

FORMULATION AND EVALUATION OF ORNIDAZOLE-LOADED TOPICAL AMPHIPHILOGEL FOR LOCALIZED ANTIMICROBIAL DELIVERY

Shresth Shukla*, Umesh Pratap Singh, Nidhi Srivastava

Department of Pharmacy, Rameshwaram Institute of Technology & Management, Lucknow, Uttar Pradesh, India

ABSTRACT

Background: Topical delivery of antimicrobial drugs can provide direct drug availability at the affected skin site while potentially limiting unnecessary systemic exposure. The performance of such formulations depends on their ability to maintain suitable physicochemical properties, release the incorporated drug in a controlled manner and interact appropriately with the skin. Amphiphilic systems combine surfactant-rich and gel-forming components and therefore provide an alternative platform for topical drug delivery.

Methods: Nine Ornidazole amphiphilic gel formulations (F1–F9) containing 1% w/w drug were prepared using Span 60, Tween 80, isopropyl myristate and distilled water. The formulations were examined for physical appearance, homogeneity, pH, drug content, spreadability, extrudability, viscosity and rheological characteristics. In-vitro drug release was investigated using a Franz diffusion cell with phosphate buffer pH 7.4 as the receptor medium. The release data obtained from the optimized formulation were fitted to mathematical kinetic models. Ex-vivo skin permeation and drug retention were subsequently assessed, followed by antimicrobial evaluation and a three-month stability study.

Results: All formulations showed acceptable physical characteristics without visible phase separation. F5 exhibited a pH of 6.43 ± 0.03 , drug content of $99.12 \pm 0.48\%$, viscosity of 8120 ± 156 cP, yield stress of 32.7 Pa, and spreadability of 7.28 ± 0.22 g/cm/s. The formulation released 81.6% Ornidazole over 12 h. Among the evaluated kinetic models, the Korsmeyer–Peppas model provided the highest correlation ($R^2 = 0.9920$) with a release exponent of 0.7098, suggesting anomalous release behaviour. After 12 h, cumulative ex-vivo permeation from F5 was 57.8%, whereas the reference formulation showed 60.2%. In contrast, F5 produced greater skin retention ($44.7 \mu\text{g}/\text{cm}^2$) than the reference ($29.8 \mu\text{g}/\text{cm}^2$). The inhibition zone produced by F5 was 21.4 ± 0.5 mm, compared with 17.8 ± 0.6 mm for the Ornidazole reference formulation. The placebo produced no measurable inhibition. Following three months of stability evaluation, F5 retained a drug content of $98.43 \pm 0.61\%$, viscosity of 7960 ± 174 cP, spreadability of 7.39 ± 0.27 g/cm/s, and 12-h drug release of $80.2 \pm 1.5\%$.

Conclusion: The optimized F5 amphiphilic gel demonstrated an appropriate combination of physicochemical properties, rheological performance, controlled drug release, enhanced dermal retention and measurable antimicrobial activity. The formulation remained comparatively stable during the three-month evaluation and may therefore serve as a promising platform for further investigation of localized Ornidazole delivery.

Keywords: Ornidazole; amphiphilic gel; topical drug delivery; Span 60; Tween 80; isopropyl myristate; controlled release; skin retention; antimicrobial activity; stability.

1. INTRODUCTION

Topical administration provides an attractive approach for treating disorders in which the therapeutic target is located within or near the skin. Direct application of a formulation can establish drug availability at the site of administration and may reduce the need for systemic exposure. [1,2] Nevertheless, successful topical therapy depends on several formulation and biological factors, particularly drug solubility, release from the vehicle, residence at the application site and interaction with the skin barrier. [3,4,5] The stratum corneum is the major barrier limiting movement of many pharmaceutical substances into deeper skin layers. Conventional topical preparations such as creams, ointments, lotions and gels are widely used because of their simplicity and established acceptability. [6,7] However, a conventional vehicle may not simultaneously provide adequate drug incorporation, controlled release, satisfactory spreading and prolonged contact with the skin. These limitations have encouraged the development of structured semisolid systems capable of modifying drug–vehicle and drug–skin interactions. Amphiphilic systems represent one such formulation approach. Their composition incorporates amphiphilic components into a structured semisolid matrix. [8] The coexistence of hydrophilic and lipophilic environments can be useful for incorporating drugs with different physicochemical characteristics, while the internal structure of the gel can influence viscosity, drug diffusion and residence time. Surfactant concentration and the nature of the gel-forming component can consequently have a substantial effect on the final pharmaceutical performance of the system. [9,10,11] Ornidazole is a

5-nitroimidazole antimicrobial drug with activity against susceptible anaerobic microorganisms and protozoal organisms. Its antimicrobial effect is associated with intracellular reduction of the nitro group and formation of reactive intermediates capable of damaging microbial DNA. The drug therefore represents a suitable candidate for investigation in localized antimicrobial delivery systems. [12,13]

A topical formulation of Ornidazole may provide an opportunity to maintain the drug near the intended site of action while regulating its release and interaction with the skin. The present study therefore focused on the development of Ornidazole-loaded amphiphilogels using Span 60, non-ionic surfactants and isopropyl myristate.

2. MATERIALS AND METHODS

2.1 Materials

Ornidazole was obtained from Tokyo Chemical Industry, India Pvt. Ltd. Span 60 was procured from CDH Fine Chem, while Tween 80, isopropyl myristate, potassium dihydrogen phosphate and sodium hydroxide were obtained from CDH Fine Chem. Methanol was obtained from Renkem Pvt. Ltd. Distilled water was supplied by the laboratory.

2.2 Preformulation Studies

The drug was examined for physical appearance, colour and odour. Solubility was investigated in purified water, 0.1 M hydrochloric acid, phosphate buffer pH 7.4, methanol and ethanol. Melting point was determined by the capillary method. The maximum absorption wavelength was determined by UV–Visible spectrophotometry over 200–400 nm. Drug–excipient compatibility was assessed by FTIR by comparing the characteristic spectral features of ornidazole with physical mixtures containing formulation components. [14,15]

2.3 Formulation Development

The amphiphilogel formulations were produced using a melt-emulsification followed by sol-to-gel transformation approach. Span 60 and the selected surfactant phase were combined and heated to approximately 60°C for 10 min under continuous stirring. [16] Isopropyl myristate was subsequently introduced into the heated system. Ornidazole was dissolved separately in methanol and incorporated gradually into the surfactant–oil mixture. Distilled water was then introduced slowly while stirring was continued until a homogeneous sol was obtained. [17,18] The preparation was allowed to cool to room temperature and kept undisturbed overnight to facilitate formation of the semisolid gel structure. Nine formulations containing 1% w/w Ornidazole were prepared. Span 60 concentration was varied between 5 and 10% w/w, while the concentration of Tween 80 was varied between 30 and 50% w/w. Isopropyl myristate was maintained at 15% w/w and distilled water was used in sufficient quantity to produce 100 g of formulation. [19,20]

Table 1: Formulation Design

Ingredient (g/100 g)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ornidazole	1	1	1	1	1	1	1	1	1
Span 60	5	5	5	7.5	7.5	7.5	10	10	10
Tween 80	30	40	50	30	40	50	30	40	50
Isopropyl myristate	15	15	15	15	15	15	15	15	15
Distilled water	49	39	29	46.5	36.5	26.5	44	34	24
Total	100	100	100	100	100	100	100	100	100

2.4 Evaluation of Formulations

Appearance, colour, consistency, homogeneity, grittiness and phase separation were evaluated visually. The pH was measured using a calibrated digital pH meter. [21] Viscosity and rheological behaviour were evaluated using a Brookfield viscometer/rheological system. [22] Shear-thinning behaviour was assessed from the change in apparent viscosity with shear rate, and thixotropic behaviour was assessed from structural recovery following applied shear. [23] Spreadability and extrudability were evaluated as formulation handling characteristics. Drug content was determined spectrophotometrically at the predetermined λ_{max} . [24]

2.5 In-vitro Drug Release and Release Kinetics

In-vitro ornidazole release was evaluated using a Franz diffusion cell with phosphate buffer pH 7.4 as receptor medium under controlled physiological temperature and continuous stirring. Samples were withdrawn at predetermined intervals and replaced with fresh receptor medium. Ornidazole was quantified by UV–Visible spectrophotometry. [25] Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models, and the coefficient of determination (R^2) was used to assess model fit. [26]

2.6 Ex-vivo Skin Permeation and Skin Retention

The optimized F5 formulation was compared with a conventional ornidazole gel/reference formulation using an ex-vivo Franz diffusion-cell model. [27] Excised skin was cleaned, mounted between donor and receptor compartments and maintained at controlled temperature with continuous stirring. Equivalent drug quantities were applied to the skin surface. [28] Receptor samples were collected at 0, 1, 2, 4, 6, 8 and 12 h and analysed spectrophotometrically. Cumulative permeation and estimated skin retention were calculated. [29,30]

2.7 Antimicrobial Activity

Antimicrobial activity was evaluated by the agar well diffusion method against a selected susceptible anaerobic bacterial test organism. [31] The placebo amphiphilogel, ornidazole reference formulation and ornidazole-loaded F5 were tested under the reported microbiological conditions. The diameter of the inhibition zone was measured in millimetres after incubation. [32,33]

2.8 Stability Study

The optimized F5 formulation was stored under the selected stability condition for three months. Samples were examined initially and after one, two and three months for appearance, pH, drug content, viscosity, spreadability and 12-h drug release. The source document reports the storage duration and evaluated attributes but does not specify the exact numerical storage condition. [34,35]

3. RESULTS AND DISCUSSION

3.1 Preformulation Findings

Table 2: Preformulation Findings

Parameter	Observation/Result
Physical state	Crystalline powder
Colour	White to off-white
Odour	Odourless
Melting point	$82.1 \pm 0.46^\circ\text{C}$
λ_{max}	311 nm

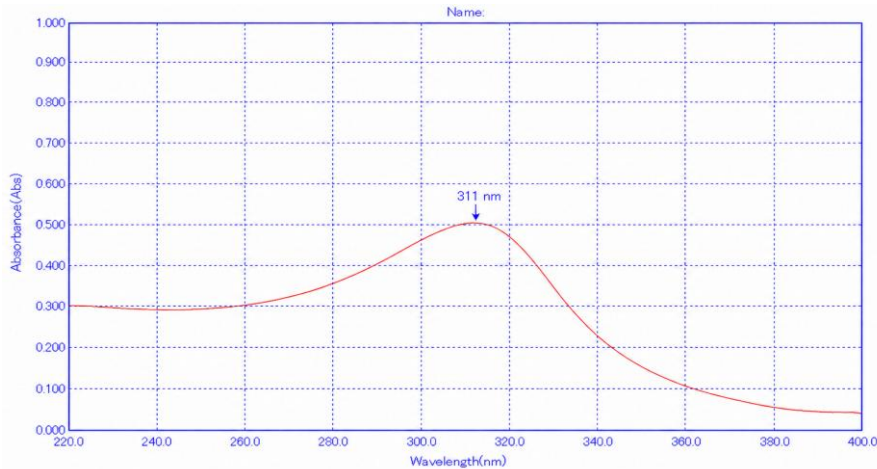


Fig1: λmax of Ornidazole

Ornidazole was obtained as a white to off-white crystalline, odourless powder. Its low aqueous solubility and substantially higher solubility in methanol and ethanol supported the use of a solvent-assisted incorporation step during formulation preparation. The observed melting point was $82.1 \pm 0.46^{\circ}\text{C}$. UV analysis produced a sharp absorption maximum at 311 nm in methanol, and the calibration curve was linear over 0.5–2.5 µg/mL with $R^2 = 0.9969$.

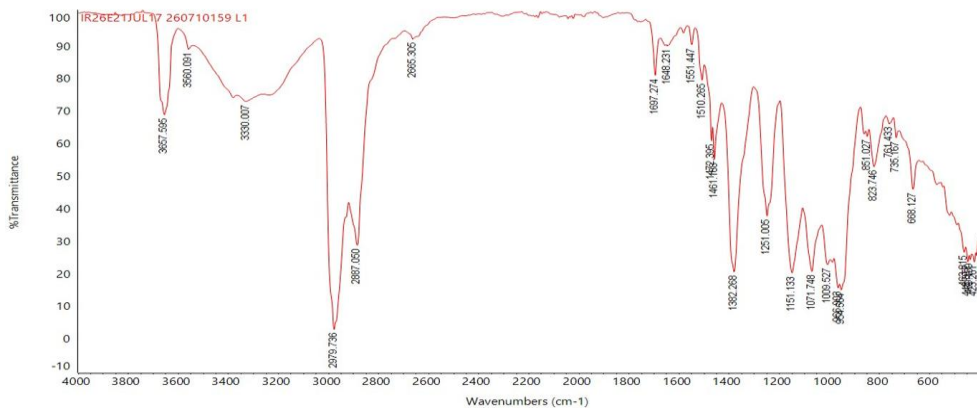


Fig 2: FTIR Spectra of Ornidazole

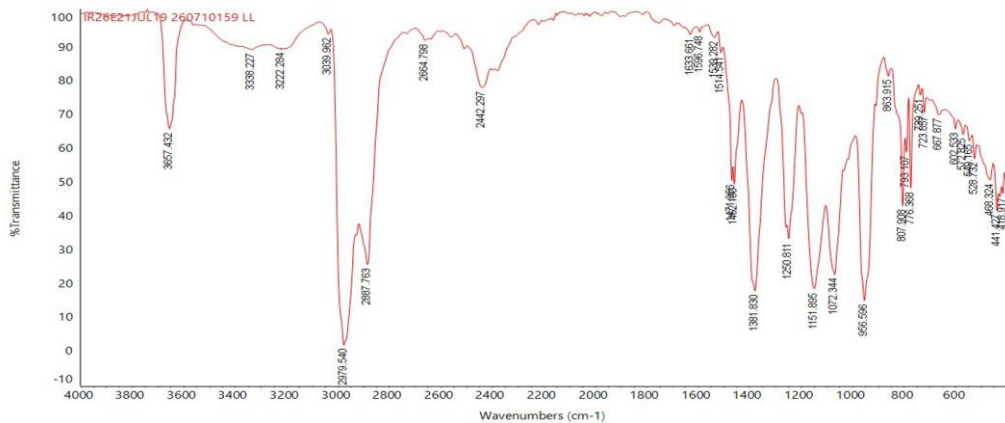


Fig 3: FTIR Spectra of Drug and Polymer Mixture

FTIR evaluation showed retention of characteristic ornidazole bands in the drug–excipient mixture and optimized amphiphilic gel. Principal spectral features were reported around 1551, 1472 and 1382 cm^{-1} , with only minor shifts in peak position and intensity and no major disappearance or new characteristic peaks. These observations indicated no evident major chemical incompatibility between ornidazole and the selected formulation components.

3.2 Physical Characteristics

Table 3: Physical Parameters

Formulation	Appearance	Homogeneity	Phase separation	pH	Drug content (%)
F1	Smooth semisolid	Good	Absent	6.21 ± 0.05	96.42 ± 0.81
F2	Smooth semisolid	Good	Absent	6.32 ± 0.04	97.18 ± 0.72
F3	Smooth, slightly viscous	Good	Absent	6.16 ± 0.05	98.86 ± 0.63
F4	Smooth semisolid	Excellent	Absent	6.13 ± 0.04	98.42 ± 0.55
F5	Smooth, uniform semisolid	Excellent	Absent	6.43 ± 0.03	99.12 ± 0.48
F6	Highly viscous semisolid	Good	Absent	6.08 ± 0.04	98.76 ± 0.52
F7	Smooth semisolid	Good	Absent	6.09 ± 0.04	98.88 ± 0.49
F8	Smooth, uniform semisolid	Excellent	Absent	6.15 ± 0.03	98.34 ± 0.51
F9	Smooth, more viscous	Good	Absent	6.02 ± 0.04	98.02 ± 0.56

All nine formulations produced white semisolid systems without visible phase separation. F5 showed a smooth, uniform semisolid appearance with excellent homogeneity. The pH values ranged from 6.02 to 6.43, with F5 at 6.43 ± 0.03 . Drug content ranged from $96.42 \pm 0.81\%$ to $99.12 \pm 0.48\%$, and F5 showed the highest reported drug content. The narrow variability indicated reproducible drug incorporation within the prepared systems.

3.3 Spreadability, Extrudability and Rheology

Table 4: Spreadability, Extrudability and Rheology Parameters

Formulation	Spreadability ($\text{g}\cdot\text{cm/s}$)	Extrudability (%)	Viscosity (cP)	Yield stress (Pa)	Thixotropy
F1	8.92 ± 0.31	96.8	$4,820 \pm 115$	18.4	Moderate
F2	8.45 ± 0.28	95.2	$5,640 \pm 128$	22.1	Moderate
F3	7.96 ± 0.26	93.6	$6,480 \pm 135$	25.8	Good
F4	7.61 ± 0.24	92.1	$7,210 \pm 142$	29.4	Good
F5	7.28 ± 0.22	90.8	$8,120 \pm 156$	32.7	Good
F6	6.41 ± 0.25	84.5	$9,460 \pm 174$	38.5	Very good
F7	6.18 ± 0.23	82.8	$10,180 \pm 182$	41.2	Very good
F8	5.94 ± 0.21	81.2	$10,920 \pm 195$	44.6	Very good
F9	5.72 ± 0.20	79.6	$11,680 \pm 208$	47.8	Very good

A progressive increase in viscosity and yield stress accompanied increasing gelator concentration, while spreadability and extrudability decreased. All formulations showed pseudoplastic flow. F5 exhibited a

viscosity of 8120 ± 156 cP, yield stress of 32.7 Pa, good thixotropic behaviour and 90.8% extrudability. These values represented an intermediate rheological profile between the lower-viscosity formulations and the more highly structured F6–F9 systems. Such shear-thinning behaviour can facilitate spreading during application while maintaining greater structural resistance at rest [19–22].

3.4 In-vitro Drug Release

Table 5: In-vitro Drug Release Study

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	18.6	16.9	15.8	14.9	14.2	13.1	12.7	11.9	11.2
2	32.8	30.5	28.7	27.1	25.9	23.8	22.9	21.8	20.6
4	51.4	48.6	46.2	44.1	42.7	39.8	38.5	36.9	35.2
6	66.8	63.4	60.5	58.1	56.4	52.7	50.8	48.9	46.7
8	78.2	74.9	71.6	69.0	67.4	63.1	60.8	58.5	55.9
12	91.8	88.6	85.7	83.4	81.6	76.2	73.8	71.4	68.9

All formulations showed progressive drug release over 12 h. F1 released 91.8% at 12 h, whereas F9 released 68.9%. F5 released 81.6%, providing an intermediate release profile. Increasing Span 60 concentration generally reduced cumulative release, consistent with greater structural density and diffusional resistance in the amphiphilic network. The combined effect of gelator and surfactant concentration therefore influenced the release rate. Similar relationships between semisolid structure, rheology and drug release have been reported for topical systems [23–26].

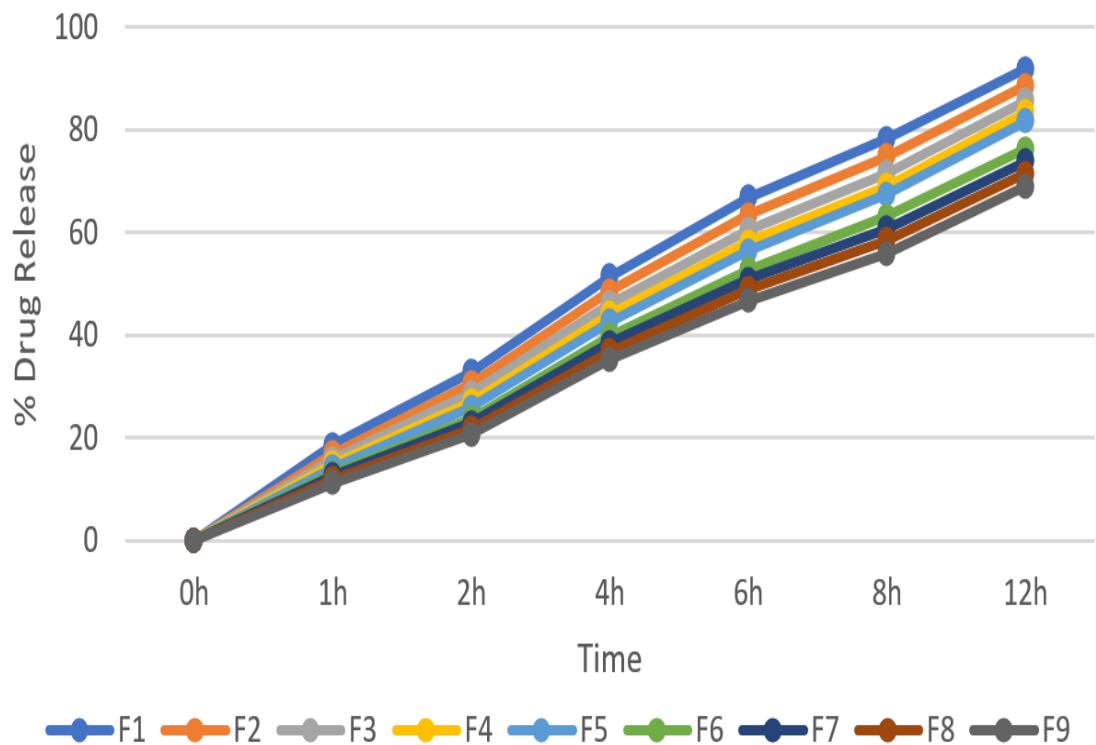


Fig 3.2.7: In vitro Drug Release of Different Formulation

3.5 Selection of the Optimized Formulation

Table 6: Optimization

Formulation	Drug content (%)	Spreadability	Viscosity (cP)	12-h release (%)
F1	96.42	8.92	4,820	91.8
F2	97.18	8.45	5,640	88.6
F3	98.06	7.96	6,480	85.7
F4	98.42	7.61	7,210	83.4
F5	99.12	7.28	8,120	81.6
F6	98.76	6.41	9,460	76.2
F7	98.58	6.18	10,180	73.8
F8	98.34	5.94	10,920	71.4
F9	98.20	5.72	11,680	68.9

F5 was selected as the optimized formulation based on the combined assessment of drug content, spreadability, viscosity and release behaviour. Its drug content was 99.12%, while its viscosity of 8120 cP and spreadability of 7.28 g·cm/s provided a balance between structural strength and application characteristics. F6–F9 exhibited progressively greater viscosity and lower spreadability together with slower release, whereas F1–F4 provided faster release with lower viscosity.

3.6 Drug-release Kinetics

Table 7: Drug Release Kinetics

Model	Regression equation	R ²
Zero-order	$y = 6.0898x + 14.539$	0.9573
First-order	$y = -0.0593x + 1.9858$	0.9873
Higuchi	$y = 28.139x - 12.667$	0.9880
Korsmeyer–Peppas	$y = 0.7098x + 1.1812$	0.9920

The Korsmeyer–Peppas model provided the highest R² (0.9920), followed by the Higuchi model (0.9880), first-order model (0.9873) and zero-order model (0.9573). The reported Korsmeyer–Peppas exponent was $n = 0.7098$. Under the interpretation used in the source study, this value indicated anomalous or non-Fickian release, suggesting that drug diffusion and matrix relaxation both contributed to ornidazole liberation.

3.7 Ex-vivo Skin Permeation and Retention

Table 8: Ex-vivo Skin Permeation and Retention

Time (h)	Reference permeation (%)	Reference retention (µg/cm ²)	F5 permeation (%)	F5 retention (µg/cm ²)
0	0	0	0	0
1	6.8	4.2	5.1	5.8
2	13.7	8.1	10.9	11.6
4	25.6	14.7	22.4	21.8
6	36.9	20.5	33.8	30.6
8	47.5	25.4	44.6	37.9
12	60.2	29.8	57.8	44.7

Both formulations demonstrated time-dependent increases in cumulative permeation and skin retention. At 12 h, the reference formulation showed 60.2% cumulative permeation compared with 57.8% for F5. In contrast, F5 showed an estimated skin retention of 44.7 µg/cm² compared with 29.8 µg/cm² for the reference.

3.8 Antimicrobial Activity

Table 9: Antimicrobial Activity

Sample	Zone of inhibition (mm)
Placebo amphiphilgel	0.0 ± 0.0
Ornidazole reference formulation	17.8 ± 0.6
Ornidazole-loaded F5 amphiphilgel	21.4 ± 0.5



Fig 3.2.11: Antimicrobial Activity (A) Placebo Amphiphilgel (B) Ornidazole Reference Formulation (C) Ornidazole-Loaded Amphiphilgel

The placebo amphiphilgel produced no measurable inhibition zone, indicating that the vehicle itself did not account for the observed antimicrobial effect. The ornidazole reference formulation produced a zone of 17.8 ± 0.6 mm, while F5 produced 21.4 ± 0.5 mm against the selected susceptible anaerobic test organism. The larger zone observed with F5 may reflect drug availability and prolonged contact with the agar medium. However, agar diffusion results are influenced by formulation viscosity and drug diffusion characteristics; consequently, inhibition-zone diameter should be interpreted as supportive in-vitro evidence rather than a direct measure of clinical efficacy.

3.9 Stability Study

Table 10: Stability Study

Parameter	Initial	Month 1	Month 2	Month 3
Appearance	Smooth	Smooth	Smooth	Smooth
pH	6.43 ± 0.03	6.45 ± 0.04	6.47 ± 0.03	6.51 ± 0.04
Drug content (%)	99.12 ± 0.48	98.94 ± 0.52	98.71 ± 0.55	98.43 ± 0.61
Viscosity (cP)	$8,120 \pm 156$	$8,080 \pm 162$	$8,020 \pm 170$	$7,960 \pm 174$
Spreadability (g·cm/s)	7.28 ± 0.22	7.31 ± 0.24	7.35 ± 0.25	7.39 ± 0.27
12-h drug release (%)	81.6 ± 1.2	81.1 ± 1.3	80.7 ± 1.4	80.2 ± 1.5

F5 maintained a smooth appearance throughout the three-month study, with no reported visible phase separation, precipitation or significant colour change. Drug content remained above 98%, decreasing from $99.12 \pm 0.48\%$ to $98.43 \pm 0.61\%$. Viscosity showed a small decrease, while spreadability increased modestly. The 12-h release changed from $81.6 \pm 1.2\%$ to $80.2 \pm 1.5\%$. Overall, the reported measurements showed only minor changes during the investigated period. The exact numerical storage condition was not provided in the source material.

4. CONCLUSION

An ornidazole-loaded topical amphiphilgel was formulated using Span 60, Tween 80 and isopropyl myristate and evaluated through a systematic sequence of preformulation, physicochemical, rheological, release, ex-vivo permeation, antimicrobial and stability studies. Among the nine formulations, F5

provided the selected balance of drug content, viscosity, spreadability and controlled release. It showed a pH of 6.43 ± 0.03 , drug content of $99.12 \pm 0.48\%$, viscosity of 8120 ± 156 cP, spreadability of 7.28 ± 0.22 g·cm/s and 81.6% drug release at 12 h. Release modelling indicated a predominant anomalous/non-Fickian pattern under the applied model. F5 also demonstrated 57.8% cumulative ex-vivo permeation and $44.7 \mu\text{g}/\text{cm}^2$ skin retention at 12 h, together with a 21.4 ± 0.5 mm inhibition zone against the selected susceptible anaerobic organism. The formulation retained its major measured quality attributes over three months. These findings support further development of amphiphilic gel-based ornidazole delivery for localized topical antimicrobial applications, with additional biological and long-term studies required to establish safety and therapeutic performance.

REFERENCES

- [1] Roberts MS, Cheruvu HS, Mangion SE, Alinaghi A, Benson HA, Mohammed Y, Holmes A, van der Hoek J, Pastore M, Grice JE. Topical drug delivery: History, percutaneous absorption, and product development. *Adv Drug Deliv Rev.* 2021;177:113929.
- [2] Gorzelanny C, Mess C, Schneider SW, Huck V, Brandner JM. Skin barriers in dermal drug delivery: which barriers have to be overcome and how can we measure them? *Pharmaceutics.* 2020;12(7):684.
- [3] Barnes TM, Mijaljica D, Townley JP, Spada F, Harrison IP. Vehicles for drug delivery and cosmetic moisturizers: review and comparison. *Pharmaceutics.* 2021;13(12):2012.
- [4] Benson HA, Grice JE, Mohammed Y, Namjoshi S, Roberts MS. Topical and transdermal drug delivery: from simple potions to smart technologies. *Curr Drug Deliv.* 2019;16(5):444-460.
- [5] Phatale V, Vaiphei KK, Jha S, Patil D, Agrawal M, Alexander A. Overcoming skin barriers through advanced transdermal drug delivery approaches. *J Control Release.* 2022;351:361-380.
- [6] Namjoshi S, Dabbaghi M, Roberts MS, Grice JE, Mohammed Y. Quality by design: development of the quality target product profile (QTPP) for semisolid topical products. *Pharmaceutics.* 2020;12(3):287.
- [7] Zhang Q, Song Y, Page SW, Garg S. Evaluation of transdermal drug permeation as modulated by lipoderm and pluronic lecithin organogel. *J Pharm Sci.* 2018;107(2):587-594.
- [8] Lai F, Caddeo C, Manca ML, Manconi M, Sinico C, Fadda AM. What's new in the field of phospholipid vesicular nanocarriers for skin drug delivery. *Int J Pharm.* 2020;583:119398.
- [9] Supe S, Takudage P. Methods for evaluating penetration of drug into the skin: A review. *Skin Res Technol.* 2021;27(3):299-308.
- [10] Iliopoulos F, Sil BC, Evans CL. The role of excipients in promoting topical and transdermal delivery: Current limitations and future perspectives. *Front Drug Deliv.* 2022;2:1049848.
- [11] Prasad V, Kumar N, Mishra PR. Amphiphilic gels as a potential carrier for topical drug delivery. *Drug Deliv.* 2007;14(2):75-85.
- [12] Esposito CL, Kirilov P, Roullin VG. Organogels, promising drug delivery systems: An update of state-of-the-art and recent applications. *J Control Release.* 2018;271:1-20.
- [13] Nikam AN, Roy A, Raychaudhuri R, Navti PD, Soman S, Kulkarni S, Shirur KS, Pandey A, Mutalik S. Organogels: "GelVolution" in topical drug delivery-present and beyond. *Curr Pharm Des.* 2024;30(7):489-518.
- [14] Martinez RM, Rosado C, Velasco MV, Lannes SD, Baby AR. Main features and applications of organogels in cosmetics. *Int J Cosmet Sci.* 2019;41(2):109-117.
- [15] Shakeel A, Farooq U, Iqbal T, Yasin S, Lupi FR, Gabriele D. Key characteristics and modelling of bigels systems: A review. *Mater Sci Eng C.* 2019;97:932-953.
- [16] Seweryn A. Interactions between surfactants and the skin—Theory and practice. *Adv Colloid Interface Sci.* 2018;256:242-255.
- [17] Kováčik A, Kopečná M, Vávrová K. Permeation enhancers in transdermal drug delivery: benefits and limitations. *Expert Opin Drug Deliv.* 2020;17(2):145-155.
- [18] Zeng J, Xu S, Lin K, Yao S, Yang B, Peng Z, Hao T, Yu X, Zhu T, Jiang F, Sun J. Long-term stable and efficient degradation of ornidazole with minimized by-product formation by a biological sulfidogenic process based on elemental sulfur. *Water Res.* 2024;249:120940.
- [19] Chiarentin L, Cardoso C, Miranda M, Vitorino C. Rheology of complex topical formulations: an analytical quality by design approach to method optimization and validation. *Pharmaceutics.* 2023;15(7):1810.
- [20] Patil PB, Datir SK, Saudagar RB. A review on topical gels as drug delivery system. *J Drug Deliv Ther.* 2019;9(3-S):989-994.

- [21] Herbig ME, Evers DH, Gorissen S, Köllmer M. Rational design of topical semi-solid dosage forms-how far are we? *Pharmaceutics*. 2023;15(7):1822.
- [22] Bakonyi M, Berkó S, Kovács A, Budai-Szűcs M, Kis N, Erős G, Csóka I, Csányi E. Application of quality by design principles in the development and evaluation of semisolid drug carrier systems for the transdermal delivery of lidocaine. *J Drug Deliv Sci Technol*. 2018;44:136-145.
- [23] Cao M, Ren L, Chen G. Formulation optimization and ex vivo and in vivo evaluation of celecoxib microemulsion-based gel for transdermal delivery. *AAPS PharmSciTech*. 2017;18(6):1960-1971.
- [24] Daryab M, Faizi M, Mahboubi A, Aboofazeli R. Preparation and characterization of lidocaine-loaded, microemulsion-based topical gels. *Iran J Pharm Res*. 2022;21(1):e123787.
- [25] Kasparaviciene G, Maslii Y, Herbina N, Kazlauskienė D, Marksa M, Bernatoniene J. Development and evaluation of two-phase gel formulations for enhanced delivery of active ingredients: sodium diclofenac and camphor. *Pharmaceutics*. 2024;16(3):366.
- [26] Vigato AA, Querobino SM, De Faria NC, Candido AC, Magalhães LG, Cereda CM, Tófoli GR, Campos EV, Machado IP, Fraceto LF, de Sairre MI. Physico-chemical characterization and biopharmaceutical evaluation of lipid-poloxamer-based organogels for curcumin skin delivery. *Front Pharmacol*. 2019;10:1006.
- [27] Oh L, et al. In vitro skin permeation methodology for over-the-counter topical dermatologic products. *Ther Innov Regul Sci*. 2020;54(3):693-700.
- [28] Bolla PK, Clark BA, Juluri A, Cheruvu HS, Renukuntla J. Evaluation of formulation parameters on permeation of ibuprofen from topical formulations using Strat-M membrane. *Pharmaceutics*. 2020;12(2):151.
- [29] Ruela AL, Perissinato AG, Lino ME, Mudrik PS, Pereira GR. Evaluation of skin absorption of drugs from topical and transdermal formulations. *Braz J Pharm Sci*. 2016;52(3):527-544.
- [30] Touitou E, Natsheh H. Topical administration of drugs incorporated in carriers containing phospholipid soft vesicles for the treatment of skin medical conditions. *Pharmaceutics*. 2021;13(12):2129.
- [31] Hmingthansanga V, Singh N, Banerjee S, Manickam S, Velayutham R, Natesan S. Improved topical drug delivery: role of permeation enhancers and advanced approaches. *Pharmaceutics*. 2022;14(12):2818.
- [32] Agonia AS, Palmeira-de-Oliveira A, Cardoso C, Augusto C, Pellevoisin C, Videau C, Dinis-Oliveira RJ, Palmeira-de-Oliveira R. Reconstructed human epidermis: An alternative approach for in vitro bioequivalence testing of topical products. *Pharmaceutics*. 2022;14(8):1554.
- [33] Badruddoza AZ, Yeoh T, Shah JC, Walsh T. Assessing and predicting physical stability of emulsion-based topical semisolid products: a review. *J Pharm Sci*. 2023;112(7):1772-1793.
- [34] Fujimura T, Shimotoyodome Y, Nishijima T, Sugata K, Taguchi H, Moriwaki S. Changes in hydration of the stratum corneum are the most suitable indicator to evaluate the irritation of surfactants on the skin. *Skin Res Technol*. 2017;23(1):97-103.
- [35] Roberts MS, Cheruvu HS, Mangion SE, et al. Topical drug delivery: History, percutaneous absorption, and product development. *Adv Drug Deliv Rev*. 2021;177:113929.

AUTHOR CONTRIBUTIONS

Shresth Shukla: Formulation development, experimental evaluation, data collection and manuscript preparation.

Umesh Pratap Singh: Supervision, study guidance and critical review.

Nidhi Srivastava: Co-supervision, methodological guidance and critical review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENT

The authors acknowledge the Department of Pharmacy, Rameshwaram Institute of Technology & Management, Lucknow, and the analytical and evaluation support provided by SAIF, Central Drug Research Institute, Lucknow.