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Research Article

Antiacne Gel Containing *Aloe vera* and Clindamycin Phosphate: Design, Characterization, and Optimization Using Response Surface Methodology

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Clindamycin phosphate is a topical antibiotic agent used to treat acne vulgaris, while *Aloe vera* has both antimicrobial and anti-inflammatory properties. The current study is aimed at formulating an antiacne gel with antioxidant and antimicrobial effects. The antiacne gels were prepared by using polymer HPMC K15M by cold dispersion method. Unveiling the intricacies of gel design, our research harnessed the power of Design Expert 11 to optimize critical parameters—viscosity, spreadability, and permeability. *In vitro* characterization tests, including pH, spreadability, viscosity, permeability, antimicrobial activity, antioxidant activity, and stability of the gels, were performed. The results of *in vitro* characterization tests showed that the gels had a mint-like odor, a pH of 6.8, and a spreadability of 21.5 g cm/sec. The gels had a viscosity of 34.2 Pa s and drug content ranging within 90%-110%, as per USP standards. Notably, in vitro permeation assays reveal an exceptional 86% drug release, showcasing the efficacy of our formulation. The uniqueness of our study lies not only in the robust optimization process but also in the multifaceted characterization. Our gel emerges as a promising candidate, exhibiting not only desired antimicrobial and antioxidant properties against acne vulgaris but also demonstrating stability under varied conditions. As we advance toward *in vivo* studies, our research paves the way for a nuanced understanding of the safety and efficacy of this distinctive antiacne gel.

1. Introduction

Acne vulgaris is an ailment of the skin that involves oil glands situated at the base of hair follicles [1]. A large percentage of teenagers (up to eighty-five percent) suffer from chronic acne inflammation, which affects their social life and psychological health [2]. Four processes can play a pivotal part in the onset of acne lesions: release of inflammatory

mediators in the skin, keratinization process alteration, increased sebum production due to increased androgen receptor sensitivity, and follicular colonization induced by *Cutibacterium acnes* [3]. Follicles containing sebum provide a lipid-rich and anaerobic environment for the *Cutibacterium acnes* to flourish, which directly augments lipogenesis. Different strains of *Cutibacterium acnes* have different resistance profiles and tend to colonize in pilosebaceous units leading to inflammation due to the activation of macrophages and keratinocyte receptors [4, 5].

Topical treatments, including antibiotics, retinoids, azelaic acid, benzoyl peroxide, and a combination of these agents, are used effectively as the first choice in mild-to-moderate acne situations [6, 7]. Using multiple synthetic agents poses the risk of moderate-to-severe side effects such as erythema, skin peeling, photosensitivity, dryness, and eczematous irritation. Effective acne treatment is observed with clindamycin, tetracycline, and erythromycin [8, 9]. Clindamycin phosphate is a common topical antibacterial used in the treatment of acne in adults [10]. Clindamycin belongs to the family of antibiotics called lincomycins. It is a 7-deoxy-7-chloro derivative of lincomycin antibiotic [11]. It acts by the inhibition of chemotactic factors by *Cutibacterium acnes* as well as by the blockage of protein synthesis of the bacteria by the inhibitory action of the 50S ribosomal subunit [12].

The conventional treatments available are not well tolerated by many due to the risk of severe side effects. The use of herbal medicines and natural remedies dates a thousand years back. The increasing side effects, costs for treatment, and resistance to antimicrobial agents have led to an increasing interest in medicinal herbs [13]. The benefits of *Aloe vera* (*A. vera*) have been increasing in recent years in both medicines and cosmetics [14, 15]. It has been reported to exhibit antibacterial, anti-inflammatory, and skin-healing activities [16, 17]. *A. vera* is a typical xerophyte that is promoted for a variety of skin conditions. Research has suggested that the various bioactive phytochemicals of the ethanolic extracts of *A. vera* impart antioxidant and healing properties to it [18].

In this study, we used clindamycin phosphate [19] and *A. vera* powder [20] as active ingredients for their antimicrobial and anti-inflammatory actions. HPMC K15M is used as a polymer to form the gel. Rheological tests showed that HPMC gel formulations showed a pseudoplastic behavior, a characteristic feature of topical gel [21]. Oleic acid is used as a surfactant and permeation enhancer. Oleic acid-based surfactants showed an ability to self-aggregate into micelles and were readily biodegradable as compared to conventional surfactants [22–24]. Eucalyptus oil was used as flavorant as well as penetration enhancer. Studies have shown that it is an essential penetration enhancer. It alters the permeability of certain drugs by the disruption of the lipid bilayer of the stratum corneum resulting in the modification of diffusivity via the stratum corneum [25]. Glycerin was used as a plasticizer. It has been seen that glycerin assists in maintaining moisture within the gel structure thus preventing it from drying. This quality is also beneficial for the skin as when the gel is applied topically, the skin remains hydrated [26].

Table 1: Formulation design by Design Expert.

Formulation	Oleic acid, X_1 (ml)	Eucalyptus oil, X_2 (ml)	Glycerin, X_3 (ml)
1	0.6	0.75	1.25
2	0.45	1	2.5
3	0.3	0.5	1.875
4	0.45	0.5	2.5
5	0.6	0.75	2.5
6	0.45	0.5	1.25
7	0.45	0.75	1.875
8	0.45	0.75	1.875
9	0.45	1	1.25
10	0.6	1	1.875
11	0.3	1	1.875
12	0.3	0.75	1.25
13	0.6	0.5	1.875
14	0.3	0.75	2.5

Table 2: Composition of optimized gel formulation.

Ingredient	Concentration
Clindamycin phosphate	1 g
Aloe vera	2 g
HPMC	3 g
Oleic acid	0.3 ml
Eucalyptus oil	1 ml
Glycerin	1.875 ml
Propylene glycol	7.5 ml
Methylparaben	0.1 g
Propylparaben	0.01 g
Distilled water	Q.s 100 ml

Table 3: Predicted outcomes of optimized gel formulation.

Response	Predicted outcome
Permeation of clindamycin phosphate	85.233%
Permeation of *A. vera*	84.933%
Viscosity	34.071 Pa s
Spreadability	20.817 g cm/sec

Propylene glycol is used as a solvent. Propylene glycol is a regular solvent that can enhance the solubility of active ingredients [27]. Methylparaben and propylparaben were used as preservatives [28].

Our primary aim was to develop an innovative antiacne gel merging clindamycin phosphate and Aloe vera utilizing the cold dispersion method and Design Expert 11 for precise optimization. The secondary aim was to investigate distinctive *in vitro* characteristics, emphasizing exceptional drug permeation, to pave the way for subsequent in vivo studies exploring the safety and efficacy of the novel formulation.

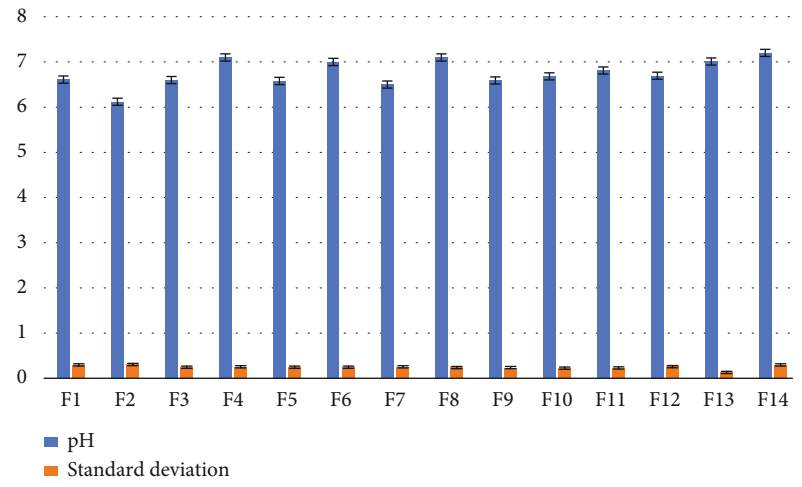

Figure 1: Illustrating the pH of formulations F1–F14.

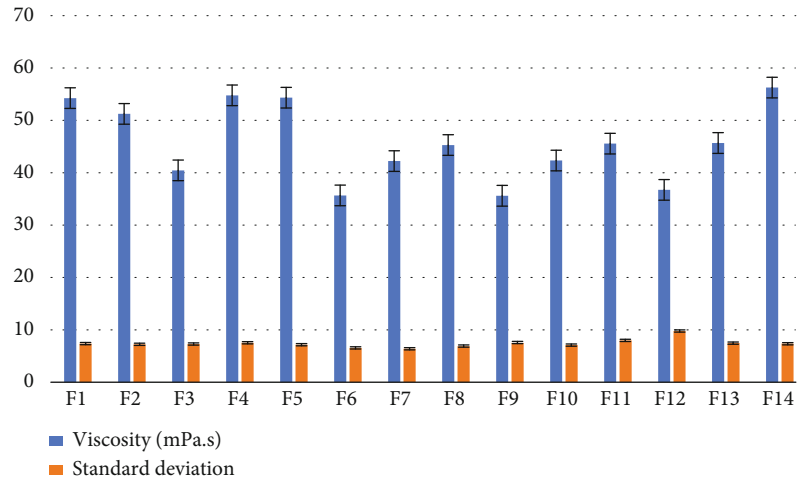

Figure 2: Illustrating the viscosity of formulations F1–F14.

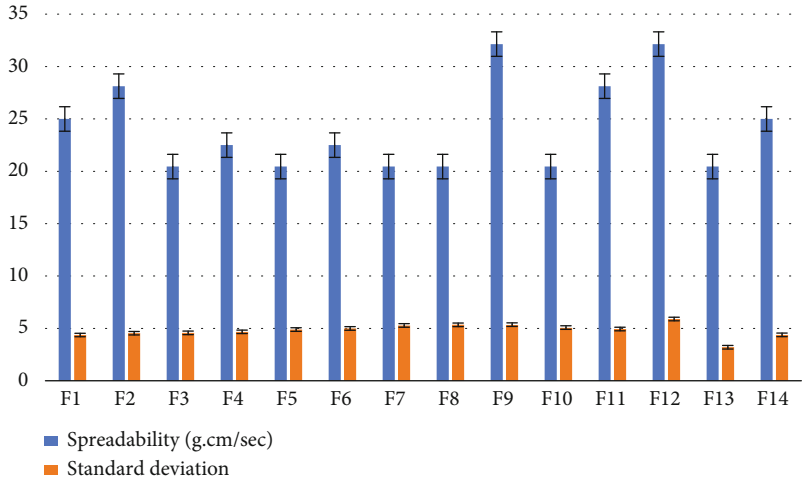

Figure 3: Illustrating the spreadability of formulations F1–F14.

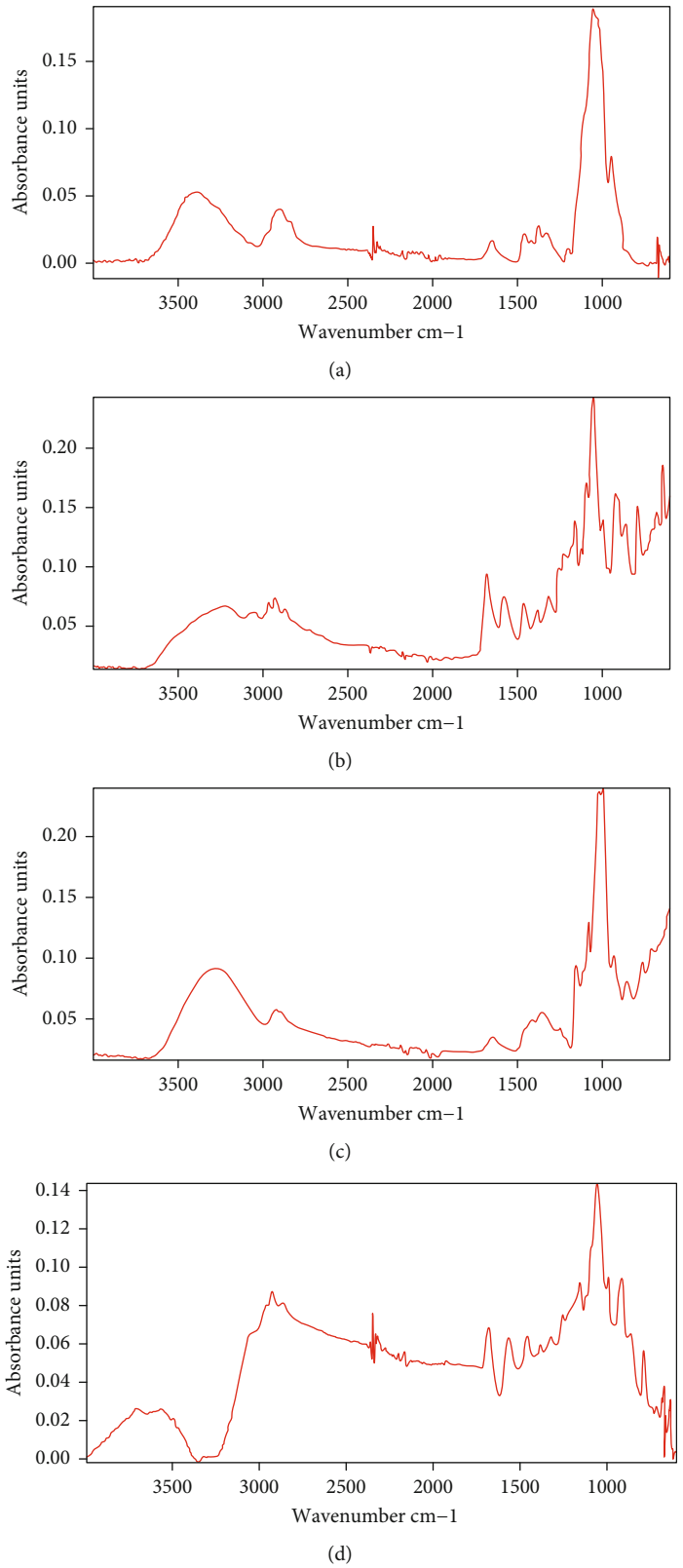

Figure 4: Illustrating FTIR of (a) HPMC K15M, (b) clindamycin phosphate, (c) Aloe vera, and (d) topical gel formulation.

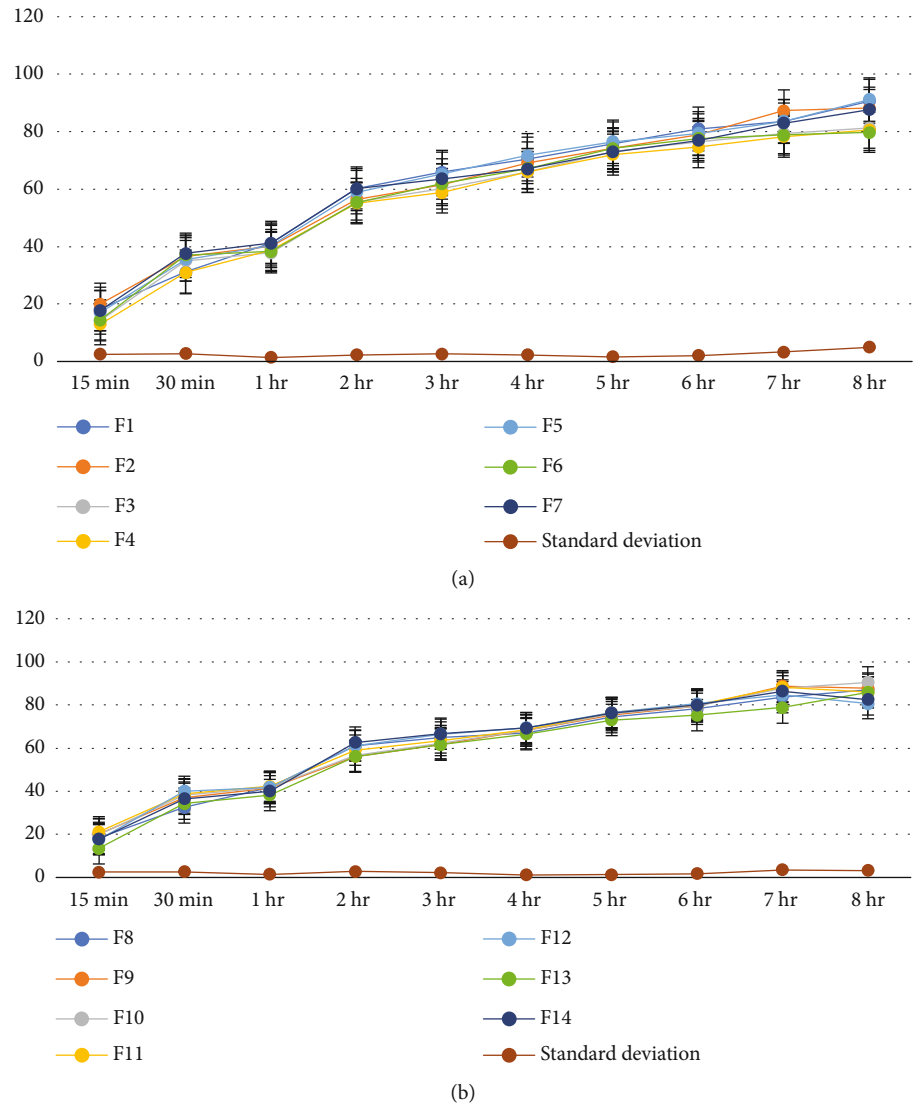

Figure 5: Illustrating *in vitro* permeation of clindamycin phosphate: (a) F1–F7 and (b) F8-F14.

2. Materials and Methods

2.1. Materials. Clindamycin phosphate (Highnoon Pharmaceuticals, Pakistan), *A. vera* powder (Sigma Pharmaceuticals, Pakistan), HPMC K15M (Highnoon Pharma, Pakistan), oleic acid (UNI-CHEM, Pakistan), eucalyptus oil (Hemani Herbals), glycerin (UNI-CHEM, Pakistan), propylene glycol (Sigma Pharmaceuticals, Pakistan), and methylparaben and propylparaben (Aldrich Pharma, Germany) are the materials used in the experiment. All other excipients were analytical grade, and distilled water was prepared in the laboratory.

2.2. Methods

2.2.1. Formulation Design by Design Expert. The clindamycin phosphate and A. vera-containing gels were prepared as per the runs suggested by Box-Behnken design (BBD). A total of 14 runs were suggested by the BBD, considering independent variables glycerin, oleic acid, and eucalyptus oil.

Mathematical modeling for variables and calculated responses was done by the Design Expert using the quadratic model.

$$Y = X_0 + X_1 + X_2 + X_3 + X_1X_2 + X_1X_3 + X_2X_3 + X_1^2 + X_2^2 + X_3. \quad (1)$$

The concentration of active ingredients and polymer was kept constant, while the surfactant (oleic acid), plasticizer (glycerin), and permeation enhancer (eucalyptus oil) were selected as variables (Table 1).

2.2.2. Formulation Method. The formulations were made using the cold dispersion method of gel preparation. 3% HPMC was soaked overnight in 100 ml distilled water. The active ingredients, 1% clindamycin phosphate and 2% *A. vera*, were added to the gel after dissolving in 7.5% propylene glycol. Oleic acid was dissolved in propylene glycol [29] and then, along with glycerin and eucalyptus oil,

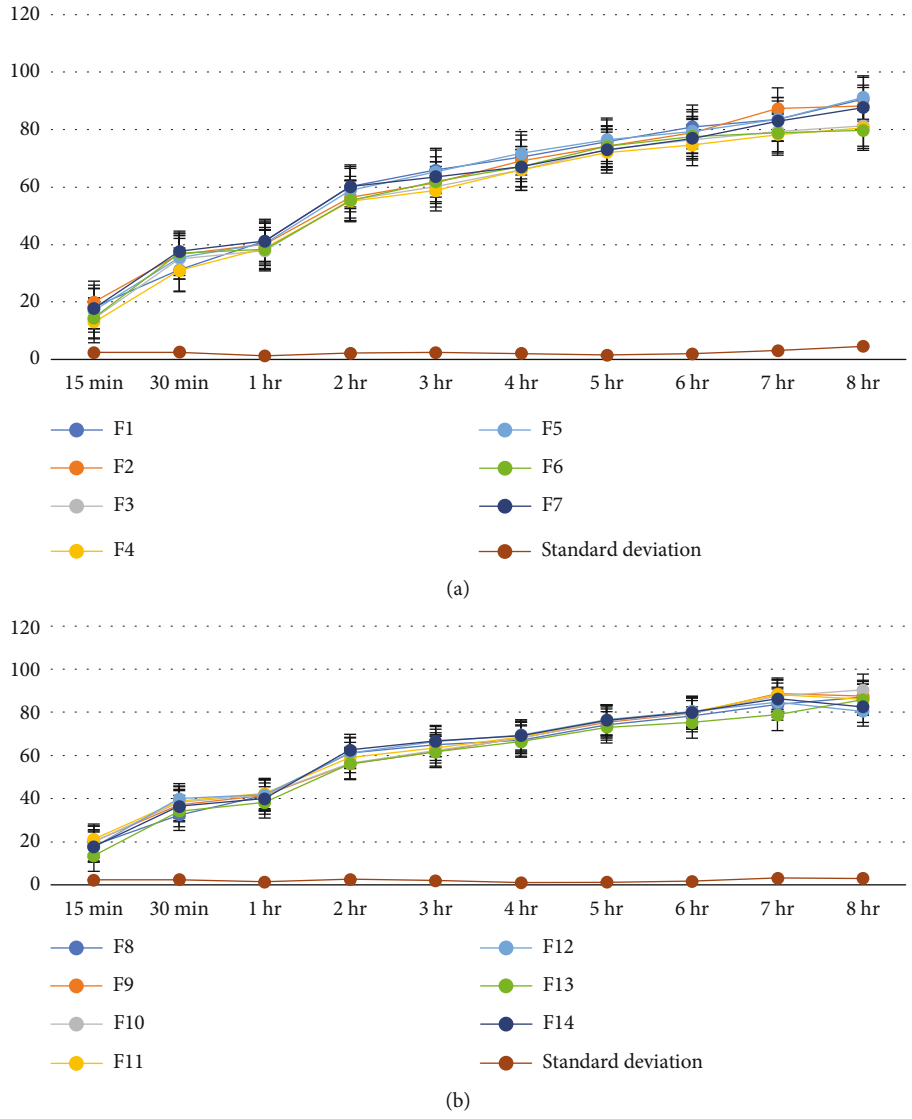

Figure 6: Illustrating *in vitro* permeation of *A. vera*: (a) F1–F7 and (b) F8-F14.

incorporated into the gel. 0.01% propylparaben and 0.1% methylparaben were added as preservatives by dissolving in 10 ml distilled water [30]. The prepared gels were stored in air-tight plastic containers.

2.3. Postformulation Studies

2.3.1. Organoleptic Evaluation. The color, odor, grittiness, consistency, and homogeneity of the gels were observed [31].

2.3.2. pH Determination. The pH of all 14 gel formulations was evaluated by a digital pH meter after calibration with standard buffers [32].

2.3.3. Spreadability. The spreadability of the gels was determined by the fixed slide method using the following formula:

$$S = \frac{M}{L} \times T, \quad (2)$$

where M is the weight of the upper slide, L is the slide length, and T is the time taken for the separation of slides [33].

Table 4: Results obtained from characterization tests on the optimized formulation.

Parameter	Result
Color	Slightly white
Odor	Minty
Homogeneity	Homogenous
pH	7.1
Viscosity (Pa s)	38.250
Spreadability (g cm/sec)	32.9
Drug content (%)	91.5

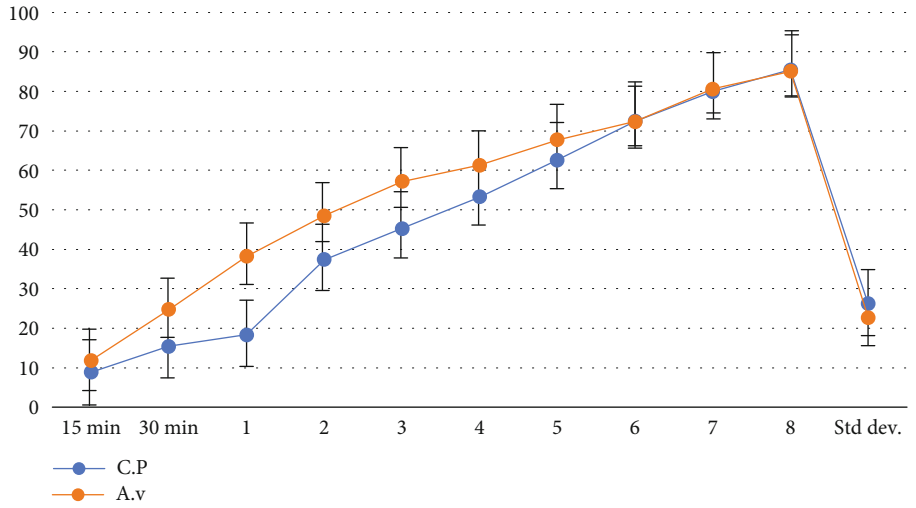

Figure 7: Illustrating the *in vitro* drug permeation of optimized gel.

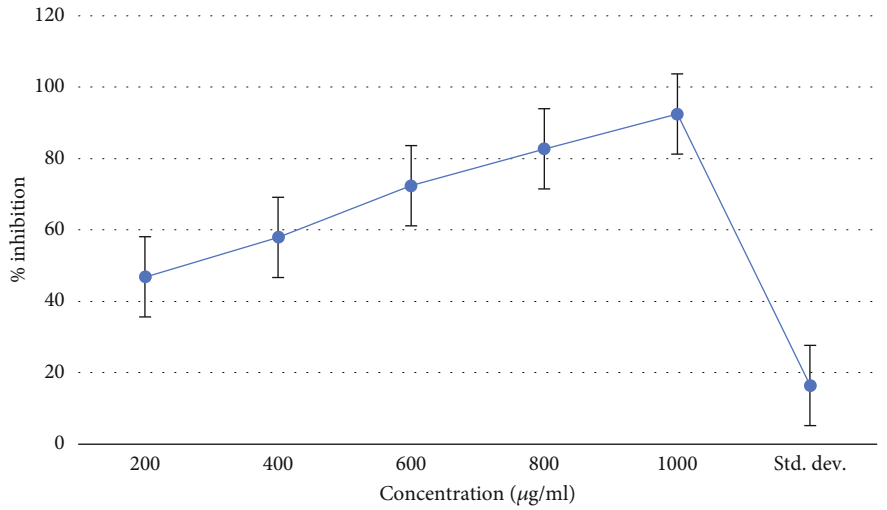

Figure 8: Illustrating total antioxidant activity of ascorbic acid (Std).

2.3.4. Viscosity. The viscosity of the gel formulations was evaluated by Brookfield viscometer by spindle no. 4 and speed of 12 rpm [34].

2.3.5. Drug Content. Drug content was determined spectrophotometrically by making a 0.9 mg/ml dilution of the topical gel. The percentage content of clindamycin phosphate and *A. vera* was determined at 210 nm and 330 nm.

$$\%\text{Drug content} = \frac{\text{Abs(sample)}}{\text{Abs(standard)}} \times 100. \quad (3)$$

2.3.6. In Vitro Drug Permeation Study. The Franz diffusion cell was used for this study. The antiacne gel was put on a SpectraPor dialysis membrane (pore size: 0.45 microns) of donor and receptor parts. A phosphate buffer of pH 7.4 was used as media. A temperature of 37°C (body temperature) and a phosphate buffer of 7.4 pH were used. Test samples (5 ml) were taken at set time intervals: 15 min, 30 min, 1 hr, and up to 8 hrs. The consolidated % drug permeation was determined after spectrophotometric evaluation [35].

2.3.7. Chemical Compatibility of Ingredients of Formulation. FTIR was conducted by placing the sample on KBr discs and observing the wavelengths using IR spectroscopy [36].

2.3.8. Total Antioxidant Activity (TAA). 2,2-Diphenyl-1-picrylhydrazyl radical scavenging assay was performed to calculate TAA. 5 μl test sample was dissolved in 3.995 ml methanolic 2,2-diphenyl-1-picrylhydrazyl and stood at room temperature for 30 min in the dark. The absorbance of both this test mixture and the blank was measured at 515 nm wavelength using UV/visible double-beam spectrophotometer (Halo DB-20, Dynamica).

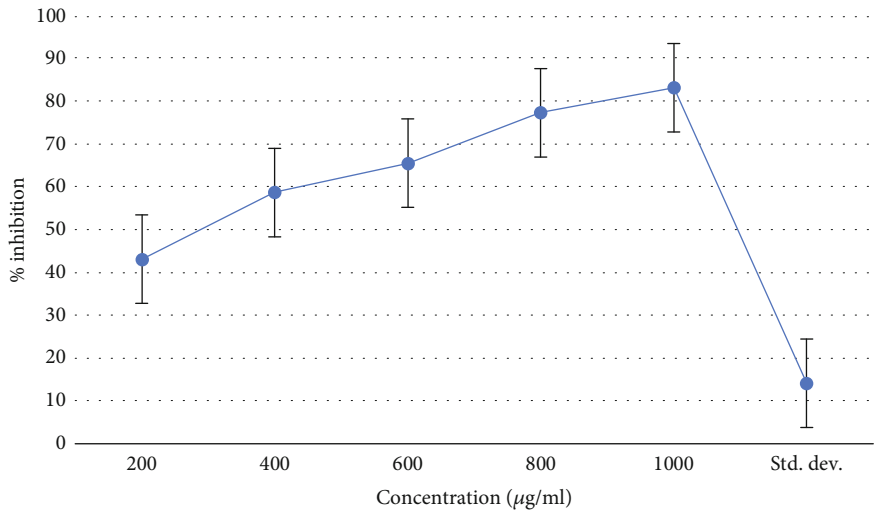

Figure 9: Illustrating total antioxidant activity of antiacne gel.

The following equation was used for calculating the % 2,2-diphenyl-1-picrylhydrazyl scavenged [37].

$$\%2,2\text{-Diphenyl-1-picrylhydrazyl scavenged} = \frac{AB - AA}{AB} \times 100. \quad (4)$$

2.3.9. Antimicrobial Activity. The cup plate method was used to determine the antimicrobial action of gels against cultures of *Cutibacterium acne* [38]. The zones of inhibition were noted after a period of incubation of 48 hrs [39].

2.3.10. Stability Studies. An accelerated stability study was performed according to ICH guidelines, i.e., 40°C/75% ± 5% RH. The gel was stored in the stability chamber at 40°C/75% ± 5% RH for 6 months [40, 41]. Any changes in the physical properties and chemical stability were noted [42].

3. Results and Discussion

3.1. Organoleptic Evaluation. The topical antiacne gels had a whitish appearance and minty odor due to the addition of eucalyptus oil. The active ingredient, 1,8-cineole of eucalyptus oil, is responsible for imparting this sharp, minty, and camphorous odor [43]. The white color of the gel was because of clindamycin phosphate, which is white in color [44]. The consistency of the gel is one of the most critical features of anti-inflammatory and analgesic topical preparations [45]. Topical gels prepared in the current study had a good consistency owing to the addition of plasticizer glycerin. Richard et al. reported that glycerin influenced the viscosity and, thus, the consistency of a topical formulation [46].

3.2. Numerical Optimization. Numerical optimization was done by the Design Expert by optimizing the responses, i.e., permeation of active ingredients, viscosity, and spreadability. The criteria for the data optimization of gels were set by minimizing the quantity of oleic acid (0.3 ml) and

Table 5: Antimicrobial activity of topical gels.

Formulation	Zone of inhibition (cm)
Standard gel (Clindacin)	2.4
Gel with *A. vera*	2.8
Gel with clindamycin phosphate and *A. vera*	3.4

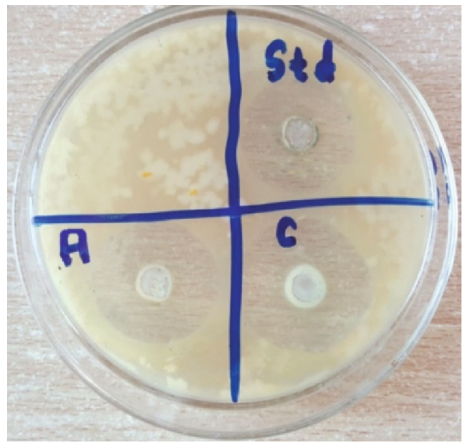

Figure 10: Illustrating antimicrobial activity of gels. A: with single-ingredient *A. vera*; C: with clindamycin phosphate and *A. vera*; Std: standard.

Table 6: Results of stability studies after 6 months.

Parameters	Results
Color	Slightly white
Odor	Mint-like
pH	6.9
Spreadability (g cm/sec)	21
Viscosity (Pa s)	34.220
Drug content (%)	89.9

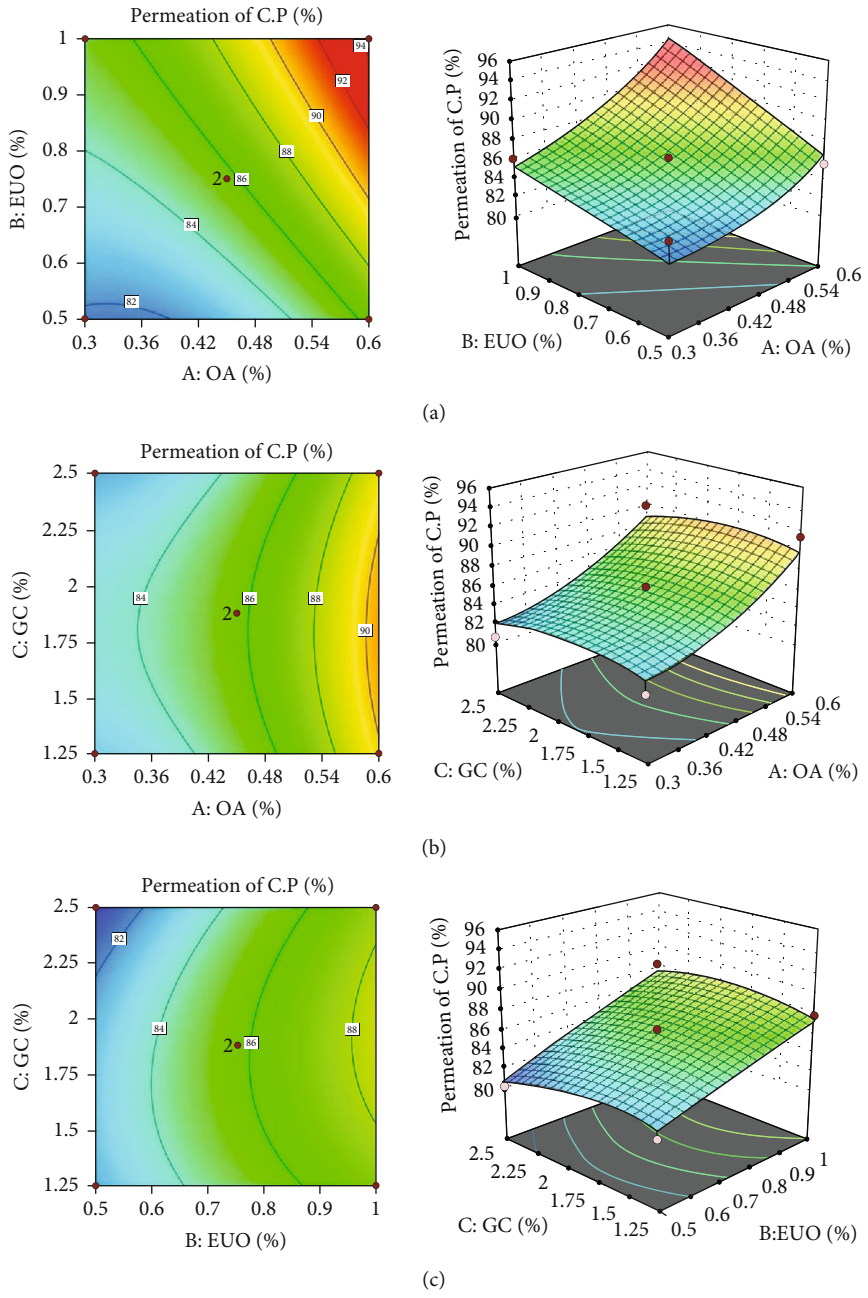

Figure 11: Illustrating the effect of variables on permeation of clindamycin phosphate: (a) EUO and OA, (b) GC and OA, and (c) GC and EUO.

maximizing that of eucalyptus oil (1 ml), while the quantity of glycerin was kept in the range 1.25 to 2.5 ml. The permeation of clindamycin phosphate was kept in the range 80.23 to 92.42%. The permeation of *A. vera* was kept in the range 80 to 91.05%. The viscosity of the gel was kept in the range 22.345 to 47.992 Pa s, and the spreadability was also kept in the range 16.07 to 25 g cm/sec. This resulted in the optimized formulations having a desirability of 1.000 and the following composition given in Table 2.

The predicted outcomes of all responses for the optimized formulation are stated in Table 3.

3.3. pH. The pH of the formulations was found to be in the range of 6.1 to 7.2 (Figure 1), which is desirable because studies show that the pH of the topical formulations must be close to that of the skin as very low pH can cause skin irritation. Lambers et al. studied the pH effect on the adhesion of resident microflora on the skin and suggested that an acidic skin pH helps the bacterial flora to remain attached to the skin. In contrast, basic pH promotes their eradication from the skin [47].

3.4. Viscosity. The viscosity of all gels ranged from 34.561 to 47.992 Pa s (Figure 2), which was consistent with other

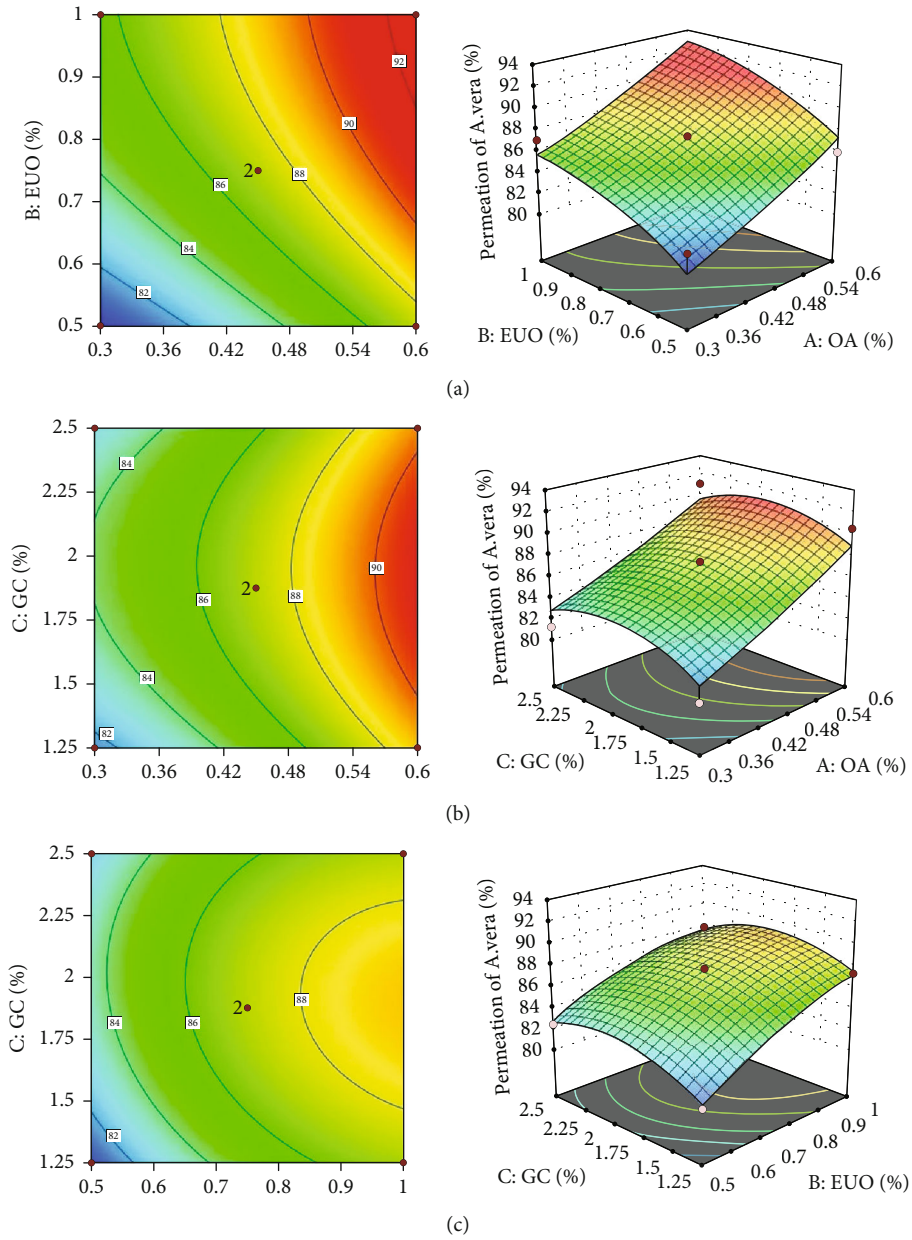

Figure 12: Illustrating the effect of variables on the permeation of *Aloe vera*: (a) EUO and OA, (b) GC and OA, and (c) GC and EUO.

antiacne gels. Research indicates that a high concentration of glycerin plasticizer can cause increased network connectivity as well as hydrogen bonding [48]. This leads to more viscous preparation, thus inferring that glycerin can increase a gel's viscosity [49]. Oleic acid can also impart a higher significant viscosity to the gelling systems by inducing network formation between the molecules [50, 51]. In the current study, the gels with a higher concentration of oleic acid and glycerin were found to have a higher viscosity. Studies have shown that the increased percentages of glycerin can increase the viscosity of the gels. In addition, with the addition of glycerin, the stability of gels also increases [52]. Sant et al. studied the effects of oleic acid, a lipid penetration-enhancing agent, on the *in vitro* release of lumiracoxib from poloxamer-based gel systems. They reported that the addition of oleic acid in the gel systems increased their viscosity significantly. This could be due to the reduction of water content in the gels due to the incorporation of oleic acid which being a viscous liquid contributes to this effect [50].

3.5. Spreadability. The spreadability laid between 16.07 and 25 g cm/sec (Figure 3). This range was found to be compatible with the studies performed by Bhalekar et al., who studied different gelling agents for clindamycin phosphate gel [33].

3.6. Drug Content. The drug contents of all gel formulations were in the specified range, i.e., 90%-110%, showing that the active content ranges of the gels followed the USP specifications.

3.7. Chemical Compatibility of Ingredients of Formulation. The IR spectrum of the formulated topical gels showed peaks at the following locations: at 3500 and 3700 cm^{-1} due to O–H stretching, 2800 to 3000 cm^{-1} indicating a strong N–H stretching, and between 2000 and 2400 cm^{-1} due to strong O≡C≡O stretching. The peak at 1500 cm^{-1} showed the presence of a strong N-O bond. The peak between 1566 and 1650 cm^{-1} indicated medium C≡C stretching. Peaks were also observed at 1650 cm^{-1} due to C=O stretching, at 1085 and 1150 cm^{-1} due to C–O aliphatic ether stretching, and at 885 to 895 cm^{-1} and at 665 to 730 cm^{-1} due to C=C bending (Figure 4).

3.8. In Vitro Permeation Study. The release profiles of all fourteen formulations made using HPMC elicited about 80 to 90% release from the formulation within 8 hrs (Figures 5 and 6). The *in vitro* permeation was quite encouraging as an acceptable amount of drug diffused into the skin from the gels. Among the formulations, F10 showed better release characteristics compared to other formulations. This could be due to the higher amount of permeation enhancers, eucalyptus oil, and oleic acid.

A lot of studies show that when penetration enhancers are used in combination, they can cause synergistic action, which promotes permeation through the skin producing better results compared to a single penetration enhancer [53]. Widely used penetration enhancers and vehicles known as cosolvents have been used in transdermal formulations. They not only increase the solubility of the drug, but they also change the skin structure and enhance the rate of penetration through the skin. So, they improve drug release and permeation as well [54].

Percutaneous absorption of the drug has been improved through the use of numerous fatty acids, such as oleic acid (OA). In this study, the use of a combination of OA plus eucalyptus oil manifests success in a lot of transdermal formulations [55].

Essential oils, along with their constituents, enhance penetration through the skin, and they are widely used in pharmaceutical products. Eucalyptus oil has been proven to be a very famous penetration enhancer in transdermal and dermal formulations [56].

3.9. Characterization of Optimized Gels. Table 4 shows the results obtained from characterization tests on the optimized formulation.

3.9.1. In Vitro Drug Permeation Study. The drug permeation through an optimized gel was found to be 86% (Figure 7). We also found that eucalyptus oil and oleic acid used in the formulation significantly enhanced the permeability of the active ingredients. Our findings were consistent with other studies; for instance, Herman A. and Herman A.P. reported that drug penetration through the skin barrier was proportional to the concentration of eucalyptus oil used in the formulation [57]. Similarly, eucalyptol—a monoterpenoid that constitutes about 90% of eucalyptus oil—was also associated with increased drug permeation through the skin [58]. In another study, Abd et al. reported that eucalyptol and oleic acid greatly enhanced the permeation of active ingredients [59].

Table 7: Analysis of variance of permeation of clindamycin phosphate.

Terms	Degree of freedom	*F*-value	*P* value	Significance
Model	9	3.81	0.1052	No
X_1	1	17.94	0.0133	Yes
X_2	1	12.54	0.0240	Yes
X_3	1	0.1287	0.7379	No
X_1X_2	1	1.05	0.3640	No
X_1X_3	1	0.0021	0.9660	No
X_2X_3	1	0.1902	0.6853	No
X_1^2	1	1.20	0.3355	No
X_2^2	1	0.0119	0.9184	No
X_3^2	1	0.7400	0.4382	No

Table 8: Analysis of variance of permeation of A. vera.

Terms	Degree of freedom	*F*-value	*P* value	Significance
Model	9	3.83	0.1042	No
X_1	1	19.29	0.0118	Yes
X_2	1	11.65	0.0269	Yes
X_3	1	0.3666	0.5776	No
X_1X_2	1	0.0016	0.9701	No
X_1X_3	1	0.0170	0.9024	No
X_2X_3	1	0.1317	0.7351	No
X_1^2	1	0.0947	0.7737	No
X_2^2	1	0.6957	0.4511	No
X_3^2	1	2.24	0.2087	No

3.9.2. Antioxidant Activity. The total antioxidant activity (TAA) of the gels (test formulations) was estimated by plotting a graph between percentage inhibition (%) and concentration (μg/ml), as shown in Figure 8, while the TTA of ascorbic acid (standard) is shown in Figure 9. Upon comparison, both the test formulations and standards followed a similar trend. *A. vera*—the primary active ingredient in the formulated gels—was responsible for the optimum antioxidant activity of the gels.

Furthermore, 2,2-diphenyl-1-picrylhydrazyl assays were also performed to confirm the antioxidant activity of the antiacne gels. The results of the 2,2-diphenyl-1-picrylhydrazyl assay confirmed that both standard (ascorbic acid) and gels (test formulations) significantly reduced the 2,2-diphenyl-1-picrylhydrazyl free radical in a concentration-dependent manner. Studies showed that nonflavonoid polyphenols in *A. vera* account for the majority of its total polyphenolic content, which is responsible for its antioxidant action [60]. Our findings were consistent with another study

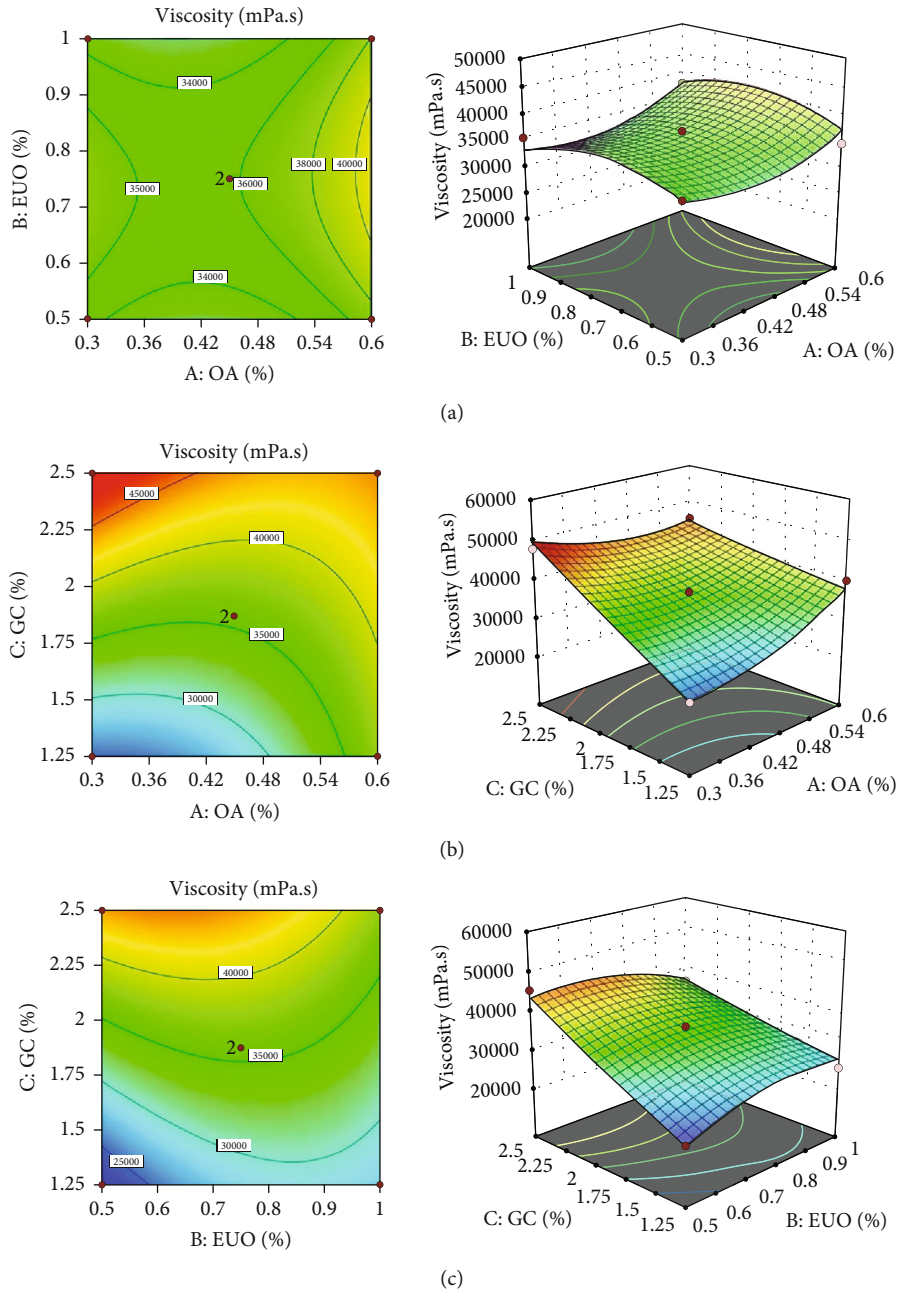

Figure 13: Illustrating the effect of variables on viscosity: (a) EUO and OA, (b) GC and OA, and (c) GC and EUO.

that reported high antioxidant activity of *A. vera* gel against 2,2-diphenyl-1-picrylhydrazyl and ABTS (free radicals) in a concentration-dependent manner [61]. Therefore, our study also suggests the potential applications of *A. vera* gels in treating various skin conditions [62].

3.9.3. Antimicrobial Activity. We tested the antimicrobial activity of a single ingredient *A. vera* (A) and compared it with a marketed clindamycin phosphate formulation (Clindacin) (Std) and a gel containing both *A. vera* and clindamycin phosphate (C). The zones of inhibition for A with single-ingredient *A. vera*, C with clindamycin phosphate and *A. vera*, and Std (standard) were measured and are shown in Table 5.

Our findings suggested a significant inhibitory effect of the gels (test formulations) on the bacterial strain *Cutibacterium acnes* as shown in Figure 10. The inhibitory effect of single-ingredient *A. vera* gel (A) was comparable to that of the marketed clindamycin phosphate formulation (Std). The inhibitory effect of gels containing both *A. vera* and clindamycin phosphate (C) was estimated to be higher than the standard and single-ingredient *A. vera* gel (A).

Since the antimicrobial activity of active ingredients is crucial in the treatment of *acne vulgaris* [19], our study suggests the potential application of *A. vera* gels in the treatment of acne. Moreover, *A. vera* gels also contain specific polysaccharides and hydroxylated phenols such as pyrocatechol that exhibit antimicrobial properties [63].

Studies indicate that the saponins, phenols, flavonoids, terpenes, and tannins present in *A. vera* impart antibacterial and anti-inflammatory properties to this plant [64]. Moreover, the comparison of conventional treatments (antibiotics) with *A. vera* has shown that *A. vera* shows higher inhibitory effects against acne-causing bacteria [65].

3.9.4. Stability Study. We subjected the formulated gels to stability testing (45°C/75% RH) to assess any changes in their characteristics after six months, and the results are shown in Table 6. The physical appearance (color, homogeneity, and texture) of all formulations was intact after week 24 (when compared to week 0) at the given conditions. The viscosity of each formulation was estimated to be between 30 Pa s and 40 Pa s, and we found no significant changes in their viscosities at week 24 (when compared to week 0). The prolonged stability of the gels can also be due to the antimicrobial action of paraben preservatives used in the formulation [66]. Moreover, the antimicrobial and antioxidant properties of *A. vera* gels can also contribute to the prolonged shelf-life of these topical gels [67].

3.10. Response Surface Methodology. The different responses, including the permeation of active ingredients, the viscosity of gels, and the spreadability of the gels, were studied by response surface methodology. Contours and 3D graphs illustrating the effects of different variables, i.e., oleic acid, eucalyptus oil, and glycerin, were generated by Design Expert.

3.10.1. In Vitro Permeation of Active Ingredients. The contour and 3D graphs of the factors affecting the permeation of active ingredients clindamycin phosphate (Figure 11) and *A. vera* (Figure 12) indicated that both surfactant oleic acid and permeation enhanced; eucalyptus oil significantly increased the permeation of drugs from the topical gels. Glycerin also increased the permeation of drugs, but its effect was lower in comparison to other factors. Moreover, the comparison of the influence of surfactant and permeation enhancer on drug permeation revealed that the surfactant had a better impact on increasing permeability.

Anwar et al. [68] also reported that oleic acid acted as a permeation enhancer in transdermal drug delivery. About 75% of eucalyptus oil is made of 1,8-cineole. The cineole is a cyclic terpene that generates liquid pools in the stratum corneum and changes its lipid structure. So this facilitates the penetration of polar and nonpolar drugs [69]. A study conducted in 2020 shows that adding glycerin can enhance drug penetration, explained through the value of flux. The value of flux increases with the increase in the concentration of glycerin. The mechanism of action of glycerin is that it hydrates the stratum corneum and increases the solubility of drugs. It can also increase the value of patches for hygroscopic moisture content [70].

Tables 7 and 8 show the analysis of variance of permeation of clindamycin phosphate and *A. vera*, respectively.

3.10.2. Viscosity. The developed graphs showed the various effects of variables on the viscosity of the topical gels (Figure 13). They indicated that the viscosity of the gels was increased by factors of oleic acid and glycerin while decreased by eucalyptus oil. A broadly used nonaqueous hydrogen bonding solvent, glycerol, is mainly used due to its good physical properties, which makes it useful for many industrial formulations. A study conducted by Matthews et al. shows that the material properties of solvents are more in glycerol than water as it follows the trend of hydrogen bonding capacity [71]. This H-bonding results in network formation that increases the viscosity of the gel to which glycerin may be added [72]. Table 9 shows the analysis of variance of viscosity of the gel formulation.

Table 9: Analysis of variance of viscosity.

Terms	Degree of freedom	F-value	P value	Significance
Model	9	9.72	0.0213	Yes
X_1	1	3.05	0.1555	No
X_2	1	0.0161	0.9052	No
X_3	1	59.60	0.0015	Yes
X_1X_2	1	0.1583	0.7110	No
X_1X_3	1	9.86	0.0348	Yes
X_2X_3	1	4.61	0.0982	No
X_1^2	1	3.89	0.1198	No
X_2^2	1	4.18	0.1103	No
X_3^2	1	0.0656	0.8104	No

3.10.3. Spreadability. The impact of the variables on the spreadability of gels, as indicated by the graphs (Figure 14), showed that the overall response was constructive. Eucalyptus oil was seen to have a positive impact on spreadability. In contrast, oleic acid and glycerin seemed to decrease the spreadability. Table 10 shows the analysis of the variance of spreadability of gel formulation.

3.11. Mathematical Modeling and ANOVA by Design Expert.

$$\begin{aligned}\text{Permeation of clindamycin phosphate} &= 85.71 + 3.47 + 2.9 \\ &\quad - 0.2938 + 1.19 - 0.0525 + 1.42 - 0.1412 - 1.11,\end{aligned}$$

$$\begin{aligned}\text{Permeation of A.vera} &= 87.18 + 3.51 + 2.73 + 0.48383 \\ &\quad + 0.045 - 0.1475 - 0.41 + 0.3888 - 1.05 - 1.89,\end{aligned}$$

$$\begin{aligned}\text{Viscosity} &= 35825 + 1794.87 - 130.25 + 7929.63 + 578 \\ &\quad - 4561.75 - 3120 + 320363 - 3321.12 + 416.12,\end{aligned}$$

$$\begin{aligned}\text{Spreadability of HPMC gels} &= 16.07 - 1.27 + 0.7512 - 1.98 \\ &\quad - 0.9375 + 0.2675 + 1.5 + 0.46 + 1.82 + 2.49.\end{aligned} \tag{5}$$

The mathematical models obtained by the Design Expert for permeation showed positive values indicating that the overall response was constructive. All three factors enhanced the permeation of both active ingredients.

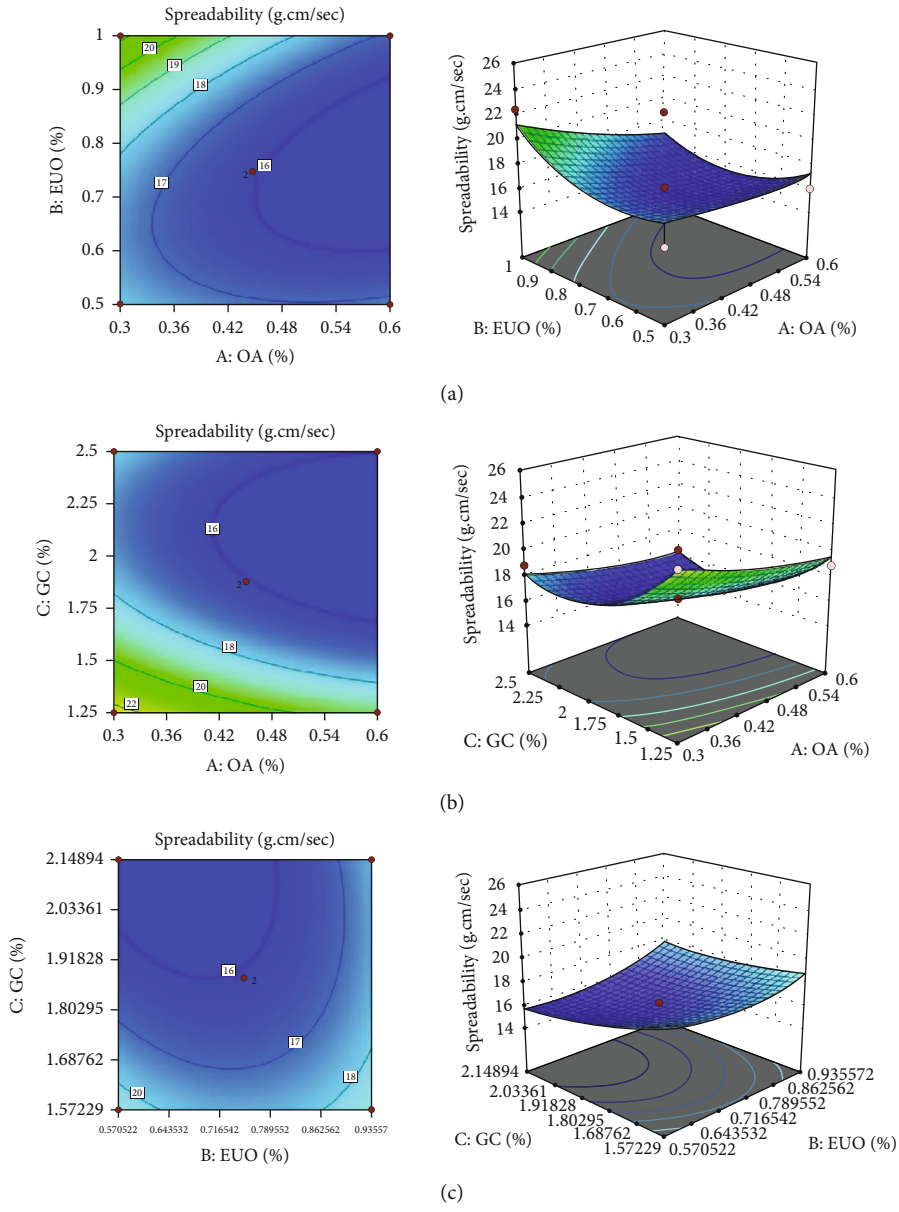

Figure 14: Illustrating the effect of variables on spreadability: (a) EUO and OA, (b) GC and OA, and (c) GC and EUO.

Table 10: Analysis of variance of spreadability.

Terms	Degree of freedom	F-value	P value	Significance
Model	9	9.72	0.0213	Yes
X_1	1	3.05	0.1555	No
X_2	1	0.0161	0.9052	No
X_3	1	59.60	0.0015	Yes
X_1X_2	1	0.1583	0.7110	No
X_1X_3	1	9.86	0.0348	Yes
X_2X_3	1	4.61	0.0982	No
X_1^2	1	3.89	0.1198	No
X_2^2	1	4.18	0.1103	No
X_3^2	1	0.0656	0.8104	No

The polynomial equation indicated that the viscosity of the gels was increased by factors X_1 and X_3 while decreased by X_2. The positive value of X_0 indicated that the overall response was positive. Oleic acid and glycerin improved the viscosity as they had a thickening effect on the gels, whereas it was observed that eucalyptus oil decreased the viscosity of the topical gels.

The impact of the variables on the spreadability of gels, as indicated by the mathematical models, showed that the response was constructive. Factor X_2 had a positive impact on spreadability. In contrast, X_1 and X_3 decreased the spreadability. This could be explained by the fact that the spreadability and viscosity are inversely proportional. So, the factors reducing the viscosity of the gels will, in turn, increase their spreadability.

4. Conclusions

In this study, we successfully developed and evaluated topical gels containing Aloe vera and clindamycin phosphate, focusing on their antimicrobial and antioxidant properties. Our comprehensive assessment included tests for organoleptic properties, pH, spreadability, in vitro permeability, skin irritation, and stability. The findings reveal that the formulated antiacne gels exhibit potent antimicrobial activity against acne vulgaris and significant antioxidant action. Notably, the gels demonstrated consistent stability and reproducibility, underscoring their potential as effective treatments for acne and other inflammatory skin conditions. The correlation of our results with existing studies further validates the efficacy of Aloe vera-containing topical gels in dermatological applications. While the current findings are promising, we acknowledge the necessity for further in vivo studies to fully ascertain the therapeutic potential of these gels. Such studies will provide deeper insights into their efficacy and safety profiles, contributing to the development of more effective acne treatments. In conclusion, our research contributes to the growing body of evidence supporting the use of Aloe vera in dermatological applications, particularly in the treatment of acne. We anticipate that these findings will pave the way for future research, potentially leading to innovative and more effective acne treatment solutions.

Data Availability

All the available data has been presented in this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Conceptualization was done by Muhammad Zaman and Muhammad Jamshaid. Data curation was carried out by Mahtab Ahmad Khan and Muhammad Jamshaid. Formal analysis was performed by Tayyaba Rana and Abdul Qayyum. Funding acquisition was done by Ghadeer M. Albadrani, Nehal Ahmed Talaat Nouh, Fatma M El-Demerdash, and Mohamed Kamel. Investigation was assisted by Mohamed M. Abdel-Daim and Abdul Qayyum Khan. Methodology was performed by Tayyaba Rana and Muhammad Zaman. Project administration was contributed by Tayyaba Rana and Muhammad Zaman. Resources were provided by Ghadeer M. Albadrani, Nehal Ahmed Talaat Nouh, Fatma M El-Demerdash, Mohamed Kamel, and Mohamed M. Abdel-Daim. Software was provided by Tayyaba Rana and Muhammad Jamshaid. Validation was participated by Mahtab Ahmad Khan and Mohamed M. Abdel-Daim. Writing of the original draft was the responsibility of Tayyaba Rana and Muhammad Zaman. Writing, reviewing, and editing were contributed by Tayyaba Rana and Muhammad Zaman, Ghadeer M. Albadrani, Nehal Ahmed Talaat Nouh, and Fatma M El-Demerdash. All authors have read and agreed to the published version of the manuscript.

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References

[1] I. B. Putra, N. K. Jusuf, and N. K. Dewi, "The role of digital fluorescence in acne vulgaris: correlation of ultraviolet red fluorescence with the severity of acne vulgaris," *Dermatology Research and Practice*, vol. 2019, Article ID 4702423, 4 pages, 2019.

[2] A. Jain, N. K. Garg, A. Jain et al., "A synergistic approach of adapalene-loaded nanostructured lipid carriers, and vitamin C co-administration for treating acne," *Drug Development and Industrial Pharmacy*, vol. 42, no. 6, pp. 897–905, 2016.

[3] J. McLaughlin, S. Watterson, A. M. Layton, A. J. Bjourson, E. Barnard, and A. McDowell, "*Propionibacterium acnes* and acne vulgaris: new insights from the integration of population genetic, multi-omic, biochemical and host-microbe studies," *Microorganisms*, vol. 7, no. 5, p. 128, 2019.

[4] S. Yang, Y. Jiang, X. Yu et al., "Polyphyllin I inhibits Propionibacterium acnes-induced IL-8 secretion in HaCaT cells by downregulating the CD36/NOX1/ROS/NLRP3/IL-1β pathway," *Evidence-Based Complementary and Alternative Medicine*, vol. 2021, Article ID 1821220, 11 pages, 2021.

[5] T. Ramezanli and B. B. Michniak-Kohn, "Development and characterization of a topical gel formulation of adapalene-TyroSpheres and assessment of its clinical efficacy," *Molecular Pharmaceutics*, vol. 15, no. 9, pp. 3813–3822, 2018.

[6] B. Kumar, K. Jalodia, P. Kumar, and H. K. Gautam, "Recent advances in nanoparticle-mediated drug delivery," *Journal of Drug Delivery Science and Technology*, vol. 41, pp. 260–268, 2017.

[7] T. Garg, "Current nanotechnological approaches for an effective delivery of bio-active drug molecules in the treatment of acne," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 44, no. 1, pp. 98–105, 2016.

[8] S. Verma, P. Utreja, and L. Kumar, "Nanotechnological carriers for treatment of acne," *Recent Patents on Anti-Infective Drug Discovery*, vol. 13, no. 2, pp. 105–126, 2018.

[9] A. Layton, "A review on the treatment of acne vulgaris," *International Journal of Clinical Practice*, vol. 60, pp. 64–72, 2006.

[10] T. A. Nguyen and L. F. Eichenfield, "Profile of clindamycin phosphate 1.2%/benzoyl peroxide 3.75% aqueous gel for the treatment of acne vulgaris," *Clinical, Cosmetic and Investigational Dermatology*, vol. 8, pp. 549–554, 2015.

[11] K. J. Silvestre, *Design, Synthesis, and Study of Lincosamide Antibiotics Containing a Bicyclic Amino Acid Moiety*, Harvard University, 2019.

[12] J. Q. Del Rosso, "Clindamycin phosphate-tretinoin combination gel revisited: status report on a specific formulation used for acne treatment," *Cutis*, vol. 99, no. 3, pp. 179–183, 2017.

[13] V. Mazzarello, M. Donadu, M. Ferrari et al., "Treatment of acne with a combination of propolis, tea tree oil, and Aloe vera compared to erythromycin cream: two double-blind investigations," *Clinical Pharmacology: Advances and Applications*, vol. 10, pp. 175–181, 2018.

[14] K. Hemminki, L. Zhang, J. Krüger, H. Autrup, M. Törnqvist, and H.-E. Norbeck, "Exposure of bus and taxi drivers to urban air pollutants as measured by DNA and protein adducts," *Toxicology Letters*, vol. 72, no. 1-3, pp. 171–174, 1994.

[15] J. K. Triantafillidis, C. Vagianos, and A. E. Papalois, "The role of enteral nutrition in patients with inflammatory bowel disease: current aspects," *BioMed Research International*, vol. 2015, Article ID 197167, 12 pages, 2015.

[16] S. Jain, N. Rathod, R. Nagi et al., "Antibacterial effect of Aloe vera gel against oral pathogens: an in-vitro study," *Journal of Clinical and Diagnostic Research: JCDR*, vol. 10, pp. ZC41–ZC44, 2016.

[17] G. Norman, J. Christie, Z. Liu et al., "Antiseptics for burns," *Cochrane Database of Systematic Reviews*, vol. 7, no. 7, article CD011821, 2017.

[18] A. A. Maan, A. Nazir, M. K. I. Khan et al., "The therapeutic properties and applications of Aloe vera: a review," *Journal of Herbal Medicine*, vol. 12, pp. 1–10, 2018.

[19] M. B. Abdel-Naser and C. Zouboulis, "Clindamycin phosphate/tretinoin gel formulation in the treatment of acne vulgaris," *Expert Opinion on Pharmacotherapy*, vol. 9, no. 16, pp. 2931–2937, 2008.

[20] L. Langmead, R. J. Makins, and D. S. Rampton, "Anti-inflammatory effects of aloe vera gel in human colorectal mucosa in vitro," *Alimentary Pharmacology & Therapeutics*, vol. 19, no. 5, pp. 521–527, 2004.

[21] P. Gao and P. E. Fagerness, "Diffusion in HPMC gels. I. Determination of drug and water diffusivity by pulsed-field-gradient spin-echo NMR," *Pharmaceutical Research*, vol. 12, no. 7, pp. 955–964, 1995.

[22] A. Naik, L. A. Pechtold, R. O. Potts, and R. H. Guy, "Mechanism of oleic acid-induced skin penetration enhancement *in vivo* in humans," *Journal of Controlled Release*, vol. 37, no. 3, pp. 299–306, 1995.

[23] M. Karakatsani, M. Dedhiya, and F. M. Plakogiannis, "The effect of permeation enhancers on the viscosity and the release profile of transdermal hydroxypropyl methylcellulose gel formulations containing diltiazem HCl," *Drug Development and Industrial Pharmacy*, vol. 36, no. 10, pp. 1195–1206, 2010.

[24] C.-W. Cho, J.-S. Choi, and S.-C. Shin, "Enhanced local anesthetic action of mepivacaine from the bioadhesive gels," *Pakistan Journal of Pharmaceutical Sciences*, vol. 24, no. 1, pp. 87–93, 2011.

[25] L. C. A. Barbosa, C. A. Filomeno, and R. R. Teixeira, "Chemical variability and biological activities of *Eucalyptus* spp. essential oils," *Molecules*, vol. 21, no. 12, article 1671, 2016.

[26] H. J. Park, J. Bunn, C. L. Weller, P. Vergano, and R. Testin, "Water vapor permeability and mechanical properties of grain protein-based films as affected by mixtures of polyethylene glycol and glycerin plasticizers," *Transactions of the ASAE*, vol. 37, no. 4, p. 1281, 1994.

[27] J. Zaroslinski, R. Browne, and L. Possley, "Propylene glycol as a drug solvent in pharmacologic studies," *Toxicology and Applied Pharmacology*, vol. 19, no. 4, pp. 573–578, 1971.

[28] P. M. Patil, S. B. Wankhede, and P. D. Chaudhari, "Stability-indicating HPTLC method for simultaneous determination of Ketoprofen, methyl paraben and propyl paraben in gel formulation," *Journal of Pharmacy Research*, vol. 6, no. 9, pp. 945–953, 2013.

[29] E. R. Cooper, E. W. Merritt, and R. L. Smith, "Effect of fatty acids and alcohols on the penetration of acyclovir across human skin in vitro," *Journal of Pharmaceutical Sciences*, vol. 74, no. 6, pp. 688-689, 1985.

[30] A. Kola-Mustapha, K. Yohanna, Y. Ghazali, and H. Ayotunde, "Design, formulation and evaluation of Chasmanthera dependens Hochst and Chenopodium ambrosioides Linn based gel for its analgesic and anti-inflammatory activities," *Heliyon*, vol. 6, no. 9, article e04894, 2020.

[31] M. X. Chen, K. S. Alexander, and G. Baki, "Formulation and evaluation of antibacterial creams and gels containing metal ions for topical application," *Journal of Pharmaceutics*, vol. 2016, Article ID 5754349, 10 pages, 2016.

[32] N. Ijaz, A. I. Durrani, S. Rubab, and S. Bahadur, "Formulation and characterization of Aloe vera gel and tomato powder containing cream," *Acta Ecologica Sinica*, vol. 42, no. 2, pp. 34–42, 2022.

[33] M. R. Bhalekar, A. R. Madgulkar, and G. J. Kadam, "Evaluation of gelling agents for clindamycin phosphate gel," *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 4, no. 7, pp. 2022–2033, 2015.

[34] V. S. Lakshmi, R. D. Manohar, S. Mathan, and S. S. Dharan, "Formulation and evaluation of ufasomal topical gel containing selected non steroidal anti inflammatory drug (NSAIDs)," *Journal of Pharmaceutical Sciences and Research*, vol. 13, pp. 38–48, 2021.

[35] S. A. Al-Suwayeh, E. I. Taha, F. M. Al-Qahtani, M. O. Ahmed, and M. M. Badran, "Evaluation of skin permeation and analgesic activity effects of carbopol lornoxicam topical gels containing penetration enhancer," *The Scientific World Journal*, vol. 2014, Article ID 127495, 9 pages, 2014.

[36] A. I. Segall, "Preformulation: the use of FTIR in compatibility studies; South Asian Academic Publications," *Journal of Innovations in Applied Pharmaceutical Science*, vol. 4, pp. 1–6, 2019.

[37] K. Sirivibulkovit, S. Nouanthavong, and Y. Sameenoi, "Paper-based DPPH assay for antioxidant activity analysis," *Analytical Sciences*, vol. 34, no. 7, pp. 795–800, 2018.

[38] N. Roy, S. Mandal, B. Mahanti, and S. Dasgupta, "Antimicrobial activity of green tea: a comparative study with different green tea extract," *PharmaTutor*, vol. 6, no. 1, pp. 23–29, 2018.

[39] Y. G. Bachhav and V. B. Patravale, "Formulation of meloxicam gel for topical application: in vitro and *in vivo* evaluation," *Acta Pharmaceutica*, vol. 60, no. 2, pp. 153–163, 2010.

[40] S. Das and A. B. Wong, "Stabilization of ferulic acid in topical gel formulation via nanoencapsulation and pH optimization," *Scientific Reports*, vol. 10, no. 1, article 12288, 2020.

[41] S. Chaniyara, D. Modi, R. Patel, J. Patel, R. Desai, and S. Chaudhary, "Formulation & evaluation of floatable in situ gel for stomach-specific drug delivery of ofloxacin," *American Journal of Advanced Drug Delivery*, vol. 1, pp. 285–299, 2013.

[42] M. Goyani, B. Akbari, S. Chaudhari, and R. Jivawala, "Formulation and evaluation of topical emulgel of antiacne agent," *International Journal of Advanced Research and Review*, vol. 3, pp. 52–68, 2018.

[43] T. Kaura, A. Mewara, K. Zaman et al., "Utilizing larvicidal and pupicidal efficacy of Eucalyptus and neem oil against Aedes

mosquito: an approach for mosquito control," *Tropical Parasitology*, vol. 9, p. 12, 2019.

[44] N. Thakur, P. Jain, and V. Jain, "Formulation development and evaluation of transferosomal gel," *Journal of Drug Delivery and Therapeutics*, vol. 8, no. 5, pp. 168–177, 2018.

[45] M. G. Dantas, S. A. Reis, C. M. Damasceno et al., "Development and evaluation of stability of a gel formulation containing the monoterpene borneol," *The Scientific World Journal*, vol. 2016, Article ID 7394685, 4 pages, 2016.

[46] C. Richard, E. Souloumiac, J. Jestin, M. Blanzat, and S. Cassel, "Influence of dermal formulation additives on the physicochemical characteristics of catanionic vesicles," *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, vol. 558, pp. 373–383, 2018.

[47] H. Lambers, S. Piessens, A. Bloem, H. Pronk, and P. Finkel, "Natural skin surface pH is on average below 5, which is beneficial for its resident flora," *International Journal of Cosmetic Science*, vol. 28, no. 5, pp. 359–370, 2006.

[48] G. Wypych, "Plasticizers use and selection for specific polymers," in *Handbook of Plasticizers*, G. Wypych, Ed., pp. 333–483, ChemTec Publishing, 2017.

[49] G. Christensen, H. Younes, H. Hong, and P. Smith, "Effects of solvent hydrogen bonding, viscosity, and polarity on the dispersion and alignment of nanofluids containing Fe_2O_3 nanoparticles," *Journal of Applied Physics*, vol. 118, no. 21, article 214302, 2015.

[50] T. Sant, A. Moreira, V. P. de Sousa, and M. B. R. Pierre, "Influence of oleic acid on the rheology and *in vitro* release of lumiracoxib from poloxamer gels," *Journal of Pharmacy & Pharmaceutical Sciences*, vol. 13, no. 2, pp. 286–302, 2010.

[51] C. V. Nikiforidis, E. P. Gilbert, and E. Scholten, "Organogel formation via supramolecular assembly of oleic acid and sodium oleate," *RSC Advances*, vol. 5, no. 59, pp. 47466–47475, 2015.

[52] J. M. Busnel, A. Varenne, S. Descroix, G. Peltre, Y. Gohon, and P. Gareil, "Evaluation of capillary isoelectric focusing in glycerol-water media with a view to hydrophobic protein applications," *Electrophoresis*, vol. 26, no. 17, pp. 3369–3379, 2005.

[53] P. Karande and S. Mitragotri, "Enhancement of transdermal drug delivery via synergistic action of chemicals," *Biochimica et Biophysica Acta (BBA)-Biomembranes*, vol. 1788, pp. 2362–2373, 2009.

[54] D. Hashmat, M. H. Shoaib, F. R. Ali, and F. Siddiqui, "Lornoxicam controlled release transdermal gel patch: design, characterization and optimization using co-solvents as penetration enhancers," *PLoS One*, vol. 15, no. 2, article e0228908, 2020.

[55] A. C. Williams and B. W. Barry, "Penetration enhancers," *Advanced Drug Delivery Reviews*, vol. 64, pp. 128–137, 2012.

[56] B. Alhasso, M. U. Ghori, and B. R. Conway, "Systematic review on the effectiveness of essential and carrier oils as skin penetration enhancers in pharmaceutical formulations," *Scientia Pharmaceutica*, vol. 90, no. 1, p. 14, 2022.

[57] A. Herman and A. P. Herman, "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," *Journal of Pharmacy and Pharmacology*, vol. 67, no. 4, pp. 473–485, 2015.

[58] E. Abd, S. Namjoshi, Y. H. Mohammed, M. S. Roberts, and J. E. Grice, "Synergistic skin penetration enhancer and nanoemulsion formulations promote the human epidermal permeation of caffeine and naproxen," *Journal of Pharmaceutical Sciences*, vol. 105, no. 1, pp. 212–220, 2016.

[59] E. Abd, H. A. E. Benson, M. S. Roberts, and J. E. Grice, "Minoxidil skin delivery from nanoemulsion formulations containing eucalyptol or oleic acid: enhanced diffusivity and follicular targeting," *Pharmaceutics*, vol. 10, no. 1, p. 19, 2018.

[60] K. M. Salawu, E. O. Ajaiyeoba, O. O. Ogbole, J. A. Adeniji, T. C. Faleye, and A. Agunu, "Antioxidant, brine shrimp lethality, and antiproliferative properties of gel and leaf extracts of Aloe schweinfurthii and Aloe vera," *Journal of Herbs, Spices & Medicinal Plants*, vol. 23, no. 4, pp. 263–271, 2017.

[61] M. H. Radha and N. P. Laxmipriya, "Evaluation of biological properties and clinical effectiveness of Aloe vera: a systematic review," *Journal of Traditional and Complementary Medicine*, vol. 5, no. 1, pp. 21–26, 2015.

[62] M. Hęś, K. Dziedzic, D. Górecka, A. Jędrusek-Golińska, and E. Gujska, "Aloe vera (L.) Webb.: natural sources of antioxidants–a review," *Plant Foods for Human Nutrition*, vol. 74, no. 3, pp. 255–265, 2019.

[63] E. Jose, S. Joseph, and M. Joy, "Aloe vera and its biological activities," *World Journal of Current Medical and Pharmaceutical Research*, vol. 3, no. 2, pp. 21–26, 2021.

[64] H. Azimi, M. Fallah-Tafti, A. A. Khakshur, and M. Abdollahi, "A review of phytotherapy of acne vulgaris: perspective of new pharmacological treatments," *Fitoterapia*, vol. 83, no. 8, pp. 1306–1317, 2012.

[65] S. Abiya, B. Odiyi, L. Falarunu, and N. Abiya, "Antimicrobial activity of three medicinal plants against acne-inducing bacteria Propionibacterium acnes," *Brazilian Journal of Biological Sciences*, vol. 5, no. 10, pp. 277–288, 2018.

[66] M. Senthilkumar and S. Dash, "Interaction of methylparaben and propylparaben with P123/F127 mixed polymeric micelles," *Colloids and Surfaces B: Biointerfaces*, vol. 176, pp. 140–149, 2019.

[67] A. Carac, R. Boscencu, S. Patriche, R. M. Dinica, G. Carac, and C. E. Gird, "Antioxidant and antimicrobial potential of extracts from Aloe vera leaves," *Revista de Chimie (Bucharest)*, vol. 4, pp. 654–658, 2016.

[68] N. Anwar, S. U. Jan, and R. Gul, "Formulation and evaluation of glibenclamide gel for transdermal drug delivery," *International Journal of Current Pharmaceutical Research*, vol. 12, pp. 35–39, 2020.

[69] A. Salimi, "The effect of herbal penetration enhancers on the skin permeability of mefenamic acid through rat skin," *Turkish Journal of Pharmaceutical Sciences*, vol. 20, no. 2, pp. 108–114, 2023.

[70] F. N. Pratama, C. Umam, L. Ameliana, and D. Nurahmanto, "The effect of glycerin as penetration enhancer in a ketoprofen solid preparation–patch on in vitro penetration study through rat skin," *Annals of Tropical Medicine and Public Health*, vol. 23, no. 3, pp. 71–83, 2020.

[71] L. Matthews, Ż. Przybyłowicz, S. E. Rogers et al., "The curious case of SDS self-assembly in glycerol: formation of a lamellar gel," *Journal of Colloid and Interface Science*, vol. 572, pp. 384–395, 2020.

[72] C. Torres, S. Moecke, A. Mafetano, L. Cornélio, R. Di Nicoló, and A. Borgesd, "Influence of viscosity and thickener on the effects of bleaching gels," *Operative Dentistry*, vol. 47, no. 3, pp. E119–E130, 2022.