

Article

Cannabidiol-Loaded Hyaluronic Acid-Based Nanogel for Inflammatory Acne: In Vitro and Open-Label, Non-Randomized Clinical Evaluation of Efficacy and Tolerability

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Abstract

Acne is a common inflammatory skin condition that significantly impacts quality of life. Standard treatments often cause skin irritation or contribute to antibiotic resistance. Cannabidiol (CBD) has demonstrated anti-inflammatory and sebum-regulating properties; however, its application is limited by poor solubility and stability. This study investigated the physicochemical properties of a CBD-loaded hyaluronic acid-graft-poly(N-isopropylacrylamide) nanogel (Hy-CBD). The biological activities of Hy-CBD, including its anti-inflammatory and antioxidant effects, were also evaluated. In addition, an exploratory clinical study was conducted to assess the safety and efficacy of the formulation in 22 Asian participants with inflammatory acne. In this open-label, non-randomized study, participants applied the gel twice daily for seven days. Assessments of skin tolerance, lesion size, redness, and pigmentation were performed at baseline, Day 2, and Day 7 using clinical examination and imaging analysis. The Hy-CBD gel was clinically tolerated, with no evidence of comedogenic or acneogenic potential. By Day 7, inflammatory lesion size was reduced by 46%, with significant improvements in redness and post-inflammatory pigmentation. All participants reported a subjective reduction in acne severity and expressed satisfaction with the treatment outcomes. These findings suggest that the Hy-CBD gel is a safe and promising delivery system for acne management. Nevertheless, larger randomized controlled studies are required to validate these preliminary findings.

Keywords: cannabidiol; acne; clinical study; nanogel; hyaluronic acid; HA-pNIPAM



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1. Introduction

Acne vulgaris is a common chronic inflammatory skin disorder affecting the pilosebaceous unit. It is caused by several factors, including excess sebum production, follicular hyperkeratinization, hormonal dysregulation, bacterial colonization, and inflammation [1]. Approximately 85% of individuals aged 12–24 years are affected by acne, which can lead to significant psychosocial impacts such as anxiety, depression, and reduced self-esteem [2–4].

Conventional management relies on topical therapies (e.g., benzoyl peroxide, antibiotics, retinoids, azelaic acid, and dapsone) and systemic agents (e.g., isotretinoin, oral antibiotics, hormonal therapy) [5]. To target multiple pathogenic pathways and mitigate antimicrobial resistance, current guidelines recommend a multimodal approach tailored to disease severity, patient tolerance, and preference [6]. However, standard treatments are frequently limited by adverse effects; topical agents commonly cause localized skin irritation, sensitivity, and dryness, whereas systemic therapies can induce systemic toxicities, or accelerate global antimicrobial resistance [7–9]. As a result, alternative microbiome-targeted interventions, such as probiotics, postbiotics, bacteriophages, and gut–skin axis modulators, are being actively explored [10,11]. In parallel, natural compounds are gaining attention as complementary options due to their broad biological activities and favorable safety profiles [12], with several phytochemicals demonstrating antimicrobial, anti-inflammatory, sebum-regulating, and wound-healing properties [13–18].

Cannabidiol (CBD) is a major non-psychoactive phytochemical derived from *Cannabis sativa* (hemp) that exhibits potent antioxidant, anti-inflammatory, antimicrobial, and sebum-regulating properties [19]. CBD exerts these effects largely by interacting with cannabinoid receptors (CB₁ and CB₂) expressed on skin cells, including keratinocytes, fibroblasts, melanocytes, and sebocytes [20]. Mechanistically, CBD-rich extracts inhibit *Cutibacterium acnes* proliferation, suppress core inflammatory pathways, such as NF- κ B and MAPK, and promote collagen synthesis [21–23]. Clinical data support these multi-targeted actions, demonstrating that topical CBD formulations effectively reduce sebum production and erythema with a highly favorable safety profile [21].

The regulatory landscape of CBD in cosmetic products remains fragmented and rapidly evolving, directly impacting the commercialization and global applicability of CBD-based formulations. In the European Union and the United Kingdom, CBD is permitted in cosmetics provided that Δ^9 -tetrahydrocannabinol (THC) content falls within strict, predefined limits; however, a unified EU legislation is still lacking, and products making therapeutic claims risk classification as medicines [24]. In the United States, hemp-derived CBD has been federally legal since 2018, contingent on a THC threshold below 0.3%, though individual state regulations vary and are not harmonized with international standards [25]. Regulatory frameworks across East Asia are considerably more restrictive: China strictly prohibits all *Cannabis sativa*-derived ingredients in cosmetics, Japan permits only THC-free preparations, and South Korea tolerates only exceptionally low residual levels with no clear pathway for mainstream consumer cosmetic commercialization [24,25].

In contrast, Thailand presents a unique regulatory environment highly relevant to this work. Having become the first Southeast Asian nation to legalize medical cannabis in 2019 [26], Thailand has since shifted toward a strictly monitored, prescription-based medical model for cannabis biomass while maintaining a distinct, permissible framework for hemp-derived cosmetics [27]. Domestic manufacturers are permitted to utilize CBD and hemp extracts under the condition that THC concentrations do not exceed 0.2% by weight [26,27]. However, these formulations are classified as high-risk cosmetics that mandate formal registration with the Thai Food and Drug Administration (FDA), and the commercial importation of finished cosmetics containing these ingredients remains prohibited.

Despite its promising biological activities, the clinical use of CBD is constrained by an unfavorable physicochemical profile [28]. It is highly lipophilic with poor aqueous solubility (approximately 0.1 µg/mL), which limits its skin permeability and results in a low baseline bioavailability of around 6% [29,30]. Furthermore, CBD is highly unstable, degrading readily when exposed to light, elevated temperature, and atmospheric oxygen [31]. Light exposure markedly accelerates active compound loss during storage [32,33], while thermal stress promotes degradation, particularly in oil-based vehicles under accelerated storage conditions [34]. It is likewise highly vulnerable to oxidative degradation [35]. Because these combined properties complicate the development of stable topical vehicles, advanced formulation strategies are essential to protect the molecule. To address these limitations, nanocarrier systems have emerged as a promising approach to simultaneously enhance the physicochemical stability, aqueous solubility, and cutaneous bioavailability of CBD [36].

Nanogels are nanoscale, crosslinked polymer networks capable of retaining high amounts of water while maintaining structural and colloidal stability. Their amphiphilic nature allows for the simultaneous encapsulation of both hydrophilic and hydrophobic compounds, facilitating controlled release, enhanced skin penetration, and prolonged cutaneous hydration [37–39]. By reducing particle size and drastically increasing the surface-area-to-volume ratio, these nanotechnology-based platforms significantly improve the apparent solubility and bioavailability of poorly water-soluble molecules [40–42]. While other nanocarriers like liposomes, solid lipid nanoparticles, and nanoemulsions are available, nanogels offer superior colloidal stability, tunable swelling behavior, and higher hydration capacities [43]. Furthermore, their key physicochemical attributes, such as matrix porosity, surface charge, and stimuli-responsiveness, can be tailored through custom polymer selection and synthesis methods [42,44–46].

Hyaluronic acid-graft poly(N-isopropylacrylamide) (HA-pNIPAM) is a thermo-responsive amphiphilic copolymer that has successfully enhanced the aqueous solubility and bioactivity of lipophilic phytochemicals, such as curcumin and asiatic acid [47,48]. Mechanistically, above its lower critical solution temperature (about 32 °C), the pNIPAM segments undergo a conformational collapse, self-assembling into hydrophobic core domains that solubilize and shield lipophilic molecules. Concurrently, the hydrophilic hyaluronic acid outer shell remains hydrated, conferring biocompatibility, hydration, and cellular uptake [47,49,50].

In a preliminary study applying this platform to CBD encapsulation, HA-pNIPAM nanogels significantly enhanced the aqueous solubility of CBD and markedly improved its stability during room-temperature storage [51]. Beyond these initial efficacy findings, previous *in vitro* and *in vivo* evaluations have confirmed the systemic safety of HA-pNIPAM carriers [47,48,51–54], and their safety profile for human topical application has been established by the patent holder [55]. Consequently, these dual-functional nanogels present a highly promising approach to overcome the intrinsic physicochemical limitations of CBD.

Building on these foundational encapsulation and stability findings, the present study evaluates the biological efficacy and clinical potential of the CBD-loaded HA-pNIPAM nanogel platform. Specifically, we investigated the *in vitro* biological properties of the CBD-nanogel formulation, including its anti-inflammatory and cellular activities. This was coupled with a preliminary clinical trial in human subjects with active inflammatory acne to assess short-term cutaneous tolerability, localized clinical responses, and the practical feasibility of this advanced nanogel vehicle for topical acne management.

2. Methods

2.1. Materials

Hyaluronic acid-graft-poly(N-isopropylacrylamide) (HA-pNIPAM) was obtained from Nabsolute Co., Ltd., Bangkok, Thailand. The ethanolic *Cannabis sativa* extract containing 3% *w/w* of CBD was sourced from Leapdelab Co., Ltd., Samut Prakan, Thailand. The final Hy-CBD gel formulation (containing 3% *w/w* Hy-CBD corresponding to 0.0003% *w/w* CBD with 0.0075% *w/w* of HA-pNIPAM) was developed according to a patent-pending process (Thailand Patent No. 2401008454) by the Faculty of Pharmaceutical Sciences, Chulalongkorn University, using Caprylic/Capric Triglyceride and Cetyl Phosphate as emollients, Ammonium Acryloyldimethyltaurate/VP Copolymer as the gelling agent, and pentylene glycol as the preservative system.

2.2. In Vitro Biological Activity Testing

2.2.1. Anti-Inflammatory Activity

RAW 264.7 macrophages were used as an inflammatory cell model, with lipopolysaccharide (LPS) serving as the inflammatory inducer and nitric oxide (NO) as the inflammatory biomarker. Cells were seeded at a density of 40,000 cells/well in a 24-well plate and incubated for 24 h prior to treatment with LPS (1 µg/mL), LPS combined with CBD (2.5 µg/mL), or LPS combined with CBD (2.5 µg/mL) loaded in 0.003–0.005% *w/v* HA-pNIPAM nanogels for 24 h. NO production was determined using the Griess assay by mixing the culture supernatant with Griess reagent and measuring absorbance at 540 nm using a CLARIOstar Plus microplate reader (CLARIOstar, BMG Labtech, Ortenberg, Germany).

2.2.2. Anti-Oxidation Activity

The antioxidant activities of CBD-loaded HA-pNIPAM nanogels were determined using a DCFH-DA-based assay. Briefly, HaCaT keratinocyte cells were seeded into a black 96-well microplate with a clear bottom at a density of 20,000 cells/well and cultured for 24 h prior to treatment. Cells were then treated with CBD (10 µg/mL) and 0.001% *w/v* HA-pNIPAM nanogels for 24 h. Following treatment, the cells were gently rinsed twice with PBS and stained in the dark with DCFH-DA solution (5 µM in serum-free MEM). After 30 min of staining, the cells were washed with PBS, and serum-free medium was added to each well. The cells were subsequently treated with 500 µM H₂O₂ in serum-free medium at 37 °C for 1 h. Finally, the cells were washed twice with PBS. The intracellular fluorescence signal was recorded using a CLARIOstar microplate reader (BMG Labtech, Ortenberg, Germany) (excitation wavelength: 485 nm; emission wavelength: 530 nm).

2.3. Clinical Study Design and Sample

The clinical evaluations were conducted by DermScan Asia Co., Ltd. (Bangkok, Thailand). The study was approved by the Specialty Independent Research Ethics Committee—SIREC (certificate number DA22A520 (5_2023), approved on 12 January 2023), and was carried out in accordance with the Declaration of Helsinki. Prior to participation, all subjects were informed about the study procedures and provided written informed consent. The study was retrospectively registered with the Thai Clinical Trials Registry (TCTR20250507005) on 7 May 2025.

Participants were selected based on the following inclusion criteria: healthy Asian males or females aged 18–45 years; Fitzpatrick skin type I to IV; presenting with inflammatory facial acne; and willing to comply with study procedures.

Exclusion criteria included: pregnancy, breastfeeding, or plans to become pregnant; active cutaneous conditions in the study area (e.g., eczema); allergies to cosmetic products; use of retinoids within the past six months; use of other acne medication within the past

month; changes in hormonal treatment (including contraceptives) within the previous three months; and use of topical or systemic treatments in the preceding weeks that may interfere with cutaneous response. Other exclusions were recent dermatologic procedures or surgery under general anesthesia in the past two months, high sun or UV exposure in the past month, or current participation in another clinical study.

2.4. Interventions

A total of 22 participants were enrolled and treated with Hy-CBD gel. Participants applied the formulation to affected acne areas twice daily (morning and evening) for seven consecutive days. To ensure complete coverage of varying lesion distributions, the gel was applied topically over active lesions rather than in a fixed mass per area; consequently, the absolute quantity applied was not standardized across subjects. For clinical evaluation, two inflammatory lesions of similar type and baseline type, size, and severity were selected per participant. These target lesions were longitudinally assessed by a single trained dermatologist at every visit (Day 0, Day 2, and Day 7).

2.5. Outcomes

2.5.1. Cutaneous Tolerance

A dermatologist assessed facial skin tolerance based on clinical signs, including erythema, edema, dryness, desquamation, and roughness. On Day 0, participants were asked about common skin sensations such as tightness, stinging, itching, and burning. Final acceptability was determined by comparing these indicators across visits.

2.5.2. Comedogenic Potential

To assess comedogenicity, lesion counts on the face were compared at Day 2 and Day 7 relative to baseline (Day 0). The dermatologist counted blackheads, microcysts, papules, and pustules (excluding the nasal pyramid, vermilion border, chin crease, and scalp rim). Changes in lesion numbers (Day 2–Day 0 and Day 7–Day 0) were analyzed descriptively.

2.5.3. Effect on Inflammatory Acne

Two similar inflammatory lesions were selected for each subject at baseline. On Day 0, 2, and 7, the dermatologist evaluated lesion size (measured with a vernier caliper), color, residual pigmentation, desquamation, and topography/depth.

2.5.4. Imaging Using the Visia® System

The VISIA® imaging system (Canfield Scientific, Parsippany, NJ, USA) was used to capture high-resolution facial images under white, UV, and polarized light. Image repositioning was standardized using an overlay display for accurate comparisons across timepoints.

2.5.5. Subjective Evaluation

On Day 2 and 7, participants completed a questionnaire to evaluate product characteristics, perceived efficacy, and willingness to continue use.

2.6. Calculation Formulas

Data are presented as raw values and descriptive statistics, including mean, median, standard error of the means (SEM), and 95% confidence intervals (CI 95%). The absolute variations (Δ) and percentage variations ($\Delta\%$) from baseline were calculated as follows:

$$\Delta = TZ_{ti} - TZ_{t0} \quad (1)$$

$$\Delta\% = \frac{TZ_{ti} - TZ_{t0}}{TZ_{t0}} \times 100 \quad (2)$$

where TZ refers to the measured value in the zone treated with the tested product, t_0 represents the baseline (before product use), and t_i represents the time point after product application.

2.7. Statistical Analysis

Background and demographic data were summarized using descriptive statistics. Data normality was assessed using the Shapiro–Wilk test ($\alpha = 0.01$). For non-normally distributed data, Friedman’s test was used, followed by the Wilcoxon signed-rank test for post hoc analysis. For normally distributed data, repeated measures one-way ANOVA and t -tests were applied. For cohort analysis, t -tests and one-way ANOVA followed by Tukey’s post hoc test were used for normal data, while the Mann–Whitney U or Kruskal–Wallis tests were used for non-normal data. Analyses were performed using Microsoft Excel for data handling, SPSS (version 21.0) for statistical testing, and GraphPad Prism 9 for graphing. A p -value < 0.05 was considered statistically significant.

3. Results

3.1. Biological Activities of CBD-Loaded HA-pNIPAM Nanogel

Figure 1a illustrates that CBD-loaded 0.003–0.005% w/v HA-pNIPAM nanogels reduced nitric oxide production to 6.72%, 8.88%, and 14.14%, respectively, in a concentration-dependent manner. In contrast, free CBD alone produced a slight reduction in nitric oxide levels of approximately 4%. These results suggest that encapsulation of CBD within the HA-pNIPAM nanogel enhanced its anti-inflammatory activity compared with free CBD. Results from the DCFH-DA assay in Figure 1b demonstrated that CBD in combination with HA-pNIPAM enhanced antioxidant activity by approximately 48%, exceeding the effect observed with free CBD alone. These findings suggest that incorporation of CBD into the HA-pNIPAM nanogel system can enhance the antioxidant activity of the active compound.

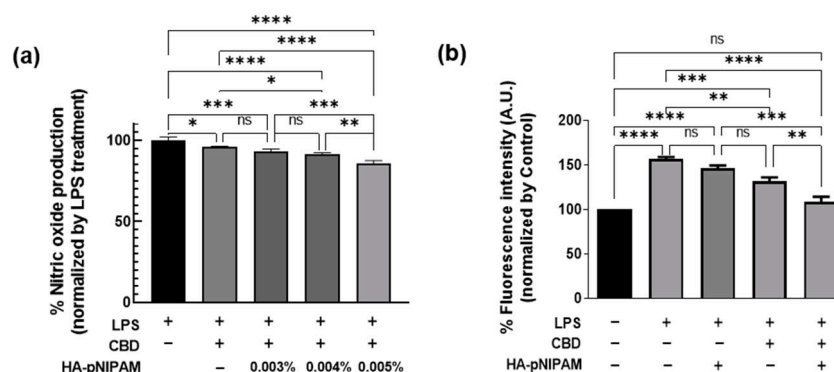


Figure 1. (a) Effect of CBD-loaded HA-pNIPAM against LPS-induced inflammation in RAW 264.7 cells. (b) Effect of CBD-loaded HA-pNIPAM against H_2O_2 -induced ROS generation in HaCaT keratinocyte cells. Data presented are mean $\pm$ SEM values of the three replications. ns indicates no significant difference; * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$, and **** $p < 0.0001$ indicate statistically significant differences between groups.

3.2. Exploratory Clinical Results

A total of 22 participants (18 females and 4 males), aged between 19 and 44 years (mean age: 26 ± 2 years), were enrolled in this study (Figure 2). Participant demographics are summarized in Table 1. All participants were of Asian descent with Fitzpatrick skin phototypes III to IV. The distribution of skin types was as follows: 59.1% greasy, 27.3% combination, and 13.6% dry skin. One participant missed the Day 2 follow-up visit, which was recorded as a minor protocol deviation.

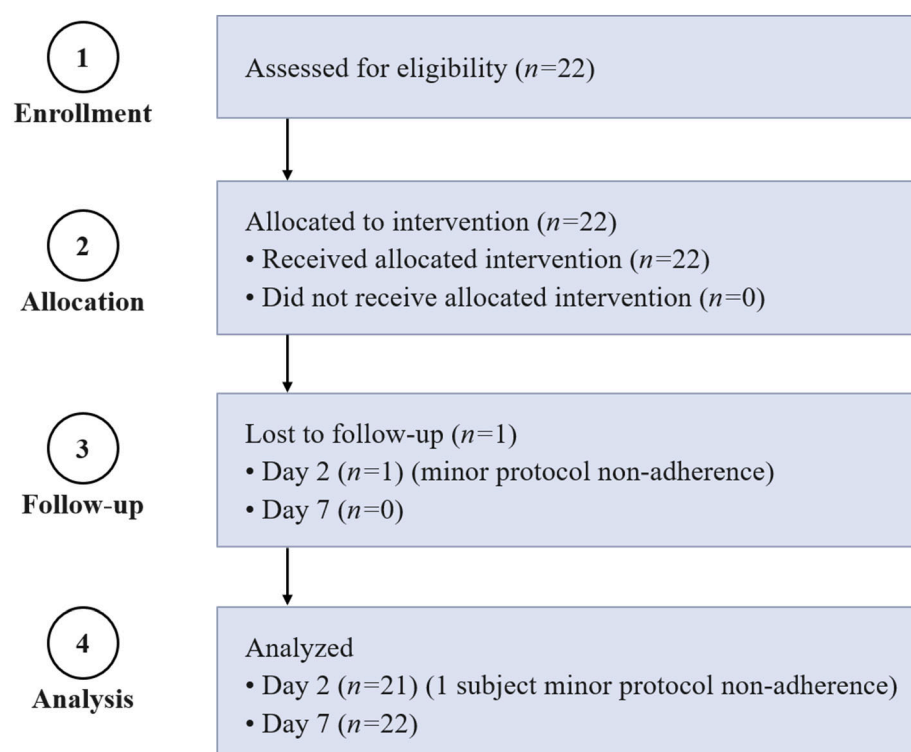


Figure 2. Flowchart of participant progression through the study using the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND).

Table 1. Demographic characteristics of study participants.

Variable	Subjects ($n = 22$)
Age, mean $\pm$ SD	26 $\pm$ 2
Sex	
Male, n (%)	4 (18.2)
Female, n (%)	18 (81.8)
Skin type	
Dry, n (%)	3 (13.6)
Combination, n (%)	6 (27.3)
Greasy, n (%)	13 (59.1)
Skin phototypes (Fitzpatrick skin type)	
Type III, n (%)	4 (18.2)
Type IV, n (%)	18 (81.8)

Cutaneous tolerance was assessed by a dermatologist through clinical examination. On Days 2 and 7 of product use, 95% of participants showed no clinical signs, while 5% showed no relevant signs. One participant reported very mild itching on Day 2, which was considered unrelated to the product. Overall, the findings from this short-term study suggest that the Hy-CBD gel demonstrated acceptable clinical tolerability.

Table 2 blackhead counts did not change, and fewer than one-third of participants showed variations in microcysts, papules, or pustules. By Day 7, no significant differences were observed in blackhead, microcyst, or papule counts. Changes in pustule counts were limited to fewer than one-third of participants. These observations suggest that the formulation did not cause retentional or inflammatory lesions, and the formulation did

not demonstrate evidence of comedogenicity or acneogenicity under the study conditions (Table 2).

Table 2. Changes in retentional and inflammatory lesions counts at Day 2 and Day 7 compared to baseline (Day 0).

Lesion Type	D0–D2 (Mean $\pm$ SEM)	D0–D7 (Mean $\pm$ SEM)
Blackheads	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Microcysts	−0.1 $\pm$ 0.2	0.2 $\pm$ 0.8
Papules	0.1 $\pm$ 0.1	−1.0 $\pm$ 0.8
Pustules	−0.05 $\pm$ 0.1	0.0 $\pm$ 0.2

Clinical efficacy was evaluated by measuring the size and characteristics of inflammatory acne lesions using a vernier caliper and clinical scoring scales. Two representative inflammatory lesions were selected per participant. The use of Hy-CBD gel for 2 and 7 days resulted in a visible and statistically significant reduction in lesion size (Table 3). For the first lesion, the average diameter decreased by 27% on Day 2 and by 46% on Day 7 ($p < 0.001$). For the second lesion, reductions of 23% and 42% were observed on the same days ($p < 0.001$). These findings provide preliminary evidence of a potential benefit of the product on inflammatory acne lesion size within a short treatment period.

Table 3. Changes in inflammatory lesion diameter compared to baseline (Day 0).

Lesion Number	Kinetics	Change in Lesion Diameter (Mean $\pm$ SEM)	Reduction (%)	Subjects Showing Reduction (%)	Statistical Significance
Lesion 1	Day 2–Day 0	−1.08 $\pm$ 0.16 *	−27%	100%	$p < 0.001$ (paired <i>t</i> -test)
	Day 7–Day 0	−1.70 $\pm$ 0.18 *	−46%	100%	
Lesion 2	Day 2–Day 0	−0.77 $\pm$ 0.16 **	−23%	86%	$p < 0.001$ (Wilcoxon test)
	Day 7–Day 0	−1.35 $\pm$ 0.14 **	−42%	100%	

* Significant difference from the initial measurement ($p < 0.001$) using a paired *t*-test. ** Significant difference from the initial measurement ($p < 0.001$) using the Wilcoxon signed-rank test.

Clinical evaluation of lesion characteristics, including color, residual pigmentation, desquamation, and topography/depth, showed significant improvements in most parameters (Table 4 and Figure 3). Color scores decreased significantly by Day 7, with reductions of 50% for Lesion 1 and 45% for Lesion 2 (both $p < 0.001$, Wilcoxon signed-rank test). Residual pigmentation followed a similar pattern, with reductions of 50% and 45%, respectively.

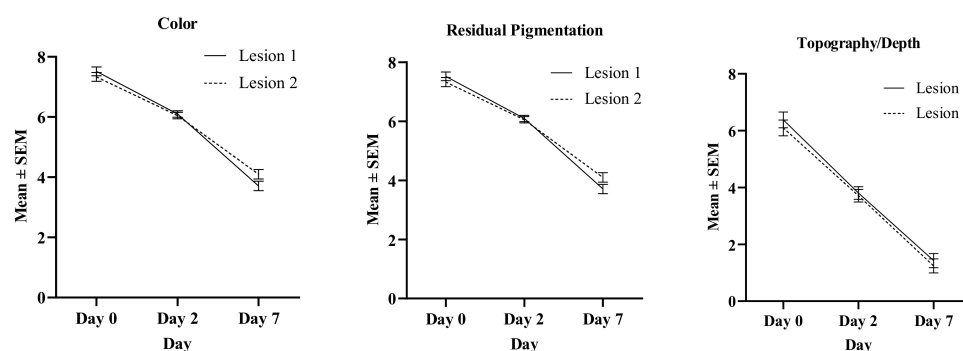


Figure 3. Mean clinical scores ($\pm$ SEM) for color, residual pigmentation, and topography/depth of inflammatory acne lesions at Day 0, Day 2 and Day 7. Color and Residual Pigmentation were recorded separately by a single dermatologist but were identical at all time points. These two reflected the same erythema-driven visual change and therefore should not be interpreted as independent outcomes.

Table 4. Clinical scores for color, residual pigmentation, desquamation/scaling and topography/depth at Day 0, Day 2, and Day 7.

Clinical Score	Inflammatory Lesion	Day	Variations in Clinical Scores (Mean $\pm$ SEM)	% of Cutaneous Variation % (Di-D0)	Statistical Significance
Color	Lesion 1	0	7.52 $\pm$ 0.15		$p < 0.001$ (Wilcoxon test)
		2	6.10 $\pm$ 0.11 *	−19%	
		7	3.71 $\pm$ 0.16 *	−50%	
	Lesion 2	0	7.33 $\pm$ 0.15		$p < 0.001$ (Wilcoxon test)
		2	6.05 $\pm$ 0.11 *	−17%	
		7	4.10 $\pm$ 0.16 *	−45%	
Residual Pigmentation	Lesion 1	0	7.52 $\pm$ 0.15		$p < 0.001$ (Wilcoxon test)
		2	6.10 $\pm$ 0.11 *	−19%	
		7	3.71 $\pm$ 0.16 *	−50%	
	Lesion 2	0	7.33 $\pm$ 0.15		$p < 0.001$ (Wilcoxon test)
		2	6.05 $\pm$ 0.11 *	−17%	
		7	4.10 $\pm$ 0.16 *	−45%	
Desquamation/Scaling	Lesion 1	0	0.43 $\pm$ 0.36		NA
		2	0.05 $\pm$ 0.08	NA	
		7	0.00 $\pm$ 0.03	NA	
	Lesion 2	0	0.38 $\pm$ 0.36		NA
		2	0.24 $\pm$ 0.08	NA	
		7	0.05 $\pm$ 0.03	NA	
Topography/Depth	Lesion 1	0	6.38 $\pm$ 0.28		$p < 0.001$ (Wilcoxon test)
		2	3.81 $\pm$ 0.22 *	−40%	
		7	1.43 $\pm$ 0.25 *	−77%	
	Lesion 2	0	6.10 $\pm$ 0.28		$p < 0.001$ (Wilcoxon test)
		2	3.71 $\pm$ 0.22 *	−39%	
		7	1.24 $\pm$ 0.25 *	−79%	

* Significant difference from baseline ($p < 0.001$) using the Wilcoxon signed-rank test. NA: Not Applicable; fewer than one-third of the panel presented a variation. Color and Residual Pigmentation were recorded separately by a single dermatologist but were identical at all time points. These two reflected the same erythema-driven visual change and therefore should not be interpreted as independent outcomes.

As presented in Table 4, the numerical scores reported for lesion color and residual pigmentation are identical across the evaluated time points. Because both parameters were assessed visually on the same target lesions by a single dermatologist using a subjective ordinal scoring scale, the assigned visual grades overlapped across the observation period (Day 0, Day 2, and Day 7). We acknowledge that subjective ordinal scoring has limited sensitivity to fully discriminate between these two closely related visual attributes. Because erythema was the predominant visible feature of the active inflammatory lesions during this short-term study, both parameters were graded concordantly. The raw data were provided as a non-editable file in Supplementary Figure S1. These outcomes are therefore retained for transparency but should be interpreted as reflecting the same underlying visual change rather than as independent measures. Consequently, future studies should incorporate objective instrumental measurements, such as colorimetry or narrow-band spectrophotometry, to independently resolve subtle changes in erythema and melanin content.

Desquamation and scaling showed minimal variation and the changes were not statistically significant, likely due to the low prevalence of these features among participants. In contrast, topography and depth improved significantly, with reductions of 77% for Lesion 1 and 79% for Lesion 2 by Day 7 (both $p < 0.001$). These results support the clinical efficacy of the Hy-CBD gel in improving the visual and structural features of inflammatory acne lesions over a short treatment period.

To investigate how sex, skin type, and skin phototype affected the clinical efficacy of the Hy-CBD acne gel, participants were grouped based on these characteristics. First, the impact of sex on the reduction in inflammatory lesion size was assessed. As shown in Figure 4a, no statistically significant difference was observed between male and female participants, suggesting that sex did not affect the outcomes. Subsequently, skin type (dry, combination, or greasy) was examined. While participants with greasy skin showed a trend toward a greater lesion size reduction (Figure 4b), this did not reach statistical significance. Finally, the effect of skin phototypes on lesion color and residual pigmentation was analyzed. A comparison of phototypes III and IV showed no statistically significant differences (Figure 4c).

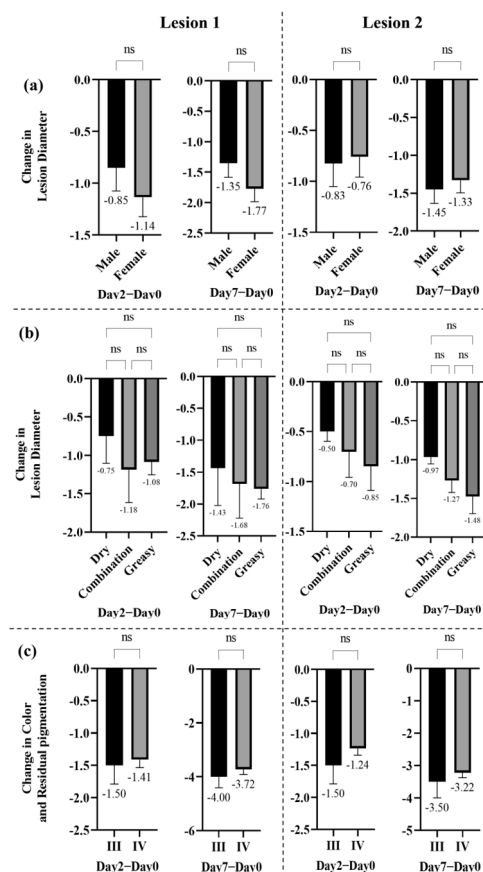


Figure 4. Subgroup analyses of the clinical efficacy of Hy-CBD gel at Day 2 and Day 7 compared to baseline. Effects of (a) sex and (b) skin type on the reduction in lesion diameter, and (c) skin phototype on changes in lesion color and residual pigmentation. Data presented are mean $\pm$ SEM values of the three replications. ns indicates no significant differences between groups.

Figure 5 shows VISIA[®] images of inflammatory acne progression in a representative participant from baseline (Day 0) through Day 2 and Day 7. At baseline, the lesion showed marked redness, swelling, and elevation. After 2 days of treatment, noticeable improvements included reduced size, redness, and swelling. By Day 7, the lesion had nearly flattened with minimal redness and no swelling. These results show the gel's effectiveness in improving inflammatory acne within a short treatment period.

In the subjective evaluation, all participants (100%) rated the Hy-CBD gel positively for its appearance, texture, and the absence of skin staining. A total of 91% reported a non-sticky finish and quick absorption. All participants (100%) reported reductions in both the number and severity of acne lesions, starting on Day 2 and continuing through Day 7.

Reduced redness (erythema) was reported in 95% of participants by Day 2 and in 100% by Day 7.

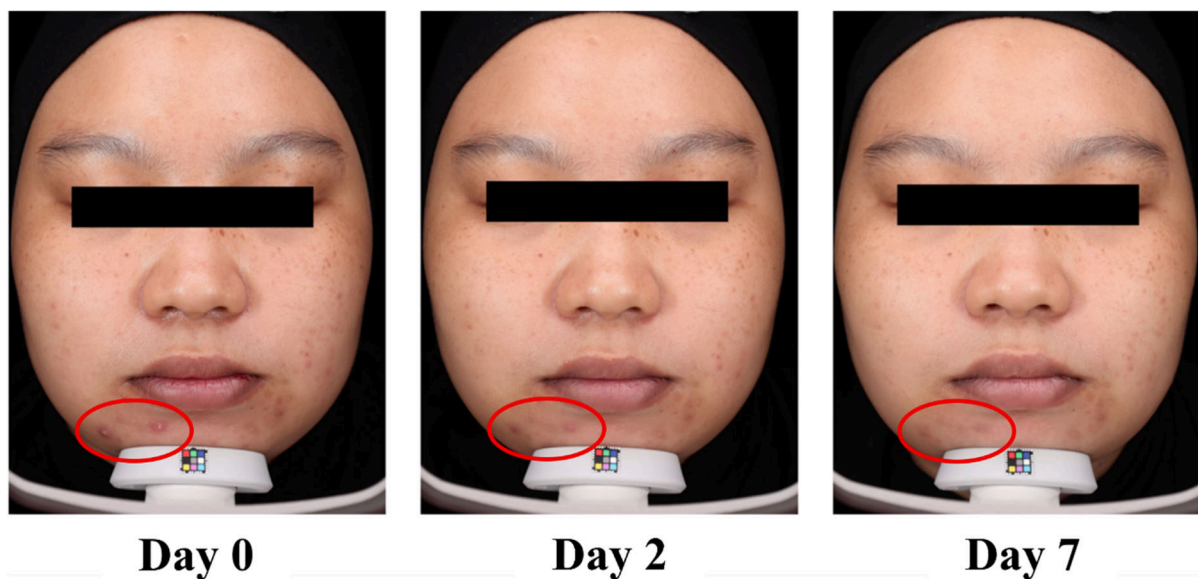


Figure 5. Representative VISIA[®] photographic images showing lesion improvement at Day 0, Day 2, and Day 7 following treatment with the Hy-CBD gel.

4. Discussion

Topical treatments are essential for managing mild-to-moderate acne, while severe cases often require a combination of systemic and topical therapies. However, conventional topical agents can cause side effects such as dryness, redness, peeling, and itching, which often lead to patient discomfort and reduced compliance [56]. A primary goal in topical acne treatment is to achieve an optimal balance between therapeutic efficacy and patient tolerability. Therefore, recent research has focused on developing vehicle formulations that can improve drug delivery while minimizing local irritation [57].

Physicochemical characterization confirmed that Hy-CBD exhibits superior properties compared to free CBD, consistent with findings by May et al. [51]. An encapsulation efficiency of $87.57 \pm 3.72\%$ was achieved at $0.25\% w/w$ HA-pNIPAM, yielding a loading capacity of $1117.42 \pm 47.73\%$ and a drug content of $100.54 \pm 0.58\%$ (Supplementary Figure S2). Nanoparticle tracking analysis and transmission electron microscopy revealed discrete spherical particles with a mean size of 258.9 ± 104.2 nm. Temperature-dependent shifts in size and polydispersity aligned with the characteristic pNIPAM thermal transition, which drove significantly higher CBD release at 37°C than at 25°C .

Incorporation of phytochemicals into the HA-pNIPAM nanogel significantly enhanced entrapment efficiency and formulation stability during storage, consistent with previous reports [48,54]. In addition, the Hy-CBD formulation retained the intrinsic biological activities of CBD, including anti-inflammatory and antioxidant effects, while further enhancing these biological responses. This improvement may be associated with enhanced cellular uptake facilitated by the nanogel delivery system, as previously observed in studies investigating the antiproliferative activity of curcumin-loaded HA-pNIPAM nanogels [47].

Preliminary screening also confirmed that encapsulation preserved the antimicrobial efficacy of CBD against *Staphylococcus aureus*, a clinically relevant opportunistic skin pathogen [58] (Supplementary Figure S3). Although *Cutibacterium acnes* is the primary organism implicated in acne pathogenesis, it was not evaluated in this study due to limited availability in our current testing facility. Based on these favorable in vitro results, only

the optimized Hy-CBD formulation was advanced to the clinical phase. Free CBD and empty HA-pNIPAM polymer arms were excluded from the human evaluation because the individual baseline properties, safety profiles, and therapeutic limitations of these separate components have already been well-established in previous literature [24,55]. Consequently, these laboratory findings provided the necessary mechanistic rationale to transition the formulation into a preliminary human trial.

This preliminary clinical study indicated favorable short-term skin tolerability for the Hy-CBD nanogel, with no clinical incidents observed by the dermatologist on Day 2 or Day 7. One participant reported mild symptoms after two days of use; however, the physician did not consider these to be related to the product. Because this evaluation was limited to a 7-day period, long-term cutaneous safety and cumulative toxicity cannot be determined from these data alone. Nevertheless, these short-term findings help minimize initial concerns regarding localized irritation often associated with topical nanocarriers.

In terms of clinical response, significant reductions in lesion size, erythema, residual pigmentation, and acne depth were observed within the 2-to-7-day window ($p < 0.001$). Subjective self-evaluations supported these results, with 95% of participants reporting a noticeable decrease in localized inflammation.

To put these preliminary outcomes into context, our results can be compared with BTX 1503, one of the most clinically advanced topical CBD formulations evaluated to date [59,60]. In a large-scale, 12-week Phase II trial, BTX 1503 demonstrated acceptable safety but missed its primary efficacy endpoint for inflammatory lesions due to a high vehicle response. The key clinical and structural differences between BTX 1503 and our Hy-CBD formulation are summarized in Table 5.

Table 5. Comparison of Clinical and Formulation Profiles between BTX 1503 and Hy-CBD.

Feature/Outcome	BTX 1503 Formulation [59,60]	Hy-CBD Nanogel (Present Study)
Vehicle or delivery system	Solution (Conventional vehicle)	Thermo-responsive HA-pNIPAM Nanogel
Study Design & Scale	Phase II, Randomized, Double-blind, Vehicle-controlled ($n = 368$; 276 active, 92 vehicle)	Preliminary, Open-label, Non-randomized ($n = 22$)
Evaluation Period	12 weeks (Long-term safety/efficacy)	7 days (Acute tolerability/initial response)
Primary Clinical Findings	Acceptable tolerability; missed primary endpoint for inflammatory lesions due to high vehicle effect.	Favorable acute tolerability; rapid reduction in lesion size and erythema ($p < 0.001$).
Delivery System Characteristics	Bound by conventional CBD lipophilicity and variable skin penetration.	Enhanced aqueous solubility and thermo-responsive sustained-release properties.

The differences in outcomes shown in Table 5 may be explained by distinct delivery characteristics. Conventional vehicles often struggle with CBD's high lipophilicity and poor aqueous solubility, leading to variable skin penetration. In contrast, the HA-pNIPAM nanogel system was designed to bypass these limitations through enhanced solubilization and sustained-release properties, which likely contributed to improved cutaneous delivery.

Nevertheless, our findings must be interpreted with strict caution. Because of the open-label, non-randomized design and the lack of a vehicle-control arm, these 7-day results represent a preliminary proof-of-concept. Further randomized, double-blind, vehicle-controlled trials over an extended duration and in larger cohorts are mandatory to validate these observations and establish true clinical efficacy.

Subgroup analyses provide preliminary evidence that the acute response to the Hy-CBD gel remained consistent across diverse patient characteristics, including sex, skin type, and Fitzpatrick phototype. Although hormonal factors substantially contribute to acne pathogenesis [61], comparable reductions in lesion size were observed in both male and female participants, suggesting a broad mechanism of action. The trend toward greater lesion-size reduction in participants with oily or combination skin is noteworthy and aligns with the documented sebostatic properties of CBD [62]. Additionally, participants with phototype III showed a slight tendency toward greater improvements in lesion color and pigmentation compared to phototype IV.

Because these subgroup trends did not reach statistical significance, they must not be over-interpreted; the small sample size and short 7-day duration prevent any definitive conclusions regarding long-term demographic or phenotypic advantages. However, they indicate that the formulation's potential benefits, such as modulating post-inflammatory pigmentation, warrant deeper investigation. Future, adequately powered trials with extended observation periods and objective colorimetric analyses are necessary to confirm these specific clinical responses.

The initial clinical improvements observed in this study likely reflect the underlying biological activity of CBD at the cellular level. Several anti-inflammatory mechanisms of CBD have been proposed, though the exact pathways are not yet fully understood. The endocannabinoid system (ECS), involving G protein-coupled receptors such as CB₁ and CB₂, is the primary system through which phytocannabinoids work [63]. In the skin, CB₁ receptors are mostly found in keratinocytes of the stratum spinosum and stratum granulosum, while CB₂ receptors are found in the stratum basale. Both CB₁ and CB₂ receptors are found in epidermal nerve fibers and in immune cells such as lymphocytes, natural killer cells, mast cells, and macrophages [64]. While CBD has low affinity for CB₁ and CB₂ receptors, it can modulate their activity at low concentrations [65,66]. CBD also acts as a CB₂ inverse agonist, potentially reducing immune cell migration and lowering inflammatory responses.

Beyond the classical ECS, CBD interacts with other molecular targets, including GPR55, PPAR- γ , and TRPVs [67]. It has been shown to inhibit the adenylyl cyclase-cAMP pathway associated with TRPV1 signaling [68]. By modulating calcium influx through TRPV channels, CBD can suppress the release of pro-inflammatory cytokines [69]. As a PPAR- γ agonist, CBD inhibits NF- κ B-mediated transcription, which downregulates inflammatory mediators such as TNF- α , IL-1 β , IL-6, and cyclooxygenases [70]. Furthermore, CBD acts as a GPR55 antagonist, promoting IL-10 release and exerting an anti-inflammatory effect [71,72].

Sebum secretion is a key factor in acne severity [73]. Combined with abnormal desquamation, a process known as hyperkeratinization leads to microcomedones, which can develop into visible acne lesions [74]. Comedogenesis refers to the formation of comedones due to follicular blockage, while acneogenesis involves inflammatory changes (folliculitis) [75]. In-use clinical studies are considered the gold standard for evaluating these effects due to their high sensitivity [76]. In our evaluation, no significant increase in either retentional or inflammatory lesions was observed. These results suggest that the formulation is unlikely to be comedogenic or acneogenic. Since acne-prone skin is particularly reactive, testing comedogenic potential of the final formulation provides valuable insights for clinicians and patients [77].

Although the final CBD concentration (0.0003% *w/w*) was low on a mass basis, it corresponded to approximately 9.5 μ M, which falls within the concentration range previously reported to exert biological activity on sebocytes and keratinocytes in vitro [78,79]. While clinical evidence at this concentration remains unavailable, a study by Oláh et al. using a full-thickness human skin organ culture (hSOC) model demonstrated that exposure to

CBD at 10 μ M over 6 days was able to reduce lipogenesis [23]. The effects observed in the present study may therefore be associated with enhanced delivery by the HA-pNIPAM nanogel system despite the low CBD concentration. Nevertheless, due to the absence of vehicle and free-CBD control groups and the lack of cutaneous pharmacokinetic data, the observed clinical improvements cannot be attributed solely to CBD and may also reflect contributions from the nanogel vehicle or the natural resolution of lesions. Accordingly, these findings should be considered preliminary and hypothesis-generating.

The expanding application of nanotechnology in topical therapeutics offers new opportunities to optimize the delivery and clinical performance of lipophilic compounds like CBD. However, because nanocarriers can alter skin penetration dynamics, cellular interactions, and local immune responses, rigorous safety assessments remain mandatory [29]. In this study, the Hy-CBD nanogel showed encouraging short-term tolerability, with no clinically significant irritation or acneogenic exacerbations observed over the 7-day evaluation period. When considered alongside the observed reductions in inflammatory lesion characteristics, these initial findings suggest that HA-based nanogels may serve as a promising, adaptable platform for topical cannabinoid therapy. Nevertheless, larger, randomized clinical trials with extended observation windows are essential to validate these findings and fully characterize the long-term safety and therapeutic efficacy of this delivery system in acne and other inflammatory dermatoses.

Limitation

Several limitations must be considered when interpreting the findings. First, the absence of a vehicle, placebo, or untreated control groups limits the ability to establish a definitive causal relationship between the formulation and the observed clinical improvements, as spontaneous lesion resolution or baseline skincare practices may have contributed. Future studies should employ randomized, vehicle-controlled, double-blinded designs. Second, the small sample size restricted statistical power and limits the generalizability of these findings to broader acne populations. Larger and more diverse cohorts are therefore needed to strengthen the external validity of these observations.

Third, while the 7-day treatment period is standard for evaluating acute cosmetic tolerability, it is entirely insufficient to determine sustained efficacy or long-term safety, particularly regarding cumulative exposure to the nanogel vehicle itself. Extended treatment and follow-up periods are mandatory in future trials. Finally, Hy-CBD nanogel was evaluated without a direct head-to-head comparison against free CBD or the empty HA-pNIPAM nanogel, preventing an exact quantification of how much the carrier system itself contributed to the clinical response. Future investigations should incorporate free CBD and blank nanogel comparator arms alongside standard treatments to better define the therapeutic advantages of this delivery platform. Despite these limitations, this study provides valuable preliminary evidence supporting the feasibility and acute tolerability of the formulation, establishing a clear foundation for future randomized controlled trials.

5. Conclusions

This study demonstrated the successful development of a CBD-loaded HA-pNIPAM nanogel formulation with enhanced biological properties compared with free CBD. Encapsulation within the HA-pNIPAM nanogel enhanced the biological efficacy of CBD, supporting its potential for further therapeutic application. In the preliminary clinical study, the Hy-CBD formulation exhibited acceptable cutaneous tolerability and was associated with a reduction in inflammatory acne lesions over a short treatment period. As conventional acne therapies are often associated with undesirable side effects, phytochemical-based alternatives with favorable safety profiles, such as CBD, may represent a valuable therapeutic

option either as a first-line treatment or as an adjunct to standard therapies. Importantly, this study evaluated CBD in its final formulation, providing clinically relevant insight into the efficacy and safety profile under practical conditions of use. The Hy-CBD gel demonstrated no observable comedogenic or acneogenic effects under the study conditions, with participants reporting satisfactory treatment outcomes. Collectively, these findings support the potential of the Hy-CBD gel as a safe and well-tolerated topical formulation for the management of inflammatory acne. Furthermore, the HA-pNIPAM nanogel system may represent a promising delivery platform for other phytochemical-based topical formulations. Nevertheless, larger-scale studies with longer follow-up periods are required to further confirm these preliminary findings and establish long-term clinical efficacy and safety of the formulation.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cosmetics13040165/s1>, Figure S1: Raw clinical evaluation scores for inflammatory acne lesions 1 and 2; Figure S2: Physicochemical properties of the CBD-loaded HA-pNIPAM nanogel; Figure S3: Antimicrobial activity of free CBD-loaded HA-pNIPAM nanogel against *Staphylococcus aureus* by disk diffusion assay.

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Informed Consent Statement: All participants provided written informed consent prior to participation.

Data Availability Statement: The corresponding authors will provide the datasets used and/or analyzed during the present work upon reasonable request.

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Conflicts of Interest: JL was a co-founder and chief technology officer (CTO) of Nabsolute Co., Ltd., while VB was the chief compliance officer (CCO). In addition, PK, KL, and KS were employed by Nabsolute Co., Ltd., and SV is the chief executive officer (CEO) of Leapdelab. These affiliations are disclosed to ensure transparency regarding potential conflicts of interest. The other authors declare no financial or personal relationships that influenced the results or interpretation of this study.

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