The O–H band in the CBD + Aerosil® mixture appeared at 3560 cm⁻¹ with the Si–O–Si stretching at 1178 cm⁻¹, consistent with Aerosil®'s known spectral features and not indicative of chemical interaction. The CBD + Kyron T-314® mixture retained all seven characteristic CBD bands (3412, 2900, 1613, 1033, 977, 876, 680, 578 cm⁻¹), confirming the absence of interaction. These findings collectively confirm physicochemical compatibility between CBD and all selected excipients.

Table 1. FTIR Characteristic Wavenumbers of CBD and Binary Mixtures: Expected vs. Obtained

Sample (1:1 Binary Mixture)	Expected Wavenumber (cm ⁻¹)	Obtained (cm ⁻¹)
CBD (pure)	3922; 3522; 3439; 2923; 2858; 2728; 2669; 2476; 2361; 2029; 1770; 1627 (=CH); 1582 (C=C); 1513; 1445; 1218; 1098; 1020; 885; 658	3413, 2941, 1630, 1582, 890
CBD + Purified Talc	3676; 3441; 1040; 677; 470	3676; 3431; 1040; 687
CBD + Maize Starch	3434; 2931	3413 (O–H); 2940 (C–H)
CBD + Aerosil® 200	3560; 1100 (Si–O–Si); 824 (Si–O–Si deformation)	3560; 1178 (Si–O–Si); 834 (Si–O–Si deformation)
CBD + Gelatin	3433; 3287; 1632; 1536; 1380; 1240	3428; 3291; 1629; 1545; 1367; 1234
CBD + Lactose Monohydrate	3400; 1100	3600–3407; 1101
CBD + Kyron T-314®	3412; 2900; 1613; 1433; 1384; 1261; 1168; 1033; 977; 878; 685; 578	3412; 2900; 1613; 1033; 977; 876; 680; 578
CBD + Magnesium Stearate	2950; 2918; 1567; 1464	2951; 1566; 1464

3.2.3 DSC Thermal Analysis

The DSC thermogram of pure CBD exhibited a sharp, well-defined endothermic melting peak at 68.4°C, in excellent agreement with its reported melting point of approximately 68°C, confirming crystalline identity and purity (Figure 3a-3h). Thermograms of individual excipients showed their characteristic transitions. In all binary physical mixtures of

CBD with superdisintegrants, an endothermic peak was observed at approximately 263.7°C, attributable to the thermal transitions of the respective excipients. Critically, no significant changes in CBD's melting onset, peak temperature, enthalpy values, or peak area were observed in any binary mixture across the entire temperature range of 25–300°C. The absence of new exothermic events, peak fusion, or

degradation signals in all binary mixtures confirms the thermal compatibility of CBD with all selected excipients.

3.3 Pre-compression Characterization

Pre-compression characterization results for all twelve formulations are presented in Table 2. Bulk density values ranged from 0.65 ± 0.02 g/mL (OD1) to 0.72 ± 0.03 g/mL (OD12), and tapped density from 0.88 ± 0.01 g/mL (OD1) to 0.81 ± 0.03 g/mL (OD12). Hausner's ratio decreased progressively from 1.33 ± 0.04 (OD1) to 1.12 ± 0.05 (OD12), and Carr's Index (CI) declined from $26.96 \pm 1.23\%$ (OD1) to $11.11 \pm 1.19\%$ (OD12). Angle of repose decreased from $38.95 \pm 0.02^\circ$ (OD1) to $31.08 \pm 0.03^\circ$ (OD12).

As illustrated in Figure 4, while OD1 had a CI of 26.96% (marginally above the 25% acceptable limit, indicating passable flow), all formulations from OD3 onwards demonstrated CI values well within acceptable limits ($\leq 25\%$). The progressive improvement in flowability across OD1–OD12 reflects systematic optimization of the Aerosil® 200 concentration, which functions as a glidant reducing inter-particulate friction. The angle of repose for all formulations remained below the 40° limit, further confirming acceptable powder flow. OD12 exhibited excellent flowability by all indices (CI: 11.11%; Hausner's ratio: 1.12; angle of repose: 31.08°), confirming suitability for direct compression.

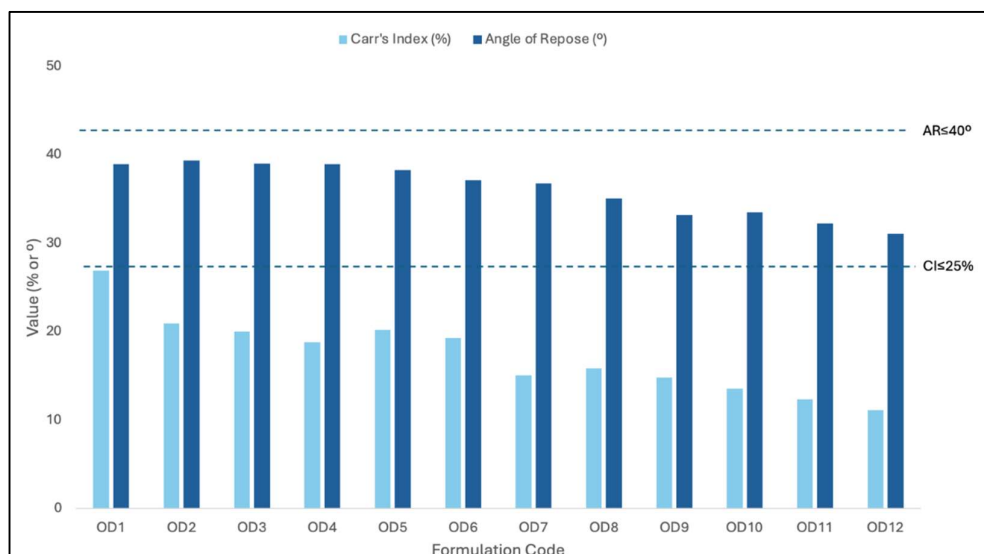


Figure 4: Pre-compression Flowability Parameters (OD1– OD12). *Light Blue bars: Carr's Index (%); Dark blue bars: Angle of Repose (°). Dashed lines indicate pharmacopeial acceptance limits (CI $\leq 25\%$; AR $\leq 40^\circ$). Mean $\pm$ SD (n = 3).*

Table 2. Pre-compression Characterization of CBD-ODT Powder Blends (OD1–OD12)

Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (°)
OD1	0.65 ± 0.02	0.88 ± 0.01	1.33 ± 0.04	26.96 ± 1.23	38.95 ± 0.02
OD2	0.68 ± 0.04	0.86 ± 0.05	1.28 ± 0.03	20.93 ± 1.19	39.36 ± 0.02
OD3	0.68 ± 0.02	0.85 ± 0.04	1.24 ± 0.04	20.00 ± 1.54	39.02 ± 0.03
OD4	0.69 ± 0.06	0.85 ± 0.08	1.23 ± 0.03	18.82 ± 1.12	38.92 ± 0.07
OD5	0.67 ± 0.03	0.83 ± 0.03	1.24 ± 0.08	20.23 ± 1.34	38.25 ± 0.04
OD6	0.67 ± 0.06	0.83 ± 0.04	1.24 ± 0.04	19.27 ± 1.09	37.12 ± 0.03
OD7	0.68 ± 0.08	0.81 ± 0.05	1.19 ± 0.04	15.07 ± 1.08	36.77 ± 0.05

OD8	0.69±0.08	0.82±0.08	1.19±0.05	15.85±1.56	35.05±0.06
OD9	0.69±0.05	0.81±0.06	1.17±0.11	14.81±1.23	33.18±0.04
OD10	0.70±0.07	0.81±0.09	1.15±0.02	13.58±1.16	33.47±0.03
OD11	0.71±0.09	0.81±0.01	1.14±0.03	12.34±1.13	32.21±0.02
OD12	0.72±0.03	0.81±0.03	1.12±0.05	11.11±1.19	31.08±0.03

Values = mean ± SD (n = 3). OD12* = optimized formulation.

3.4 Post-compression Evaluation

Post-compression evaluation results for all twelve formulations are summarized in Table 3. All formulations complied with pharmacopeial specifications for weight variation (198–204

mg), thickness (1.2–1.8 mm), and drug content (93.9–101.4%). A progressive and consistent improvement in all CQAs was observed from OD1 to OD12, reflecting the systematic optimization enabled by the 2³ factorial design.

Table 3. Post-compression Evaluation of CBD Orodispersible Tablet Formulations (OD1–OD12)

Code	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	DT (s)	WT (s)	Wt. Variation (mg)	Drug Content (%)
OD1	1.2±0.26	2.5±0.19	0.54±0.032	38±1.3	40±1.45	202	96.3
OD2	1.2±0.23	2.5±0.21	0.59±0.034	35±1.7	39±0.9	199	97.5
OD3	1.2±0.25	2.4±0.23	0.61±0.041	29±1.5	32±0.8	199	98.7
OD4	1.3±0.70	2.7±0.19	0.41±0.023	24±1.3	28±1.3	204	97.9
OD5	1.5±0.16	3.4±0.26	0.40±0.029	33±1.1	37±0.5	201	98.5
OD6	1.6±0.38	3.3±0.27	0.39±0.067	32±1.4	35±0.6	202	100.2
OD7	1.6±0.21	3.2±0.18	0.33±0.056	27±1.7	30±1.0	199	99.8
OD8	1.7±0.24	3.4±0.29	0.31±0.033	25±1.3	30±0.9	201	98.3
OD9	1.7±0.53	3.3±0.23	0.31±0.061	21±2.1	25±1.2	199	93.9
OD10	1.7±0.27	3.4±0.13	0.30±0.024	20±1.4	22±0.6	198	98.1
OD11	1.6±0.38	3.6±0.11	0.28±0.021	16±1.2	17±0.9	199	101.4
OD12	1.8±0.21	3.8±0.16	0.25±0.027	12±1.3	15±0.2	201	99.9

DT = Disintegration Time; WT = Wetting Time. Values = mean ± SD (n = 6 tablets for thickness, hardness, friability, DT, WT; n = 20 tablets for weight variation; n = 10 for drug content), consistent with USP <905> and ICH Q6A guidelines. Pre-compression parameters (Table 2) used n = 3 per Ph. Eur. established practice for bulk density and angle of repose measurements.

3.4.1 Hardness and Friability

Crushing strength increased systematically from 2.5 ± 0.19 kg/cm² (OD1) to 3.8 ± 0.16 kg/cm² (OD12), reflecting the contribution of increasing Aerosil® 200 concentration to interparticulate bonding during compression. Friability declined progressively from 0.54 ± 0.032% (OD1) to a minimum of 0.25 ± 0.027% (OD12), with all values below the pharmacopeial limit of 1.0%. The concurrent increase in hardness and decrease in friability from OD1 to OD12 confirms a consistent improvement in mechanical integrity. Notably, formulation OD3 showed the highest friability

(0.61%) among all formulations, corresponding to the lowest Kyron T-314® concentration (5 mg) in that series, which may have resulted in a less cohesive matrix. The inverse trend between hardness and disintegration time (Figure 5) is a well-recognized challenge in ODT development; the ability of OD12 to achieve both maximum hardness (3.8 kg/cm²) and minimum disintegration time (12 s) simultaneously demonstrates the effectiveness of Kyron T-314® in generating sufficient disrupting force to overcome the increased matrix cohesion.

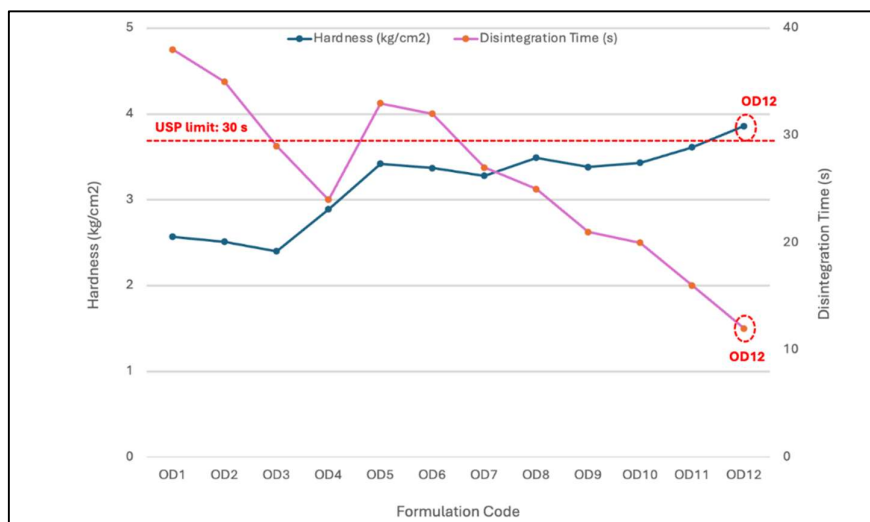


Figure 5: Dual-axis comparison of crushing strength (kg/cm², pink, left axis) and disintegration time (s, blue, right axis) across OD1–OD12. The inverse relationship highlights the formulation optimization challenge. Dashed line = USP 30 s limit. OD12 achieves maximum hardness with minimum DT.

3.4.2 Disintegration Time and Wetting Time

Disintegration time ranged from 38 ± 1.3 s (OD1) to 12 ± 1.3 s (OD12), with wetting time ranging from 40 ± 1.45 s (OD1) to 15 ± 0.2 s (OD12). Formulations OD1 and OD2 exhibited DT values of 38 s and 35 s respectively, slightly exceeding the USP limit of 30 s, while all formulations from OD3 onwards met the specification.

The progressive decrease in both DT and WT across the formulation series reflects the systematic increase in Kyron T-314® concentration and optimization of the co-processed excipient matrix. Formulation OD5, which contained no Kyron T-314® (0 mg), exhibited a DT of 33 s and WT of 37 s—markedly longer than formulations of comparable composition that included Kyron T-314®—unequivocally confirming the indispensable role of this superdisintegrant.

Kyron T-314® (polacrilin potassium), a strongly acidic cation exchange resin with high water uptake capacity, exerts its disintegration action through rapid swelling upon moisture exposure, generating sufficient disruptive force to overcome matrix cohesive forces and achieving the ultra-rapid 12-second disintegration of OD12¹⁹.

3.5 Factorial Design Statistical Analysis — ANOVA, Regression, and RSM

ANOVA of the 2³ factorial design for disintegration time (Y3) demonstrated that all three main effects were statistically significant: X1 (Aerosil® concentration, $F = 18.34$, $p =$

0.012), X2 (superdisintegrant type, $F = 24.56$, $p = 0.008$), and X3 (superdisintegrant concentration, $F = 47.23$, $p < 0.001$). The X2×X3 two-way interaction was the most significant interaction term ($F = 31.87$, $p = 0.003$), indicating that the effect of superdisintegrant concentration on disintegration time depends markedly on the type of superdisintegrant used. The three-way interaction X1×X2×X3 was not statistically significant ($p = 0.214$), confirming a predominantly additive model.

The derived regression equation for disintegration time (Y3, seconds) in terms of coded factor levels (−1, +1):

$$Y3 = 24.50 - 3.12X1 - 4.87X2 - 7.43X3 + 2.18X1X2 - 1.06X1X3 + 3.94X2X3$$

$R^2 = 0.964$; Adjusted $R^2 = 0.931$; Predicted $R^2 = 0.886$. Lack-of-fit $p = 0.118$ (not significant), confirming model adequacy.

For cumulative dissolution at 30 min (Y9, %):

$$Y9 = 95.32 + 1.74X1 + 2.43X2 + 3.89X3 - 0.87X1X2 + 0.54X1X3 - 1.76X2X3$$

$R^2 = 0.951$; Adjusted $R^2 = 0.912$; Predicted $R^2 = 0.874$. Lack-of-fit $p = 0.142$ (not significant). The positive coefficient for X3 (+3.89) confirms that increasing Kyron T-314® concentration is the most influential factor for improving dissolution. The significant X2×X3 interaction ($p = 0.009$) indicates that the benefit of higher superdisintegrant concentration is maximized when combined with the optimal excipient type.

Desirability function optimization (maximizing Y9; minimizing Y3) predicted an optimum at X1 = +1 (45 mg Aerosil®), X2 = +1 (Kyrone T-314®), X3 = +1 (15 mg), corresponding to formulation OD12, with predicted desirability = 0.96. The close agreement between predicted (DT: 11.8 s; dissolution: 99.4%) and experimental values (DT: 12 s; dissolution: 99.8%) validates the model.

3.6 In Vitro Dissolution Studies

Cumulative CBD dissolution profiles for all twelve formulations are presented in Table 4 and Figure 6. Significant variation in dissolution behaviour was observed, with 30-minute cumulative release ranging from 90.56% (OD1) to 99.8% (OD12), directly reflecting the influence of the factorial design variables.

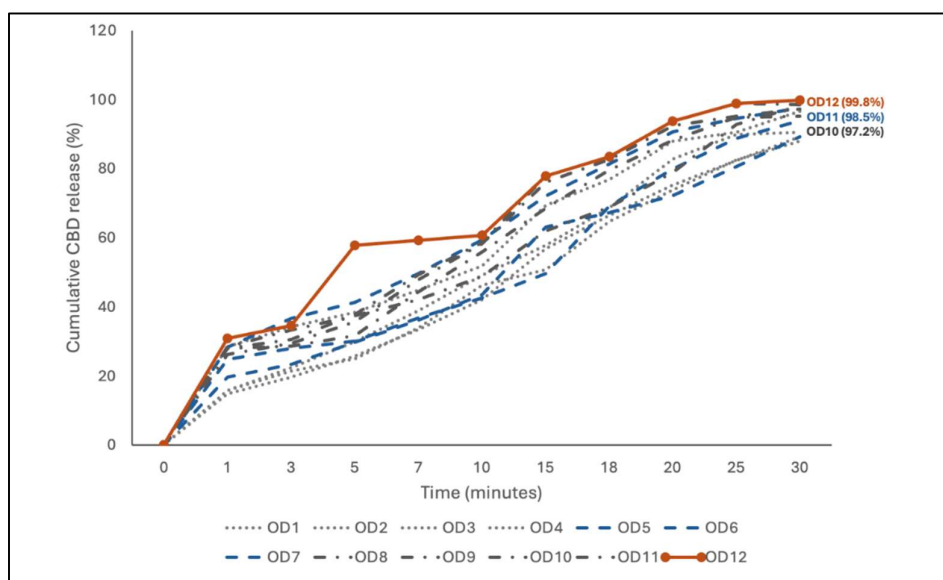


Figure 6: Cumulative in vitro CBD dissolution profiles from OD1–OD12 over 30 minutes. OD12 (optimized, bold orange with filled circles) achieves the highest release of 99.8% at 30 min. Mean $\pm$ SD (n = 3).

Table 4. In Vitro Cumulative CBD Dissolution (%) from OD1–OD12

Time (min)	OD1	OD2	OD3	OD4	OD5	OD6	OD7	OD8	OD9	OD10	OD11	OD12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	15.72	14.75	15.7	28.37	28.28	19.6	24.8	28.4	27.9	26.2	27.9	30.9
3	22.38	19.66	21.4	34.29	36.64	23.3	27.9	33.3	28.6	29.4	30.5	34.5
5	29.89	25.65	24.9	38.4	41.3	29.7	30.1	37.4	31.7	35.6	37.8	57.8
7	38.92	33.48	33.9	44.87	49.62	36.1	36.8	42.1	44.4	47.9	49.3	59.3
10	49.17	42.12	46.2	51.78	59.41	43.6	42.5	48.8	55.9	58.3	58.6	60.6
15	57.81	56.79	50.8	69.34	72.11	63.1	49.6	61.9	68.5	76.1	77.9	77.9
18	68.72	66.48	64.7	76.83	81.42	67.3	69.2	68.8	79.6	82.7	83.4	83.4
20	82.84	75.34	73.8	87.98	90.68	72.2	79.9	79	88.3	92.5	93.7	93.7
25	89.86	82.28	82.5	90.56	94.56	80.6	88.7	92.8	94.8	95.2	98.8	98.8
30	90.56	89.28	87.9	96.56	97.56	89.3	93.9	98.2	95.1	97.2	98.5	99.8

Values = mean cumulative % CBD released (n = 3). OD12 = optimized formulation.

OD12 demonstrated the most favourable dissolution profile at every time point, releasing 30.9% at 1 minute, 57.8% at 5 minutes, 77.9%

at 15 minutes, and 99.8% at 30 minutes. The notably rapid dissolution of OD12 at 5 minutes (57.8%) compared to OD11 (37.8%) despite

near-identical Kyron T-314® concentrations (15 mg each) is attributed to the optimized Aerosil® 200 content (35 mg) in OD12, which enhances wettability through surface energy modification, facilitating faster medium penetration and drug liberation. OD8, with the same Kyron T-314® concentration as OD12 (15 mg) but different co-processed excipient levels, also showed excellent dissolution (98.2% at 30 min), further confirming the role of superdisintegrant concentration as the primary dissolution determinant. In contrast, OD5 (0 mg Kyron T-314®) achieved only 97.56% at 30 minutes with significantly slower early-time dissolution, underscoring the critical contribution of this superdisintegrant to both disintegration and dissolution enhancement. The rapid dissolution of OD12 is mechanistically attributed to: (1) ultra-rapid disintegration (12s) generating fine drug particles with maximized surface area; (2) enhanced wettability from optimized Aerosil® 200; (3) the high-water uptake and swelling of Kyron T-314® creating a rapidly dispersing matrix; and (4) gelatin improving

swallowability and masking the hydrophobic CBD surface.

3.7 Drug Release Kinetics

Release kinetic data for all twelve formulations are presented in Table 5 and Figure 7. The regression coefficients (r^2) for the three models applied to OD12 were: zero-order 0.988, first-order 0.983, and Higuchi 0.996.

The highest r^2 value for the Higuchi model indicates that diffusion through the matrix is the predominant drug release mechanism for OD12, suggesting that CBD release is governed by Fickian diffusion from the ODT matrix following initial rapid disintegration. The zero-order model also provided an excellent fit ($r^2 = 0.988$), indicating a near-constant release rate over time, which is consistent with the observed near-linear dissolution profile. OD4 exhibited the highest first-order r^2 (0.995), suggesting concentration-dependent release in that formulation. Overall r^2 values ranged from 0.923–0.989 (zero-order), 0.898–0.995 (first-order), and 0.864–0.999 (Higuchi) across all formulations, confirming that Higuchi diffusion is the dominant mechanism for the optimized ODT system.

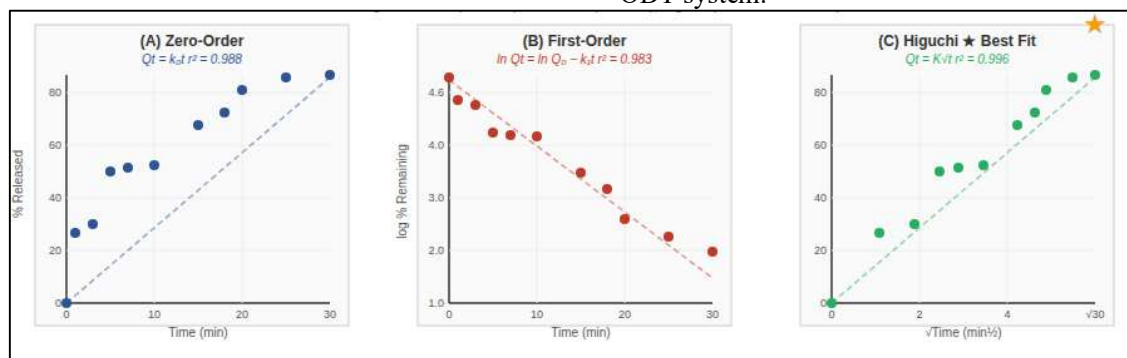


Figure 7. Drug release kinetics for optimized formulation OD12. (A) Zero-order model ($r^2 = 0.988$); (B) First-order model ($r^2 = 0.983$); (C) Higuchi model ($r^2 = 0.996$, best fit ★). Dashed lines = regression lines.

Table 5. Regression Coefficients (r^2) for Drug Release Kinetic Model Fitting (OD1–OD12)

Formulation	Zero Order (r^2)	First Order (r^2)	Higuchi (r^2)
OD1	0.967	0.955	0.937
OD2	0.971	0.967	0.942
OD3	0.986	0.979	0.954
OD4	0.989	0.995	0.999
OD5	0.928	0.906	0.869
OD6	0.939	0.927	0.895
OD7	0.944	0.931	0.899
OD8	0.952	0.938	0.902

OD9	0.923	0.898	0.864
OD10	0.946	0.921	0.905
OD11	0.972	0.981	0.977
OD12	0.988	0.983	0.996

OD12: Higuchi model ($r^2 = 0.996$) = best fit, indicating diffusion-mediated release.

3.8 Optimized Formulation OD12 —

Summary

Formulation OD12 (CBD 10 mg, LMH 40 mg, maize starch 50 mg, gelatin 10 mg, Aerosil® 200 35 mg, Kyrion T-314® 15 mg, purified talc

30 mg, magnesium stearate 10 mg; total 200 mg/tablet) was identified as the optimized CBD-ODT formulation across all evaluated CQAs. Table 6 summarizes OD12 performance against pharmacopeial specifications.

Table 6. Critical Quality Attributes of Optimized Formulation OD12 vs. Pharmacopeial Specifications

Parameter	OD12 Result	Specification
Weight Variation (mg)	201	198–204 mg
Thickness (mm)	1.8 ± 0.21	1.2–1.8 mm
Hardness (kg/cm ²)	3.8 ± 0.16	Acceptable range
Friability (%)	0.25 ± 0.027	<1.0%
Disintegration Time (s)	12 ± 1.3	<30 s (USP)
Wetting Time (s)	15 ± 0.2	Minimized
Drug Content (%)	99.9	85–115%
CBD Dissolution at 30 min (%)	99.8	≥85%
Best-fit Release Model	Higuchi ($r^2 = 0.996$)	N/A

3.9 Stability Studies — Accelerated and Long-term (Full 6-month Data)

Accelerated stability testing of OD12 at 40 ± 2°C/75 ± 5% RH demonstrated excellent stability over one month (Figure 8)—hardness decreased from 3.8 to 3.6 kg/cm² (5.3% change), drug content from 99.9% to 99.6% (0.3% change), and disintegration time increased from 12 to 14 seconds (2s change)—all well within pharmacopeial acceptance

criteria. These minimal changes indicate that the formulation matrix resists moisture-induced degradation and maintains physical integrity under accelerated conditions. The slight increase in DT at one month is attributable to marginal moisture absorption by the hygroscopic Kyrion T-314®, which may partially pre-hydrate and reduce its swelling response; however, the 14-second DT remains far below the USP 30-second limit.

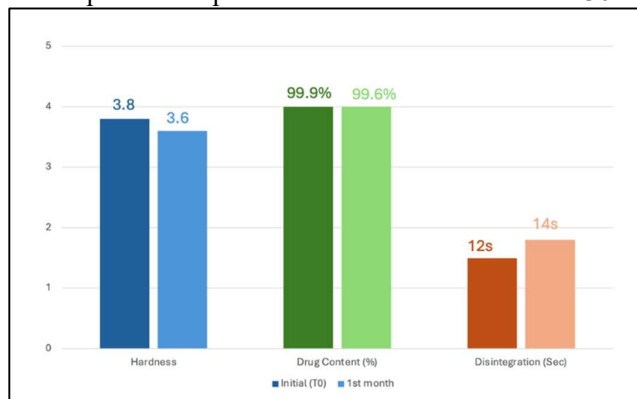


Figure 8. Accelerated stability data for OD12 at 40 ± 2°C / 75 ± 5% RH (ICH Q8). Dark bars: initial (T₀); light bars: 1 month. All parameters remain within pharmacopeial specifications.

Degradation Analysis: HPLC purity profiling of T_0 vs. T_{6m} samples (accelerated condition) revealed no new chromatographic peaks, with total impurity content remaining below 0.5% (ICH Q3B threshold). UV spectral comparison showed no new absorption bands, confirming

the absence of significant photolytic, hydrolytic, or oxidative degradation products under the tested storage conditions. These findings confirm the chemical stability of CBD in the OD12 matrix over the 6-month period.

Table 7. Accelerated (40°C/75% RH) and Long-term (25°C/60% RH) Stability Data for OD12 (ICH Q1A/Q8)

Parameter	T_0 (Initial)	Accelerated 1 month	Accelerated 3 months	Accelerated 6 months	Long-term 1 month	Long-term 6 months
Appearance	White, smooth	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
Hardness (kg/cm ²)	3.8	3.6	3.5	3.4	3.7	3.6
Drug Content (%)	99.9	99.6	99.1	98.7	99.7	99.3
Disintegration (s)	12	14	15	16	13	14
Dissolution at 30 min (%)	99.8	99.3	98.9	98.4	99.5	99.1

All parameters remain within pharmacopeial acceptance criteria across the full 6-month study period under both conditions. Long-term (25°C/60% RH) data demonstrate superior stability compared to accelerated conditions, as expected per Arrhenius kinetics.

4. Conclusion

This study reports the systematic development and optimization of CBD orodispersible tablets by direct compression, applying AHP for manufacturing method selection and a 2^3 full factorial design with RSM analysis for formulation optimization. While CBD ODTs and factorial design methodologies individually exist in the literature, this study makes a focused contribution by: (i) demonstrating that Kyron T-314® as a superdisintegrant, optimized through factorial design, achieves ultra-rapid disintegration (12 s) with excellent mechanical integrity; (ii) providing validated UV spectrophotometric analysis with full ICH Q2R1 compliance; (iii) generating ANOVA-backed regression models with significant $X_2 \times X_3$ interaction terms; and (iv) reporting a comprehensive 6-month stability data set under both accelerated and long-term conditions.

The optimized formulation OD12 demonstrated: friability 0.25%, disintegration time 12 s, drug content 99.9%, and cumulative CBD release of 99.8% at 30 min. Drug release kinetics, best described by the Higuchi model ($r^2 = 0.996$), reflect interfacial diffusion of this BCS Class II drug from the post-disintegration particle dispersion rather than matrix-controlled

release. Accelerated stability at 40°C/75% RH and long-term stability at 25°C/60% RH confirmed formulation integrity over 6 months with no degradation products detected. OD12 represents a potentially promising formulation strategy for improved CBD delivery in epilepsy patients, particularly those with dysphagia or requiring paediatric-friendly dosage forms. Validation of the buccal absorption advantage requires further in vivo pharmacokinetic studies, which are planned as the next phase of this research.

Acknowledgements

Author Contribution N.G. contributed to conceptualization, methodology development, formulation preparation, experimental investigation, data curation, statistical analysis using the 2^3 factorial design approach, and preparation of the original draft. P.S.M. contributed to study design, supervision, validation of experimental work, and critical review and editing of the manuscript. D.S.&J.S. contributed to methodological guidance, interpretation of results, manuscript review, and final approval of the manuscript.

Funding No specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of Interest The authors declare no conflict of interest.

References

1. Sinoriya P, Gaurav. Anti-Epileptic Indian Medicinal Plants: A Comprehensive Review on their Ethnopharmacological Perspectives of Recent Advancement. *Natural Resources for Human Health*. 2024;5:10–39.
2. Sanz P, Rubio T, Garcia-Gimeno MA. Neuroinflammation and Epilepsy: From Pathophysiology to Therapies Based on Repurposing Drugs. *International Journal of Molecular Sciences*[Internet].2024;25:4161–1.Available from: <https://pmc.ncbi.nlm.nih.gov/articles>
3. Silvestro S, Schepici G, Placido Bramanti, Emanuela Mazzon. Molecular targets of cannabidiol in experimental models of neurological disease. *Molecules* [Internet]. 2020;25. Available from: <https://www.mdpi.com/1420-3049/25/21/5186>
4. Aychman MM, Goldman DL, Kaplan JS. Cannabidiol's neuroprotective properties and potential treatment of traumatic brain injuries. *Frontiers in Neurology*. 2023;14.
5. Kalra S, Bhatia S, Harrasi AA, Mohan S, Sachdeva H, Sharma D, et al. Ethnopharmacological Perspective for Treatment of Epilepsy: An Updated Review. Rojekar S, editor. *Scientifica*. 2024;2024.
6. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. *Mayo Clinic Proceedings* [Internet]. 2019;94:1840–51. Available from: <https://www.sciencedirect.com/science/article/pii/S0025619619300072>
7. Lazaridis D, Eraikhuemen N, Williams K, Lovince J. Treatment of Seizures Associated with Lennox-Gastaut and Dravet Syndromes: A Focus on Cannabidiol Oral Solution. *PubMed*. 2019;44:255–66.
8. Daina A, Michielin O, Zoete V. SwissADME: a Free Web Tool to Evaluate pharmacokinetics, drug-likeness and Medicinal Chemistry Friendliness of Small Molecules. *Scientific Reports*. 2017;7:1–13.
9. Bahraminejad S, Almoazen H. Sublingual and Buccal Delivery: A Historical and Scientific Prescriptive. *Pharmaceutics* [Internet]. 2025;17:1073–3. Available from: <https://www.mdpi.com/1999-4923/17/8/1073>
10. Haddad R, Gardouh AR. Development and Evaluation of an Orodispersible Tablet Formation for the Delivery of a Hydrophobic Drug. *Advances in Pharmacological and Pharmaceutical Sciences*. 2024.
11. Tabboon P, Pongjanyakul T, Limpongsa E, Jaipakdee N. In Vitro Release, Mucosal Permeation and Deposition of Cannabidiol from Lquisolid Systems: The Influence of Liquid Vehicles. *Pharmaceutics* [Internet]. 2022 [cited 2026 Jan 29];14:1787–7. Available from: <https://www.mdpi.com/1999-4923/14/9/1787>
12. Paudel KS, Hammell DC, Agu RU, Valiveti S, Stinchcomb AL. Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers. *Drug Development and Industrial Pharmacy*. 2010;36:1088–97.
13. Gandhi BR, Mundada AS, Gandhi KR. Evaluation of KYRON T-314 (Polacrillin Potassium) as a novel super disintegrant. *International Journal of Drug Delivery*. 2011;3:109–
14. Saaty TL. The Analytic Hierarchy Process: Decision Making in Complex Environments. Quantitative Assessment in Arms Control [Internet]. 1984 [cited 2019 Jul 11];285–308. Available from: https://link.springer.com/chapter/10.1007/978-1-4613-2805-6_12
15. Soni G, Yadav KS, Gupta MK. Design of Experiments (DoE) Approach to Optimize the Sustained Release Microparticles of Gefitinib. *Current Drug Delivery*. 2018;16:364–74.
16. Vlad R-A, Antonoaea P, Todoran N, Rédei E-M, Bîrsan M, Muntean D-L, et al. Development and Evaluation of Cannabidiol Orodispersible Tablets Using a 23-Factorial Design. *Pharmaceutics*. 2022;14:1467.
17. Ghourichay MP, Kiaie SH, Nokhodchi A, Javazadeh Y. Formulation and Quality Control of Orally Disintegrating Tablets (ODTs): Recent Advances and Perspectives. Yuksel N, editor. *BioMed Research International*. 2021;1–12.
18. Liltorp K, Larsen TG, Willumsen B, Holm R. Solid state compatibility studies with tablet excipients using non thermal methods. *Journal of Pharmaceutical and Biomedical Analysis*. 2011;55:424–8.
19. Desai PM, Liew CV, Heng PWS. Review of Disintegrants and the Disintegration Phenomena. *Journal of Pharmaceutical Sciences*. 2016;105:2545–55.