Development and Optimisation of an Antibacterial Transdermal Delivery System for Localised Activity

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Abstract—**A sustained-release transdermal patch of azithromycin and clindamycin was developed to enhance localised antibacterial therapy for cutaneous infections while minimising systemic exposure. Patches were prepared by solvent casting using an ethyl cellulose backing and a drug–polymer matrix of HPMC E15 and PVP K30 with PEG 400 as plasticiser. A 323^232 factorial design identified HPMC and PEG levels as critical factors affecting drug release and mechanical strength, enabling optimisation via Design-Expert®.**

FTIR confirmed drug–excipient compatibility, and the optimised formulation (HPMC 0.79 g, PEG 1.8 g) showed sustained release (~74% at 18 h), adequate tensile strength (~3 N/mm²), acceptable moisture content (~5.7%), and good flexibility. Antimicrobial testing against S. epidermis species demonstrated activity comparable to marketed topical formulations.

The optimised transdermal film offers a promising localised delivery system for acne and superficial skin infections, providing prolonged drug residence in pilosebaceous units with potential for reduced dosing frequency and systemic side effects.

Index Terms—**Transdermal, antibacterial, topical, Azithromycin, Clindamycin, acne.**

I. INTRODUCTION

Bacterial infections of the skin and pilosebaceous unit frequently require localized, sustained antimicrobial therapy to achieve effective concentrations at the site of infection while minimizing systemic exposure [1,3]. Conventional oral antibiotics can cause systemic adverse effects, promote antimicrobial resistance, and require frequent dosing that undermines adherence[4,5]. Topical formulations reduce systemic exposure but often fail to deliver sufficient drug into deeper epidermal and follicular layers where pathogens and inflammatory processes persist.[6,7]

Transdermal and mucocutaneous delivery systems offer a targeted, sustained alternative by maintaining a controlled concentration gradient across the skin and enhancing penetration into pilosebaceous units. A well-designed transdermal film can combine the dosing accuracy and stability of solid dosage forms with the local action and convenience of topical therapy, potentially reducing systemic side effects, lowering dosing frequency, and improving patient acceptability. [8,9]

Azithromycin is a lipophilic azalide antibiotic with broad-spectrum antibacterial activity and notable anti-inflammatory properties. Its pharmacokinetic profile high tissue penetration and prolonged intracellular residence makes it a suitable candidate for localized, sustained delivery to cutaneous infection sites. Incorporating azithromycin into a solvent-cast transdermal matrix composed of film-forming polymers and appropriate plasticizers can enable prolonged local release, improved drug residence in pilosebaceous units, and reduced systemic exposure. [4,19]

Clindamycin is a lipophilic lincosamide antibiotic with broad-spectrum activity against anaerobic bacteria and Gram-positive organisms, along with notable anti-inflammatory effects that are beneficial in acne and other cutaneous infections. Its pharmacokinetic characteristics effective tissue penetration and accumulation within pilosebaceous units make it a suitable candidate for localized, sustained delivery to skin infection sites. Incorporating clindamycin into a solvent-cast transdermal matrix composed of film-forming polymers and appropriate plasticizers can enable prolonged local release, enhanced drug retention within the pilosebaceous apparatus, and minimized systemic exposure. [5,20]

This study aimed to develop and optimise a sustained-release transdermal patch intended for localized bacterial skin infections, with acne vulgaris as a representative indication. Using a 3^2 factorial design, critical formulation variables affecting drug

release and mechanical properties were identified and optimized. The work focuses on formulation methodology, physicochemical compatibility, in vitro release, and antimicrobial performance to evaluate the patch as a potential localized therapy for superficial and follicular bacterial infections.

The initial formulation development was carried out using azithromycin as the model drug to establish the solvent-cast transdermal matrix system. Subsequently, the optimized formulation was prepared using clindamycin, which is more widely preferred for topical application due to its proven efficacy against acne-causing bacteria, favorable safety profile, and superior retention within pilosebaceous units. This substitution enabled the evaluation of the optimized matrix for enhanced localized therapy while minimizing systemic exposure.

II. MATERIALS AND METHODS

Materials

Azithromycin and Clindamycin (Aarti Pharma, Mumbai). Polymers and excipients: Hydroxypropyl methylcellulose E15 (HPMC E15), Ethyl cellulose (EC), Polyvinylpyrrolidone K30 (PVP K30), Polyethylene glycol 400 (PEG 400), and absolute ethanol. S. epidermis species was procured from MTCC housed at IMTECH, Chandigarh. All reagents were analytical grade and used as received.

Patch Preparation Overview

Transdermal patches were prepared by a solvent casting method to produce a backing membrane and a drug-loaded polymer matrix. The design objective was a sustained local delivery system for cutaneous and follicular bacterial infections, maximizing local drug residence while minimizing systemic exposure.[1,2,10]

Backing Membrane Preparation

Ethyl cellulose was used to form the backing layer. EC (1.0 g) was dissolved in 8 mL of absolute ethanol under magnetic stirring until a homogeneous solution formed. The solution was cast onto petri plates lined with release liner and dried in a hot air oven at 60 °C for 15 minutes to yield uniform backing membranes.

Table 1: Polymer Drug Matrix Preparation

Name of ingredients	Quantity per petri plate	Activity
Clindamycin HCL	1g	Antibacterial
HPMC E15	0.79 g	Polymer
PVP K30	0.15g	Co-polymer
PEG 400[14]	1.80g	Plasticizer
EC	1g	Backing membrane
Ethanol	q.s	Vehicle

Two solutions were prepared:

Solution A Polymer Matrix HPMC E15 (600 mg) was dispersed in 5 mL ethanol and allowed to hydrate. PEG 400 (0.21 g) was dissolved in 5 mL of ethanol and added as a plasticiser with continuous stirring. PVP K30 (0.83 g) was then incorporated dropwise to obtain a homogeneous viscous matrix.

Solution B Drug Solution Azithromycin (1.0 g) was dissolved in 5 mL of ethanol to form the drug solution.

Combination and Casting

Solution B was slowly added to Solution A under stirring to ensure uniform drug distribution. The combined mixture was sonicated for 10 minutes to remove entrapped air. The drug polymer dispersion was poured onto the preformed EC backing membrane, spread evenly, and dried in a hot air oven at 60 °C for 30 minutes. After cooling to room temperature, films were cut into 1 × 1 cm squares for evaluation.

Figure 1: Photograph of formulated transdermal patch

Experimental Design and Optimisation

A (3^2) factorial design was employed to optimise two independent variables: HPMC concentration (factor A) and PEG concentration (factor B). Each factor was studied at three levels (low, medium, high) to evaluate effects on % cumulative drug release and tensile strength. Nine formulation batches were prepared and analysed. Design-Expert software was used for model fitting, generation of response surfaces, and selection of the optimized formulation.[11,12,13,18]

Table 2: Formulation plan for factorial studies

Formula	Independent Variables	
	HPMC Concentration(mg)	PEG Concentration(g)
F1	400	0.18
F2	400	0.21
F3	400	0.23
F4	600	0.18
F5	600	0.21
F6	600	0.23
F7	800	0.18
F8	800	0.21
F9	800	0.23

Physicochemical Characterization

FTIR Compatibility

Fourier transform infrared spectra of pure azithromycin and clindamycin, individual excipients, and the final films were recorded to assess potential chemical interactions. The spectra were compared for characteristic peak shifts, broadening, or disappearance that could indicate drug–excipient incompatibility. The analysis confirmed the preservation of key functional group peaks, suggesting chemical compatibility of both antibiotics with the selected polymers and plasticisers.

UV–Visible Spectroscopy and Calibration

Stock solutions of azithromycin and clindamycin were prepared separately and serially diluted to construct calibration curves for quantitative analysis. Absorbance scans in the range of 200 to 400 nm were performed to determine the respective λmax values of each drug. Both drugs exhibited linear calibration curves over the tested concentration ranges, validating the method for drug content estimation and in vitro release studies.

Melting Point and Solubility

The melting points of azithromycin and clindamycin were determined using the capillary method to confirm drug identity and purity. Solubility was assessed qualitatively in water and selected organic solvents to guide formulation development. Both drugs showed limited aqueous solubility but adequate solubility in suitable organic solvents, supporting their incorporation into solvent-cast polymeric films.

Mechanical and Physical Tests

Tensile Strength Tensile strength was measured by mounting 1 × 1 cm film strips between fixed and movable grips and recording the force at break. Results were expressed as N/mm².

Folding Endurance Folding endurance was determined by repeatedly folding a film strip at the same point until visible cracking occurred. The number of folds to failure was recorded for three replicates.

Moisture Content Moisture content was measured using a moisture analyser and reported as % w/w to assess film flexibility and storage stability.

Figure 2: Moisture estimation using Karl Fisher technique.

In Vitro Drug Release Study

Drug release from patches was evaluated using Franz diffusion cells. The receptor compartment was filled with an appropriate medium and maintained at 32 ± 0.5 °C to simulate skin surface temperature. Samples

were withdrawn at predetermined intervals up to 18 hours and analysed spectrophotometrically at the established λmax. Cumulative % drug release was calculated and used as a primary response for optimisation.

Antimicrobial Activity

Antibacterial activity against S. epidermis species was evaluated using the disc diffusion method. The zones of inhibition produced by the optimized transdermal patch were compared with those of a marketed azithromycin and clindamycin formulation with a solvent control. All experiments were conducted in triplicate to ensure reproducibility. (6,7,16)

Data Analysis and Model Fitting

Response data (% drug release and tensile strength) were analysed by ANOVA using Design-Expert software. Polynomial models were fitted and model adequacy assessed by R^2 and lack-of-fit tests. Response surface plots and contour maps guided the selection of the optimised formulation.

Stability and Future Evaluations

Optimised patches were identified for further stability testing, skin irritation assessment, and in vivo pharmacokinetic and efficacy studies to confirm local delivery performance and safety prior to clinical translation.

Table 3: Stability study plan: 1 month duration

Condition	Temperature	Relative Humidity	Purpose
Refrigerated	5 ± 3 °C	—	Evaluate cold stability
Room temperature	25 ± 2 °C	60 ± 5% RH	Real-time condition
Accelerated	40 ± 2 °C	75 ± 5% RH	Predict long-term stability

III. RESULTS AND DISCUSSION

Preformulation and compatibility

FTIR analysis showed that the characteristic peaks of both azithromycin and clindamycin were retained in their respective drug–excipient mixtures, with no disappearance or significant shifts in functional group bands. This observation indicates the absence of chemical interactions or degradation during formulation and supports the chemical compatibility of both antibiotics with HPMC, PVP, EC, and PEG 400. (14,15)

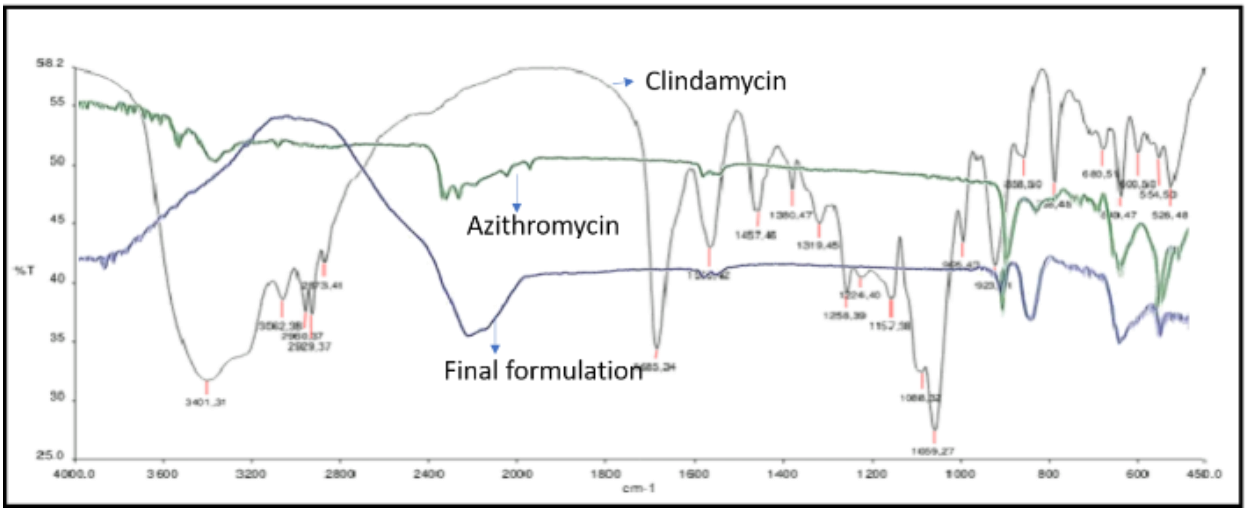
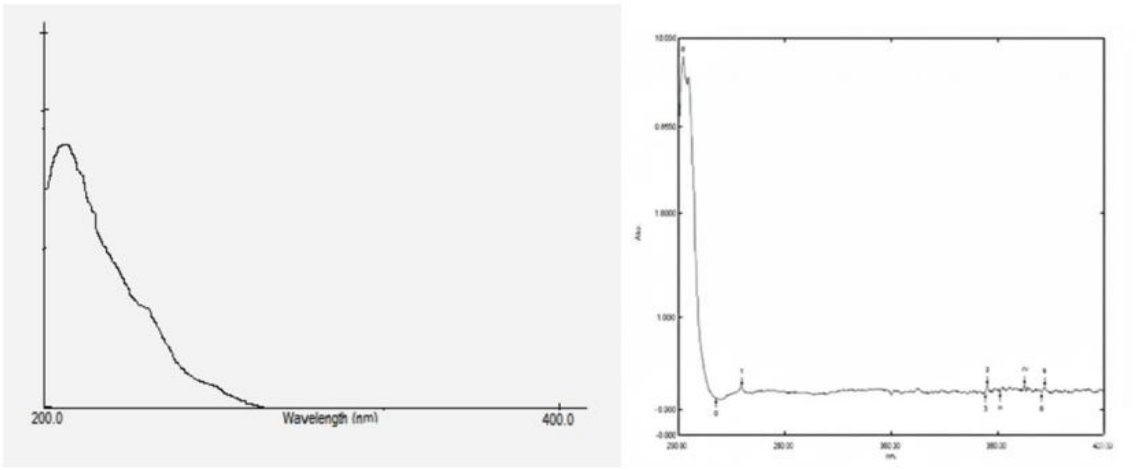


Figure 3:: FTIR spectra of azithromycin, clindamycin, and drug–excipient mixture showing retention of characteristic functional group peaks, indicating compatibility with selected polymers.

UV–Vis calibration produced a linear calibration curve at the selected (\lambda_{\text{max}}) (used for release quantification), with an acceptable correlation coefficient, confirming the method's suitability for in-vitro release analysis.



Azithromycin Clindamycin

Figure 4: UV–Vis calibration curve (λmax)

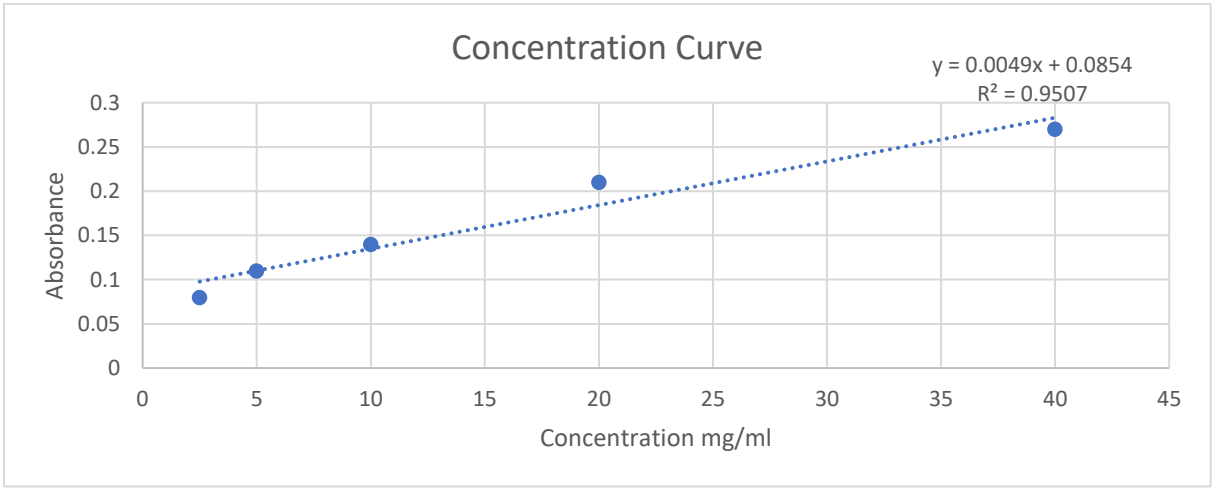


Figure 5: Concentration curve for Azithromycin

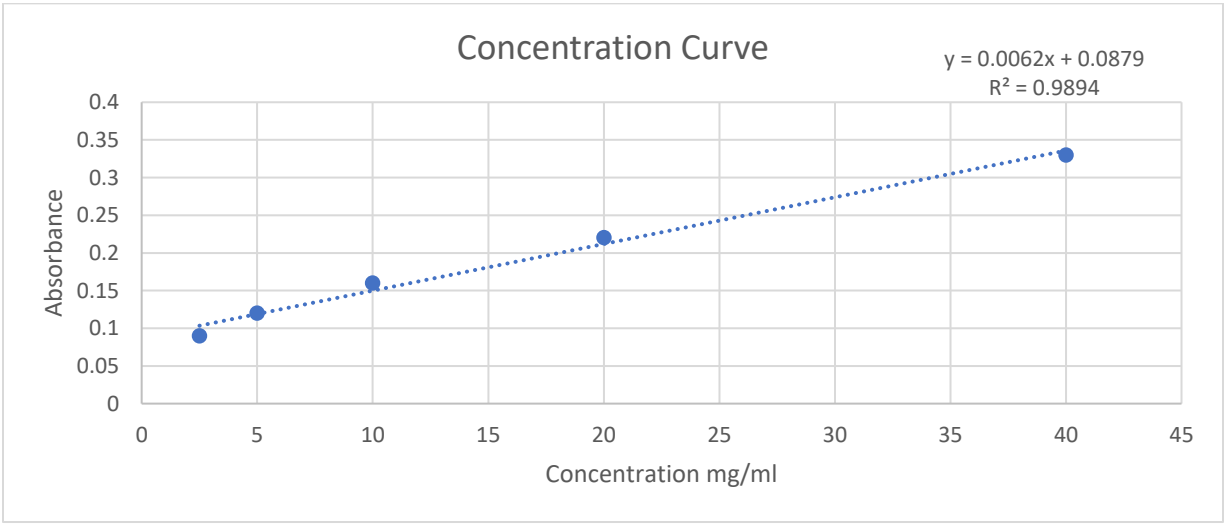


Figure 6: Concentration curve for Clindamycin

Mechanical and physical properties

Tensile strength. Measured tensile strength values across the nine batches ranged from low to high consistent with varying HPMC and PEG levels. Increasing HPMC concentration increased tensile strength, while increasing PEG tended to reduce it, reflecting PEG's plasticizing effect. The optimized batch (HPMC 0.79 g, PEG 1.8 g) achieved a tensile strength near the target value and acceptable handling robustness for a transdermal film. [13,14] Folding endurance and moisture content. Folding endurance values indicated good flexibility for the optimized patch; moisture content (~5.7% w/w) provided sufficient plasticity without compromising stability. These physical attributes suggest the film will tolerate routine handling and application.

Table 4: Mechanical and physical properties

Test	Ideal Batch data	Acceptance criteria
Appearance	Uniform, no cracks, no phase separation	No visible defects; color consistent
Thickness	150 micro meter	As per requirement
Drug content (assay)	99.5% of label claim	95–105%
In vitro release	74 % drug release in 18 hrs.	NA
Adhesion	3 N/mm2	0.5–5 N/ mm2
Flexibility / fold endurance	122 times	NA
Moisture content	5.70% w/w	NA

The mechanical profile balances strength and flexibility required for skin application. The observed relationships between polymer/plasticizer levels and mechanical endpoints align with polymer science expectations and justify the factorial approach.

In vitro drug release and optimization

Release profile. Franz cell studies showed sustained release from all batches, with cumulative release at 18 hours ranging up to ~74% for the optimized formulation. Release kinetics approximated a diffusion-controlled mechanism consistent with a hydrophilic matrix system containing HPMC. The optimized patch provided a prolonged local release that would be expected to maintain therapeutic concentrations in superficial and follicular tissues while limiting systemic exposure. [11,12,18]

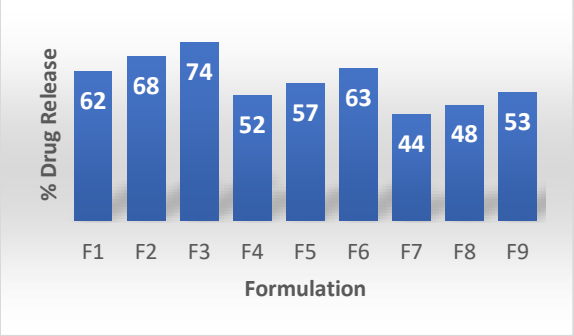


Figure 7: In vitro cumulative drug release profiles for nine batches

Statistical optimisation. The (3^2) factorial design produced polynomial models for % drug release and tensile strength:

Table 5: Release kinetics fitting parameters

Formula	Independent Variables		Dependent Variables	
	HPMC Concentration(mg)	PEG Concentration(g)	R1(Drug Release, %)	R2(Tensile Strength, N/mm^2)
F1	400	0.18	62	2.1
F2	400	0.21	68	2
F3	400	0.23	74	1.8
F4	600	0.18	52	3.1
F5	600	0.21	57	3
F6	600	0.23	63	2.7
F7	800	0.18	44	4
F8	800	0.21	48	3.9
F9	800	0.23	53	3.7

The equation derived for these dependent variables of the factorial formulations are:

% Drug Release = +57.04 – (9.83 x A) + (5.33 x B) – (0.7500 x AB) + (0.8750 X A^2) + (0.3750 X B^2)

Tensile Strength = +2.99 + (0.9500 x A) – (0.1667 x B) + (0.0000 x AB) – (0.0250 X A^2) – (0.0750 X B^2)

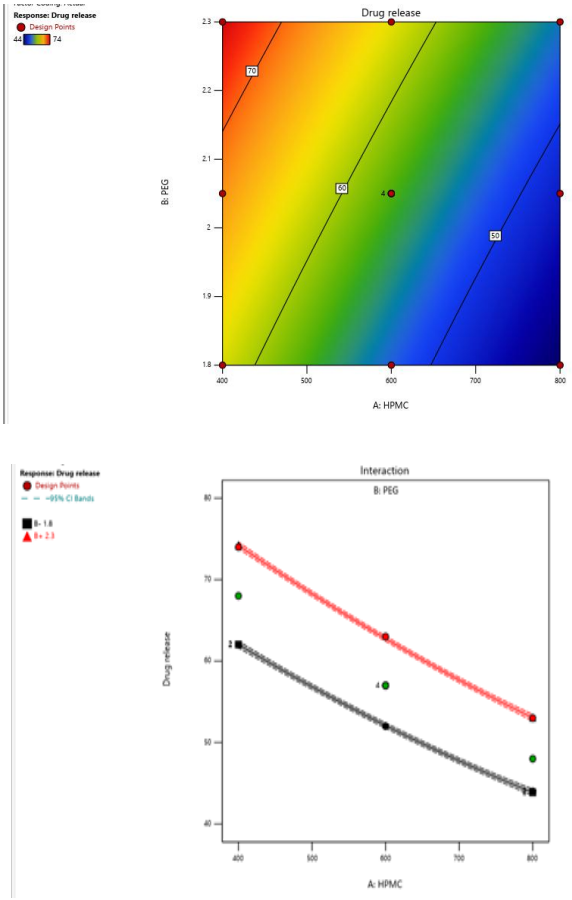
where,

A = HPMC concentration

B = PEG concentration

The R^2 values in Fit Statistics on using ANOVA for Quadratic Model were 0.9997 and 0.9991, for % Drug Release and Tensile Strength, respectively. This implies that the selected dependent variables were significant for the optimization process.

The negative coefficient for A in the release model confirms that higher HPMC slows release by increasing matrix density; the positive coefficient for B confirms PEG accelerates release via increased hydrophilicity. The optimization achieved a practical compromise: sustained release with acceptable mechanical integrity.



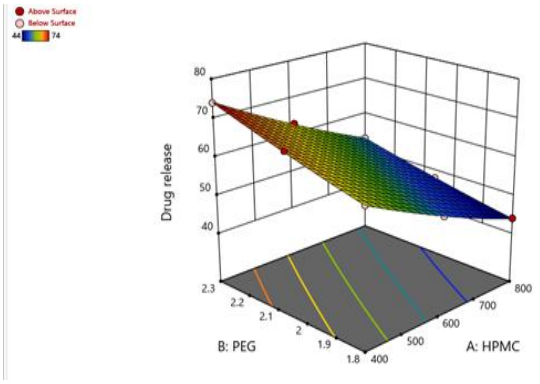


Figure 8: Response surface and contour plots for % drug release.

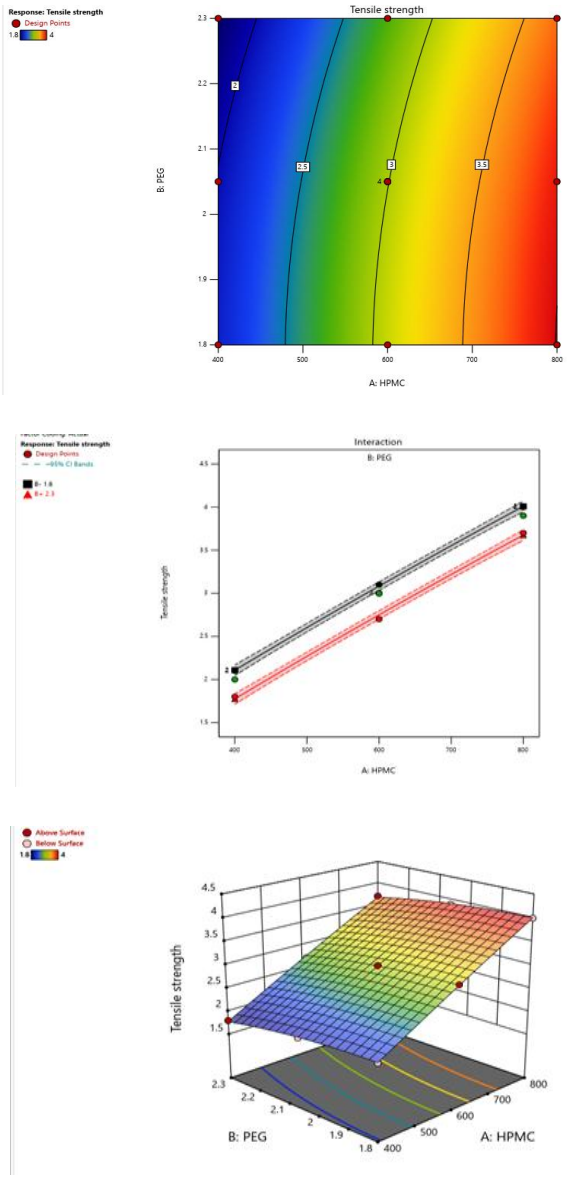


Figure 9: Response surface and contour plots for tensile strength.

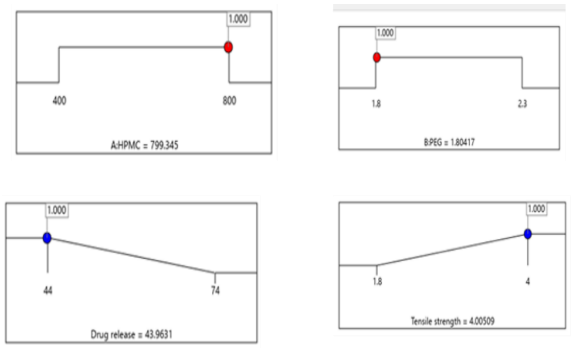


Figure 10: Desirability plot for optimised batch

Figure 11: Zone of inhibition observed and compared with marketed preparation

Antimicrobial activity

Zone of inhibition. The optimised patch produced a clear zone of inhibition against S. epidermis species in the disc diffusion assay, comparable to the marketed azithromycin (Azithral®) and Clindamycin (Clindac-Ap Gel) formulations used as references. This demonstrates that the drug retained antimicrobial potency after formulation and that the patch can deliver active drug to exert local antibacterial effects. (6,7, 16,20)

The in vitro antimicrobial results support the patch's potential for localized treatment of superficial and follicular bacterial infections. While disc diffusion is qualitative, the comparable activity to a marketed product is encouraging and justifies further quantitative microbiological and in vivo efficacy testing.

Table 6: Antimicrobial study data

Sample	Zone of Inhibition (mm) –			Mean ± SD (mm)
	Replicate 1	Replicate 2	Replicate 3	
Optimized Transdermal Patch	21	22	23	22.0 ± 1.0
Marketed Azithromycin Gel	22	23	22	22.3 ± 0.6
Marketed Clindamycin Gel	23	24	22	23.0 ± 1.0
Solvent Control	0	0	0	0 ± 0

The formulation strategy produced a stable, mechanically robust, and sustained-release transdermal film that preserves azithromycin's chemical integrity and antimicrobial activity. The factorial design efficiently identified the critical formulation levers (HPMC and PEG) and quantified their effects on release and mechanical properties, enabling rational optimization. The optimized patch addresses the goals stated in the Introduction: localized delivery to cutaneous/follicular infection sites, reduced systemic exposure, and improved dosing convenience.

IV. CONCLUSION

The solvent-cast transdermal films developed in this study, incorporating azithromycin and subsequently optimized with clindamycin, demonstrated chemical compatibility, mechanical robustness, and sustained local drug release suitable for the treatment of superficial and follicular bacterial skin infections. Optimization using a 323^232 factorial design identified HPMC and PEG as key formulation variables, yielding an optimized patch (HPMC 0.79 g, PEG 1.8 g) that achieved approximately 74% cumulative drug release over 18 hours while maintaining acceptable tensile strength, folding endurance, and moisture content.

In vitro antimicrobial testing confirmed the retention of antibacterial activity for both azithromycin and clindamycin against S. epidermis species. Collectively, these findings support the developed transdermal patch as a promising localised delivery platform capable of reducing systemic exposure, enhancing drug residence in pilosebaceous units, and improving patient convenience compared with conventional oral or topical therapies.

Future Aspects and Recommended Next Steps

To advance the topical antimicrobial patch from in vitro proof-of-concept to clinical application, a comprehensive translational development strategy was formulated. Ex vivo studies will quantify drug permeation through full-thickness human or porcine skin and assess follicular deposition via analysis of follicular casts, confirming targeted delivery to pilosebaceous units [8,9]. In vivo safety and efficacy will be evaluated through dermal irritation and sensitisation assays, followed by small animal models of superficial and follicular infections to demonstrate therapeutic benefit and local tolerability [16,17]. Pharmacokinetic profiling will include both local and systemic assessments to confirm minimal systemic absorption and to establish exposure–response relationships within target tissues. Stability studies under ICH guidelines will be conducted to ensure product integrity, alongside the development of moisture-resistant primary packaging.[15] Manufacturability will be assessed through scalability of mixing, casting, and drying processes, with attention to batch reproducibility and cost efficiency; alternative manufacturing routes will be explored if necessary. For pediatric applications, excipient safety including sweeteners and preservatives will be reviewed, and formulations adapted to age-specific risk profiles. Regulatory planning will involve mapping requirements for topical/transdermal antimicrobials across target markets, defining pivotal clinical endpoints, and integrating antimicrobial stewardship principles to mitigate resistance [9]. Formulation refinement will explore strategies such as drug nanoparticles, ion-exchange complexes, permeation enhancers, and multilayer films to enhance local deposition and extend therapeutic duration without increasing systemic exposure. Comparative studies will assess patient acceptability and usability relative to standard topical and oral regimens, quantifying adherence and preference [7,16]. Finally, commercial viability will be evaluated through targeted market analysis, identifying priority indications, pricing strategies, and potential partners for clinical development and commercialisation. Collectively, these steps aim to bridge preclinical validation with regulatory submission and eventual clinical use.

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