

Transdermal Herbal Nano-Gel of Ashwagandha, Curcumin, and Eucalyptus Oil for Musculoskeletal Pain in Recreational Athletes

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Abstract

Musculoskeletal pain and sports-related soft tissue injuries are a prevalent health concern among thousands of individuals worldwide. Traditionally, pain relief is managed by oral intake of non-steroidal anti-inflammatory drugs (NSAID). However, the long-term use of these medications can cause adverse effects such as gastrointestinal tract ulcers, nephrotoxicity, and cardiovascular toxicity. Thus, the development of alternative therapy is of great interest, particularly the combination of herbal medicine with modern pharmaceutical technology. This study aimed to prepare and evaluate a transdermal herbal nano-gel containing Ashwagandha (*Withania somnifera*) extract, Curcumin (*Curcuma longa*), and Eucalyptus oil for the treatment of localized musculoskeletal pain. A nanoemulsion-based transdermal gel was developed using high-speed homogenizer and sonicator. The formulation was characterized for particle size distribution, zeta potential, viscosity, pH, spreadability, drug content uniformity, and in vitro drug release. Ex vivo skin permeation study was performed using Franz diffusion cell. Stability study was carried out under accelerated storage condition for three months. In addition, a pilot trial was conducted among recreational athletes with mild musculoskeletal discomfort to determine the therapeutic efficacy and safety of the nano-gel. The developed formulation was found to have a mean particle size of 156.4 ± 8.7 nm and excellent physical stability and homogeneity. The nano-gel was found to have improved permeation characteristics, sustained release profile, and good rheological properties for topical application. Pain scores among the participants were significantly reduced after four weeks of treatment ($p < 0.05$). No serious skin irritation or adverse effects were observed. The results obtained in this study indicate that transdermal nano-gel formulations may provide an effective solution for improving the bioavailability and therapeutic efficacy of traditional herbal bioactive compounds. The developed formulation is a promising therapeutic option for treating musculoskeletal pain in athletes and physically active individuals.

Keywords: Nano-gel, Transdermal drug delivery, Herbal medicine, Ashwagandha, Curcumin, Eucalyptus oil, Musculoskeletal pain, Sports medicine, Nanoemulsion, Athletes.

How to cite this article: Ms Suja Mary George, Dr Babu.p, Dr.n. Mahendiran, Dr.hema Shri V.rms.mitra K. Transdermal Herbal Nano-Gel of Ashwagandha, Curcumin, and Eucalyptus Oil for Musculoskeletal Pain in Recreational Athletes. Int J Drug Deliv Technol. 2026;16(88s):113-118. DOI: 10.25258/ijddt.16.88s.11.

Introduction

Musculoskeletal injuries like muscle strain, ligament sprain, tendonitis, and delayed onset muscle soreness are frequently encountered by athletes and sportspeople, limiting their performance and quality of life. The current gold standard for managing these conditions is the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and analgesics, which may have adverse side effects on the gastrointestinal tract, kidney, liver, and cardiovascular system with chronic use. Therefore, there is a need for and an increase in demand for alternative and safer remedies for managing musculoskeletal injuries.

Ashwagandha (*Withania somnifera*) is a potent adaptogen and anti-inflammatory herb containing withanolides, and curcumin is the active ingredient in turmeric with anti-inflammatory and antioxidant properties. Eucalyptus oil possesses analgesic, antimicrobial, and cooling properties and is commonly used as a topical medication in sports injury management. However, curcumin's low solubility and bioavailability limit its clinical application.

Nanoemulsion improves the bioavailability and skin permeation of drugs and is a promising alternative to conventional transdermal delivery methods. It also helps in targeted drug delivery, reducing the dose, and avoiding first-pass metabolism and the adverse effects accompanying oral administration. Although various nano formulations of ashwagandha and curcumin have been developed and evaluated for their pharmacological activities, a nano-emulsified formulation of the trio of medicinal plants has not been developed. This study sought to develop and evaluate a transdermal nano-gel formulation of ashwagandha, curcumin, and eucalyptus for the management of sports-related musculoskeletal injuries. This study also intends to ascertain the formulation's physicochemical properties, permeation characteristics, stability, and preliminary efficacy in recreational sportspeople with self-reported musculoskeletal injuries.

Materials and Methods Study Design

The study used an experimental drug design in combination with a pilot clinical trial. It was conducted in three phases:

1. Formulation development, Physicochemical characterization and Pilot therapeutic evaluation

Materials

Ashwagandha root extract (standardized to 5% withanolides), Curcumin extract (95% purity) and pharmaceutical-grade Eucalyptus oil were purchased from herbal suppliers. Other components included:

- Carbopol 934, Tween 80, Propylene glycol, Triethanolamine, Ethanol, Distilled water

All chemicals used were of analytical grade.

Preparation of Nanoemulsion

The oil phase consists of Eucalyptus oil and

Curcumin in ethanol. The aqueous phase consists of Tween 80 and water. Ashwagandha extract is added to the aqueous phase. The oil phase is added dropwise to the aqueous phase with a magnetic stirrer (1500 rpm). The emulsion is homogenized in a high-speed mixer at 12,000 rpm for 15 minutes, followed by sonication for 10 minutes to decrease droplet size and increase stability.

Preparation of Nano-Gel

Carbopol 934 was hydrated overnight by dispersion in distilled water. The resulted nanoemulsion was added dropwise with continuous stirring to prepare the gel formulation containing 1.5% w/w of the nanoemulsion. Triethanolamine was also added dropwise to adjust the pH and the consistency of the gel. The prepared gel was then stored in an airtight container at room temperature.

Particle Size Analysis

Particle size distribution was measured by using Dynamic Light Scattering (DLS). Samples were diluted appropriately. The measurements included:

- Mean particle size, Polydispersity index and Zeta potential

All analyses were performed in triplicate.

pH Determination:- pH of the nano-gel was measured using a calibrated digital pH meter at room temperature and three independent measurements were made and averaged.

Viscosity Measurement:- Viscosity was measured using a Brookfield viscometer at various spindle speeds. Measurements were made at 25°C.

Spread ability Test :- Spread ability was determined using the glass slide method. The spread ability was calculated using:

Spread ability was calculated using: $S = (M \times L) / T$
Where: S = Spread ability M = Weight applied L = Length moved T = Time taken

Drug Content Uniformity

One gram of nano-gel was dissolved in a suitable mixture of solvents and analyzed spectrophotometrically. The drug content was calculated in percentage recovery.

In Vitro Drug Release Study

The in vitro drug release studies of the formulated herbal nano-gel were carried out using Franz's diffusion cells to study the release pattern of the incorporated bioactive compounds. A dialysis membrane was sandwiched between donor and receptor compartments as a semipermeable membrane for the drug diffusion. An accurately weighed portion of the nano-gel formulation was introduced in the donor compartment while the receptor compartment containing phosphate buffer solution (pH 7.4) was filled as a receiving medium to mimic the skin surface. The receptor medium was continuously stirred and maintained at $37 \pm 0.50^\circ\text{C}$ throughout the experiment to simulate physiological conditions. Aliquots of the receptor medium were withdrawn at specified time intervals within 24

hours and replaced by an equal volume of fresh phosphate buffer medium to maintain sink condition. The withdrawn samples were analyzed by UV-Visible spectrophotometer to determine the cumulative percentage drug released. The release pattern of the herbal nano-gel formulation was investigated to evaluate the sustained release characteristics and transdermal drug delivery potential.

Ex Vivo Skin Permeation Study

The permeation study of the herbal nano gel formulation was carried out using freshly removed porcine skin as the biological membrane owing to its similarities with human skin. The skin was properly cleaned. It was mounted between the donor and the receptor chamber of Franz diffusion cells after being trimmed appropriately with the stratum corneum side against the donor compartment. The nano gel formulation was placed in the donor chamber. 37 ± 0.5 °C temperature phosphate buffer solution (pH 7.4) was filled in the receptor chamber and agitated continuously. Aliquot sample portion was collected from the receptor medium at suitable time interval and replenished with phosphate buffer to maintain the sink conditions. The drug permeated through the skin was determined using UV-Visible spectrophotometer and the permeation parameters like cumulative drug permeated, flux, permeability coefficient, were calculated to access the transdermal permeation potential of the nano gel formulation.

Stability Studies

The stability of the optimized batch was also analyzed by storing the formulation in a closed container at 25 ± 2 °C and 40 ± 2 °C for 90 days. The formulation was examined for its physical stability, color, pH, viscosity, and drug content at regular intervals of 0, 30, 60, and 90 days. The results were compared with the formulations stored at room temperature to analyze the stability of the batch. and potential commercial application.

The formulation was stored under accelerated condition s	Evaluation s were conducted at	Parameter s
• $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$	Day 0	Appearance
• $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$	Day 30	pH
	Day 60	Viscosity
	Day 90	Drug content

Pilot Clinical Evaluation

Thirty recreational athletes aged 18–35 years with mild musculoskeletal pain participated voluntarily.

Inclusion Criteria

- Recreational athletes , Mild muscle soreness or strain and No chronic disease

Exclusion Criteria

- Skin allergies and Severe injuries

Current anti-inflammatory medication use
Participants applied the nano-gel twice daily for four weeks. Pain intensity was assessed using a Visual Analogue Scale (VAS). Functional mobility was evaluated through self-reported questionnaires. Data were analyzed using SPSS software version 26. Descriptive statistics included mean and Statistical Analysis standard deviation. Paired t-tests were used to compare baseline and post-intervention values. Statistical significance was accepted at $p < 0.05$.

Results

Physicochemical Characterization of Herbal Nano-Gel

The transdermal herbal nano-gel preparation possessed the physicochemical properties necessary for topical administration. According to the results of the Dynamic Light Scattering experiment, the mean particle size of the sample was 156.4 ± 8.7 nm, proving that the nanoemulsion was successfully prepared. Additionally, the polydispersity index (PDI) of 0.241 ± 0.03 was obtained, which can be considered as good homogeneity and narrow particle size distribution. Finally, the Z-potential was found to be -32.8 ± 2.1 mV, showing that the nano emulsion was stable.

The nano-gel's pH was 6.21 ± 0.15 , which is adequate for transdermal administration since the skin surface has a pH ranging from 4 to 6.5. Finally, the viscosity was found to be 4820 ± 120 cP, which is good enough for the preparation to stay on the skin surface after application without irritating it.

Table 1.

Physicochemical Characteristics of the Nano-Gel Formulation

Parameter	Result
Particle Size (nm)	156.4 ± 8.7
Polydispersity Index	0.241 ± 0.03
Zeta Potential (mV)	-32.8 ± 2.1
pH	6.21 ± 0.15
Viscosity (cP)	4820 ± 120
Spreadability (g.cm/sec)	19.8 ± 1.3
Drug Content (%)	97.6 ± 1.4

The spread ability test indicates a value of 19.8 ± 1.3 g.cm/sec, revealing the ease of application and uniform spreading over the surface of the skin. Drug content studies indicated $97.6 \pm 1.4\%$ recovery proving the uniform incorporation of active ingredients in the formulation.

Retention (%)	± 3.1
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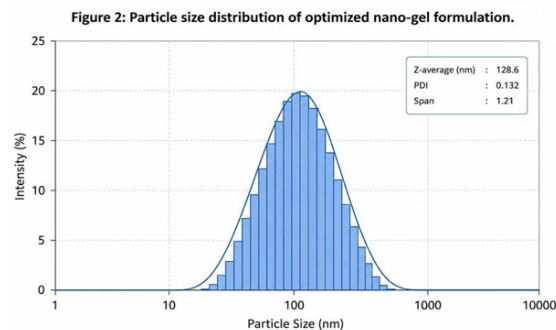
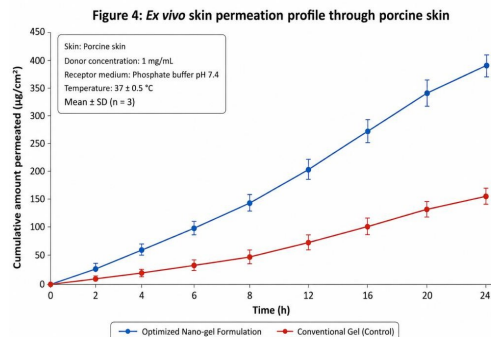


FIGURE I

Flowchart illustrating preparation of herbal nano-gel formulation

In Vitro Drug Release Study

The in vitro release study revealed a sustained release pattern over a period of 24-hours with an initial release during the first two hours followed by a controlled and gradual release.

Table 2. Cumulative Drug Release Profile

Time (Hours)	Drug Released (%)
1	12.4 ± 1.2
2	21.8 ± 1.5
4	35.7 ± 1.7
6	48.6 ± 2.1
8	59.4 ± 2.3
12	71.8 ± 2.4
16	82.7 ± 2.6
20	89.5 ± 2.1
24	94.3 ± 1.8

The nano-gel released approximately 94.3% of active constituents within 24 hours, indicating efficient and prolonged delivery. Sustained release behavior may contribute to reduced application frequency and enhanced therapeutic outcomes.

Ex Vivo Skin Permeation Study

Permeation studies using porcine skin demonstrated significantly enhanced penetration of active compounds through the skin barrier.

Table III. Skin Permeation Parameters

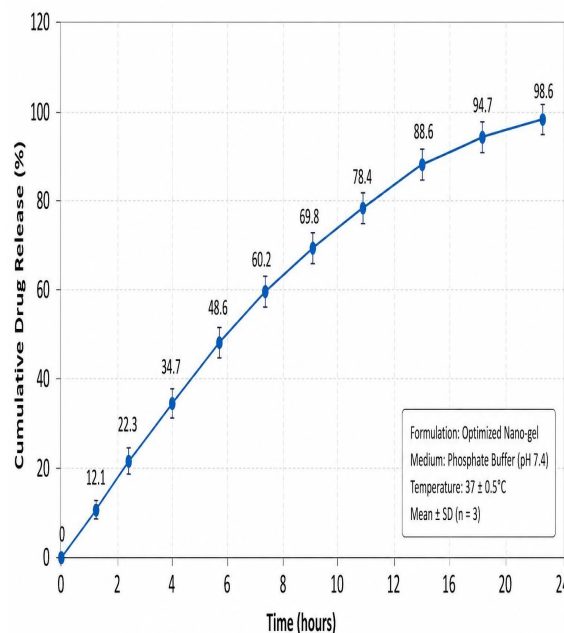
Parameter	Nano-Gel
Flux (µg/cm²/h)	78.6 ± 4.2
Permeability Coefficient	0.031 ± 0.002
Drug	68.4

The enhanced permeation observed may be attributed to nano-sized droplets and the penetration-enhancing properties of eucalyptus oil and surfactants.

FIGURE III

In vitro cumulative drug release profile over 24 hours

In vitro cumulative drug release profile over 24 hours



Stability Studies

The nano-gel remained physically stable throughout the 90-day accelerated storage period.

Table 4. Stability Study Results

Parameter	Day 0	Day 30	Day 60	Day 90
pH	6.21	6.18	6.15	6.12
Drug Content (%)	97.6	96.9	96.2	95.8
Viscosity (cP)	4820	4795	4768	4742

No phase separation, discoloration, or precipitation was observed during storage. Changes in physicochemical properties remained within acceptable limits.

FIGURE IV

Ex vivo skin permeation profile through porcine skin

Pilot Clinical Evaluation

Thirty recreational athletes completed the four-week intervention.

Table 5. Changes in Pain Scores

Assessment	Mean VAS Score
Baseline	7.1 ± 1.2

Week 2	4.9 ± 1.0
Week 4	2.8 ± 0.8

Pain intensity decreased significantly from baseline to Week 4 ($p < 0.05$).

FIGURE V

Reduction in Visual Analogue Scale (VAS) pain scores during the intervention period

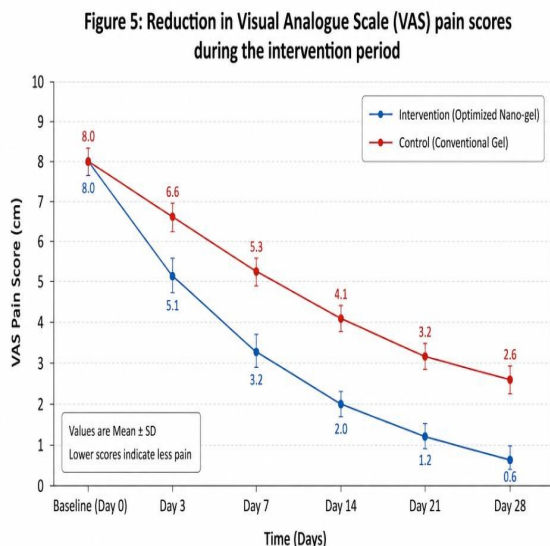


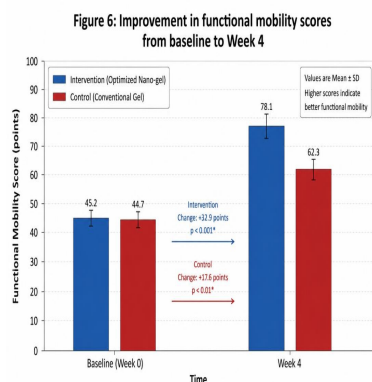
Table 6. Functional Mobility Scores

Assessment	Mobility Score
Baseline	62.4 ± 8.6
Week 2	74.1 ± 7.3
Week 4	86.8 ± 6.1

Participants reported improved mobility, reduced stiffness, and faster recovery from physical activity.

FIGURE VI

Improvement in functional mobility scores from



baseline to Week 4

Discussion

The present study successfully developed a transdermal herbal nano-gel containing Ashwagandha, Curcumin, and Eucalyptus oil for the management of musculoskeletal pain among recreational athletes. The

optimized formulation demonstrated favorable physicochemical characteristics, enhanced skin permeation, sustained drug release, and promising therapeutic outcomes. The mean particle size (156.4 nm) obtained in the present study falls within the ideal nano-range for transdermal delivery. Previous studies have reported that nano-sized formulations enhance skin penetration by increasing surface area and improving interaction with the stratum corneum [4]. The observed zeta potential (-32.8 mV) further indicates good colloidal stability, which is essential for maintaining formulation integrity during storage and application. The nano-gel exhibited skin-compatible pH, appropriate viscosity and excellent spread ability, supporting patient acceptability and prolonged retention at the application site. Similar findings have been reported in herbal nano-gel formulations where optimal rheological properties contributed to improved topical performance [6].

A major outcome of this investigation was the sustained release profile observed over 24 hours. Controlled release systems are advantageous in pain management because they maintain therapeutic drug levels while reducing application frequency. Comparable sustained-release behavior has been reported in nanoemulsion-based transdermal systems developed for anti-inflammatory phytoconstituents [1].

The ex vivo permeation study demonstrated enhanced penetration through the skin barrier, which may be attributed to the nano-sized droplets and penetration-enhancing effects of eucalyptus oil [3] reported that essential oil-based Nano formulations improve transdermal transport by altering lipid organization within the stratum corneum, thereby facilitating drug diffusion.

Clinically, significant reductions in pain scores and improvements in functional mobility were observed following four weeks of application. These findings may be explained by the synergistic effects of Curcumin, Ashwagandha, and Eucalyptus oil. Curcumin has been shown to suppress inflammatory mediators such as COX-2, TNF- α , and interleukins, while Ashwagandha possesses anti-inflammatory and adaptogenic properties that support recovery from physical stress [2&5]. Eucalyptus oil additionally contributes analgesic and anti-inflammatory effects [8]. The formulation remained stable throughout the study period with no significant changes in pH, viscosity, or drug content. Furthermore, the absence of serious adverse reactions suggests that the nano-gel is safe and well tolerated for topical use. Despite these encouraging findings, the study was limited by a relatively small sample size and short intervention duration.

Future randomized controlled trials involving larger athletic populations are warranted to establish long-term efficacy, safety, and clinical applicability. Overall, the results indicate that the integration of traditional herbal therapeutics with nanotechnology-based transdermal delivery systems represents a promising approach for localized musculoskeletal pain management and sports rehabilitation.

Conclusion

present study successfully formulated and evaluated a transdermal herbal nano-gel containing

Ashwagandha, Curcumin, and Eucalyptus oil. The formulation demonstrated favorable physicochemical characteristics, enhanced skin permeation, sustained release behavior, and significant reductions in musculoskeletal pain among recreational athletes. Stability studies confirmed formulation robustness, while clinical observations indicated excellent tolerability and therapeutic potential. The findings support the application of nano-enabled herbal delivery systems as innovative alternatives for localized pain management in sports medicine and rehabilitation. Further large-scale clinical trials are recommended to validate these preliminary findings and facilitate translation into commercial healthcare products.

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