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Formulation And Evaluation of Ketoconazole Microemulsion-Loaded Hydrogel with Olive Oil as a Penetration Enhancer

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ABSTRACT:
The aim of the present research work was to develop ketoconazole microemulsion- loaded hydrogel formulation containing olive oil as permeation enhancer. Screening of oils, surfactants, and cosurfactants were done based on solubility studies. The microemulsion was characterized for optical transparency, Cannoning electron microscopy, zeta potential, % drug content, dilutability and Dispersion Stability. In-vitro drug release studies were carried out using Franz diffusion cells using porcine skin membrane. The Carbopol 934P, Xanthan gum and HPMC-K100M as a gelling agent were used to construct the microemulsion-based hydrogel for improving the viscosity of microemulsion for topical administration. Three formulation were prepared of ketoconazole loaded microemulsion (KM1-KM3) with different concentration of olive oil. The SEM image of optimized best formulation showed that globules were spherical in shape and had smooth surface. Zeta potential result of optimized microemulsion (KM2) and its diluted form (100 times diluted with 0.1N HCl) was found to be -4.37mV. The medication content of KM-2 was 97.44±0.54% higher than that of other formulations. Out of all the formulations, formulation KM-2 had the highest penetration flux, measuring µg/cm2/hour. Over a 24-hour period, KM-2 tracked the zero-order release (r2 = 0.941). The KT-loaded microemulsion-based hydrogel gel formulation seemed to be a homogeneous, thick semisolid with the appropriate homogeneity and clarity upon visual inspection. Using an accelerated temperature investigation, the generated microemulsion formulations' stability was evaluated. For up to three months, stability tests were conducted on the drug concentration, pH, and viscosity of the optimal formulation, KMG-3, at 40 °C/75% RH. The current work demonstrated significantly enhanced skin penetration of the microemulsion and enabled its use in transdermal medication delivery. Considerable research has not yet been done to expand and examine its potential uses as a novel transdermal medication delivery technology.
KEYWORDS: *Microemulsion, ketoconazole, olive oil, permeation enhancer*

INTRODUCTION

Because the medicine penetrates the underlying layers of skin or mucous membranes, topical formulations are utilised to produce localised effects at the application site. The primary benefit of topical administration systems is their capacity to administer medications more precisely to a particular location (local action). It enables the use of medications with a limited therapeutic window and a short biological half-life to extend the duration of effect. [1]

Around 40% of novel chemical entities have low water solubility, which is a significant problem for contemporary drug delivery methods and results in inadequate absorption, bioavailability, and dosage proportionality. Oral administration, however, is frequently inappropriate when the medication is heavily metabolised by the liver's first pass action or experiences substantial gastrointestinal tract degradation. These drawbacks accelerated the hunt for a different drug delivery method, such as topical hydrogel based on microemulsions. [2] Ketoconazole, a low-solubility antifungal agent, was chosen as the study's medication.

The skin acts as a natural barrier for topical medication, making drug distribution challenging. In light of this, microemulsions are made that have a high drug loading capacity, little skin irritation, and the potential to lower the stratum corneum's diffusion barrier by dissolving its lipids and improving drug penetration. [3, 4]

An alternate method is provided by microemulsions, which are transparent and thermodynamically stable systems with a high drug loading capacity, low viscosity, and micron-range globule size that enhances

permeability. The current study is on using nigella oil, a natural permeation enhancer, in conjunction with ketoconazole microemulsion-based gel to treat onychomycosis. [5]

As a fungistatic drug, ketoconazole, an imidazole antifungal medication, ideally prevents the production of fungal ergosterol, resulting in fungal cell wall abnormalities. 9. Furthermore, the formulation's use of Nigella sativa oil offers a synergistic antifungal by improving penetration through the nail plate. [6]

Olive oil is a vegetable oil obtained by pressing whole olives (the fruit of Olea europaea) consist bioactive compounds like phenolic compounds, which have antioxidant and other pharmacological property. [7]

MATERIALS AND METHODS

Materials: Ketoconazole was a generous gift sample from Premier Drug House, Kandivali (West), Mumbai. Propylene glycol was purchased from Loba Chemie Pvt Ltd (India). Carbopol 934P Ultrez was purchased from Lubrizol Pvt Ltd (India). All other solvents and reagents used were of analytical grade.

Infra-Red Spectral Analysis: To determine the identify of the medications, infrared spectroscopy was used. In a KBr press, 3-5 mg of each medication were compressed with 100-150 mg of potassium bromide to create a pellet with a diameter of around 1 mm. Using an FTIR Brukers Alpha, the pellet was placed in an 80 IR chamber and scanned between wave numbers 4000-600 cm^{-1}. [8]

Formulation Development of Microemulsion: The goal of pharmaceutical development research must be to choose a stable formulation and the appropriate dosage form. This research to follow explanation of each step that goes into creating the final technique. These specifics are meant to help identify important process features and that must be managed to provide a high-quality output. [9]

Solubility study of oil: To determine the best oil to employ as the oil phase in a microemulsion that offers a high rate of ketoconazole skin penetration. To dissolve the medication, 100 mg of ketoconazole was added to about 10 g of precisely weighed oil in a 25 ml glass beaker. The mixture was then stirred at a moderate speed using a magnetic stirrer. Another 10 mg of ketoconazole was added when the medication had completely dissolved, and stirring was continued. The medication was added continuously until the solution was saturated. Lastly, a UV spectrophotometer set to 225 nm was used to calculate the total amount of medication consumed Oleic acid was selected as the vehicle for the microemulsion oil phase after it was discovered to have consumed the most ketoconazole. [10, 11]

Surfactants and co-surfactants: Titration was performed on a variety of nonionic surfactants, such as span 20, tween 20, and co-surfactants, such as propylene glycol, isopropyl alcohol, and n-butanol; these surfactants do not ionise to a significant degree in the solution and are highly compatible with both anionic and cationic substances; ultimately, the best surfactant and co-surfactant for the system were determined to be tween-20 and propylene glycol. [12, 13]

Table 1: Solubility of ketoconazole in various oils at 25 °C

S. No.	Drug solubility (in mg/10 g of oil)	Oils
1	180	Olive oil
2	150	Castor oil
3	140	Isopropyl myristate
4	120	Isopropyl palmitate
5	130	Oleic acid

Table 2: Surfactant and co-surfactants for optimization of formulations

S. No.	Surfactant: co- surfactant	Concentration ratio	Appearance
1	Tween-20: propylene glycol	1:1 2:1	Clear Clear
2	Tween-20: isopropyl alcohol	1:1 2:1	Slightly cloudy Clear
3	Tween-20: n-butanol	1:1 2:1	Cloudy Clear
4	Span-20: propylene glycol	1:1 2:1	Clear Cloudy
5	Span-20: isopropyl alcohol	1:1 2:1	Slight cloudy Cloudy
6	Span 20: n-butanol	1:1 2:1	Cloudy Cloudy

I) Formulations: One percent w/w ketoconazole was dissolved in an oily phase made of olive oil. After that, a combination of surfactant and co-surfactant was added to the ketoconazole solution. Lastly, to create a microemulsion, a suitable amount of water was added to the ketoconazole solution mixture drop by drop. [14, 15]

Figure 1: Formulated microemulsion

Evaluation of Microemulsion

Optical Transparency: By examining the sample in a clear, transparent container with adequate light to prevent reflection into the eyes and viewing it against a black and white lighted background, the formulation's optical transparency was ascertained. [16]

Scanning Electron Microscopy (SEM): The microstructure of microemulsions was characterised using scanning electron microscopy (SEM). LED 1455VP, Germany, was used to measure the samples' SEM. [17]

Zeta Potential: Malvern Instruments Limited's NanoZS-90 zeta sizer was used to calculate the formulations' mean particle size. With a suitable dilution with filtered water and a filter of 0.5 µm, the reading was taken at a 90 ° angle to the incident beam at 25 °C. 2.43 ms/cm was set as the sample's conductivity. The Malvern Instruments Limited zeta sizer NanoZS-90 was used to measure the zeta potential.

Drug Content Study: Using a micropipette, 100 µl of the preparations were aseptically transferred to sterile 25-ml volumetric flasks after the vials (n=3) containing them had been shaken for two to three millimetres; the final volume was then adjusted using phosphate buffer with a pH of 7.4. The UV-Visible spectrophotometer was used to measure the concentration of ketoconazole at 225 nm.

Dilutability: To see if there were any indications of separation, the microemulsions were diluted with double-distilled water in ratios of 1: 10 and 1: 100.

Dispersion Stability: The chosen formulations were centrifuged for 30 minutes at 3000 rpm. For the heating and cooling cycle (freeze thaw cycle), formulations without phase separations were used.

Formulation of Microemulsion-Loaded Hydrogel: After hydrating carbopol 934p, HPMC K 15M, and xanthan gum in a set amount of water for at least four hours, the previously prepared microemulsion was added gradually while being constantly stirred until a clear, viscous solution was achieved. Triethanolamide was then added in a predetermined quantity to create various hydrogel-thickened microemulsions. [18]

Table 3: Compositions of the Selected Microemulsion Formulation KM-2

Formulation	**Ingredient in (gm)**			
	Carbopol-934P	Water	Triethanolamine	Gel
KMG-1	1.5	48	0.5	50
KMG-2	1.5	48	0.5	50
KMG-3	1.5	48	0.5	50
	Xanthan gum	Water	Triethanolamine	Gel
KMG-4	1.5	48	0.5	50
KMG-5	1.5	48	0.5	50
KMG-6	1.5	48	0.5	50
	HPMC K15M	Water	Triethanolamine	Gel
KMG-7	1.5	48	0.5	50
KMG-8	1.5	48	0.5	50

KMG-9	1.5	48	0.5	50

Figure 2: Formulated hydrogel

Evaluation of Hydrogel

Physical appearance: To ascertain the physical appearance, colour, and homogeneity of the KT loaded microemulsion based gel formulation, a visual inspection of the generated gel formulation was conducted under bright light. [19]

Viscosity: The Brookfield viscometer was used to measure the viscosity of the hydrogel based on microemulsion. To determine the viscosity of the microemulsion-based hydrogel, a 250 ml beaker was filled with 175 g of the hydrogel.

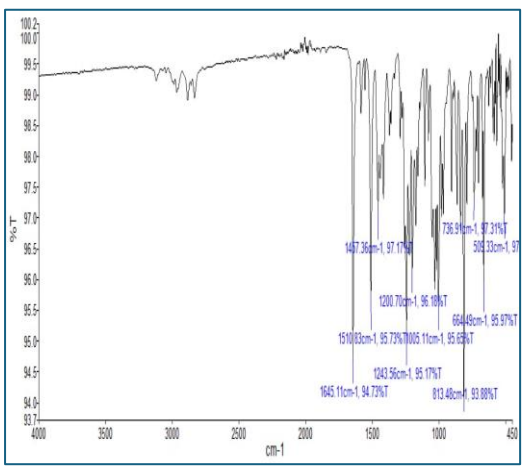
pH: The pH was measured using a pH paper. 25 millilitres of filtered water were used to dissolve a precisely weighed 2.5 gramme hydrogel based on microemulsion. The pH of the all prepared formulation were measured three times, and the average findings were calculated.

Determination of spreadability: Spreadability is a crucial metric for evaluating the topical gel formulation's homogeneity and application simplicity. When applied to the skin or other afflicted areas, spreadability refers to how quickly the gel spreads. The force needed to cause a particular deformation is known as hardness. A lower hardness rating makes a sample more spreadable. The created gel formulation's spreadability was tested using the TA-XT plus texture analyser (Stable Microsystem, UK). [20]

Stability Study: Hydrogel based on specific microemulsion formulations was put in a high-density polyethylene container and stored in a stability chamber that was kept at 40 °C and 75% relative humidity. The duration of the stability studies was three months. At regular intervals, the microemulsion formulation was tested and examined for variations in the drug content percentage. [21]

RESULTS AND DISCUSSION

FTIR Study: To investigate drug incompatibility with excipient and reaction conditions, the FTIR spectra of "pure drug" and "drug entrapped microemulsion" were compared. To determine whether the principal peaks of the drug entrapped in the excipient and the peaks of the pure drug are concordant, they were compared. According to the spectral analysis, the peaks of the pure drug and drug polymer mixture did not significantly alter in the FTIR spectrum of pure ketoconazole. Consequently, it may be concluded that no particular interaction between the medication and the polymers was noticed.



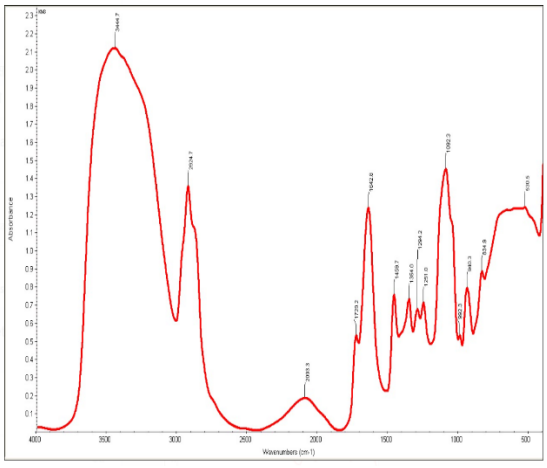


Figure 3: FTIR Spectrum of pure drug (ketoconazole) Figure 4: FTIR Spectrum of formulation KM-1

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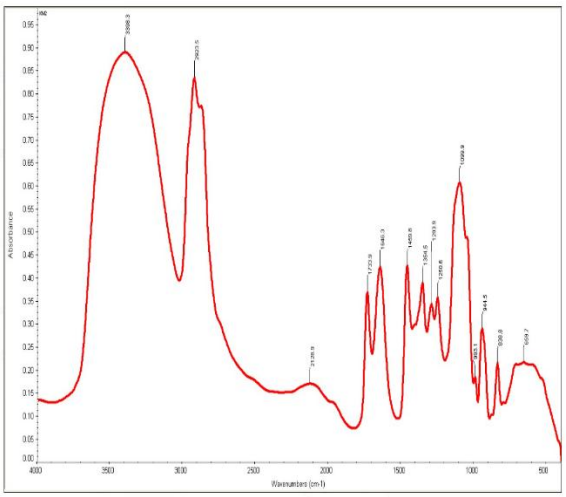

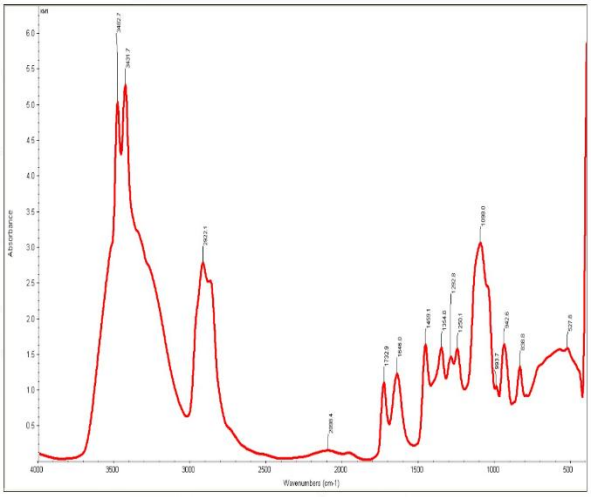

Figure 5: FTIR Spectrum of formulation KM-2 Figure 6: FTIR Spectrum of formulation KM-3

Evaluation Of Microemulsion

Optical Transparency: The optical transparency of the microemulsion (KM1 to KM3) was investigated. Comparing the KM2 formulation to the other microemulsion formulations, it was optically clear, transparent, and aesthetically pleasing.

Scanning Electron Microscopy (SEM): SEM was used to describe the morphology of KM-2. The globules were spherical in shape and had a smooth surface, according to the SEM image of the optimal formulation. Because of the percentage of the ingredients, the SEM data also suggested the presence of an isotropic dispersion of spherical droplets, which led to the supposition of inverse micelles.

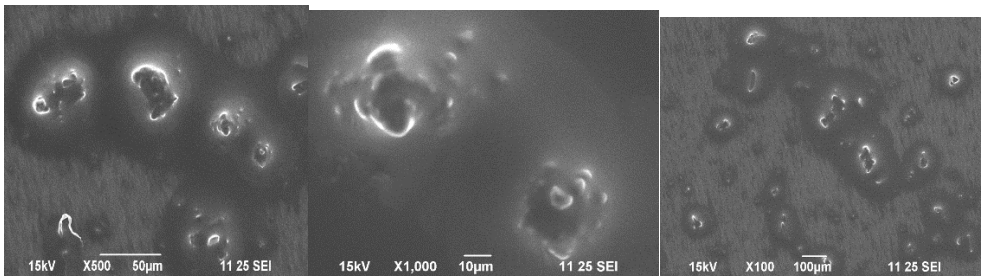

Figure 7: SEM Image of microemulsion formulation

Zeta Potential Measurements: The zeta potential results of the optimised microemulsion and its diluted version (100 times diluted with O.IN HCl) were determined to be -6.34 mV and -3.14 mV, respectively. Because of the droplets' tiny negative charge, aggregations won't occur.

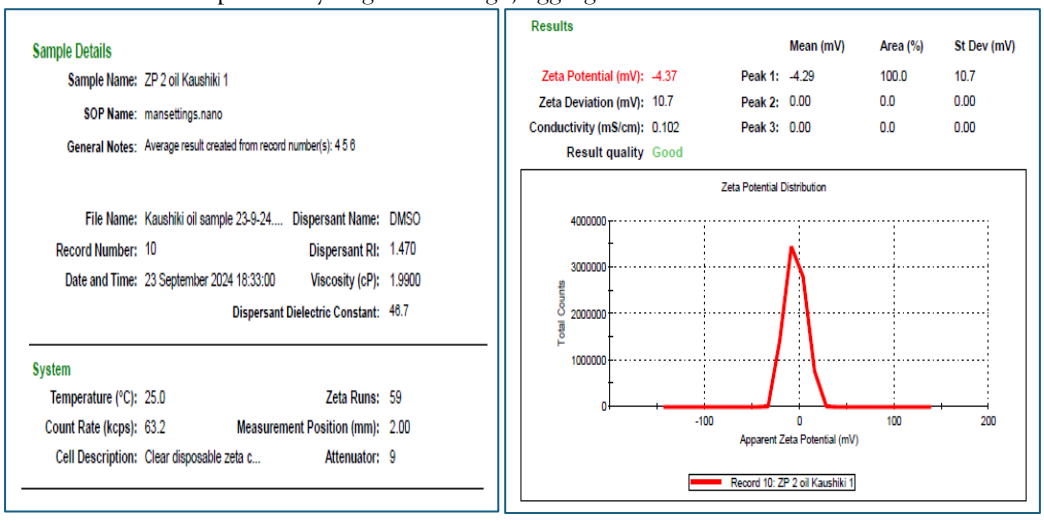

Figure 8: ZP of Microemulsion KM2

Drug Content: The mean % medication content in microemulsion prepared formulations (KM-1 to KM-3) was determined to be accordingly. 80.41±0.32%, 97.44±0.54%, and 93.56±0.36%. The medication content of KM-2 was 97.44±0.54% higher than that of other formulations.

Dilutability: To check for separation, the resulting microemulsions were diluted with double-distilled water in 1:10 and 1:100 ratios. There were no indications of phase separation in the optimised microemulsion. The microemulsion's dilutability is less than 100 times.

In-vitro drug release study The in-vitro skin permeation studies were used to assess the microemulsion formulations' penetration capabilities. The in-vitro skin penetration of KM(1-3) ketoconazole microemulsions through excised goat skin was investigated. The permeation fluxes (µg/cm^2/hour) for each of these microemulsions via the goat skin were calculated by plotting the amount of ketoconazole that penetrated through the goat skin over a 24-hour period against the function of time. Out of all the formulations, formulation KM-2 had the highest penetration flux, measuring µg/cm2/hour.

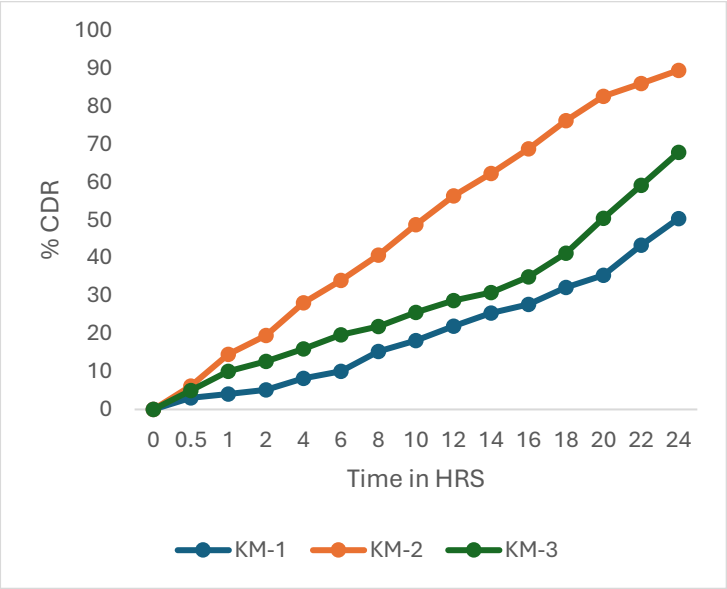

Figure 9: in-vitro Skin Permeation rate of Microemulsions

Evaluation of Prepared Hydrogel

Physical appearance: The KT-loaded microemulsion-based hydrogel gel formulation seemed to be a homogeneous, thick semisolid with the appropriate homogeneity and clarity upon visual inspection. The gel did not contain any lumps or substances that had not dissolved.

Spreadability study: Since spreadability is a crucial gel formulation parameter for topical administration, the gel should have a respectably high spreadability value. Indicating that the gel formulation had strong spreadability and would require a short spreading time, the created gel's spreadability was found to be 18.634 g. cm^2/sec.

pH Determination: KMG-1, KMG-2, and KMG-3 pH readings (6.1±0.04, 5.17±0.03, and 5.35±0.06) alone. The pH changed the least in every instance. Because skin has a pH between 5.5 and 7.0, the optimised microemulsion formulation (KMG-2) has a pH of 6.35±0.02, making it appropriate for topical and transdermal use.

Viscosity: Viscosity of microemulsion systems (KMG-1, KMG-2, and KMG-3) showed a steady increase in produced formulations (51.6±0.6 cps, 106.5±0.5 cps, and 117.2±0.2 cps). As would be expected from microemulsions, all samples displayed Newtonian flow characteristics.

Stability Study: Using an accelerated temperature investigation, the generated microemulsion formulations' stability was evaluated. For up to three months, stability tests were conducted on the drug concentration, pH, and viscosity of the optimal formulation, KMG-3, at 40 °C/75% RH. After three months, drug degradation was determined to be within the range of 96.23%, 96.01%, and 95.36 percent. After three months, the viscosity readings were between 0 and 1 cps, while the pH only altered by 6 to 5 units. The microemulsions were chemically stable for three months, according to the stability studies' overall findings.

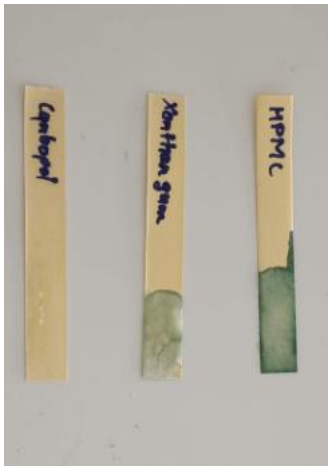

Figure 10: pH of formulations

CONCLUSION

Olive oil was used as the carrier for the microemulsion oil phase because it has absorbed the most ketoconazole. The optimal surfactant and co-surfactant were determined to be tween-20 and propylene glycol in the proper ratios. Ketoconazole microemulsion was created as a 24-hour controlled release dosage form that also lessened the adverse effects of oral conventional dosages. The current work demonstrated significantly enhanced skin penetration of the microemulsion and enabled its use in transdermal medication delivery. Considerable research has not yet been done to expand and examine its potential uses as a novel transdermal medication delivery technology.

REFERENCES

1. Gupta GD, Gaud RS. Anti-inflammatory activity of carrageenan induced paw edema in rats. Indian J of Pharma Sci, 2006; 68:356-359.
2. Gloster HM, Brodland DG. The epidemiology of skin cancer. Dermatology Surg, 1996; 22:217–226.
3. Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. Clin Dermatol. 2010; 28(2): 151–159.
4. Vishvakarma P, Kaur J, Chakraborthy G, Vishwakarma DK, Reddy BB, Thanthati P, Aleesha S, Khatoon Y. Nephroprotective Potential of Terminalia Arjuna Against Cadmium-Induced Renal Toxicity by In-Vitro Study. Journal of Experimental Zoology India. 2025 Jan 1;28(1)
5. Elkeeb R, Ali Khan A, Elkeeb L, Hui X, Maibach HI. Transungual drug delivery: Current status. Int J Pharm. 2010; 384(1–2):1–8.
6. Bachhav DG, Sisodiya D, Chaurasia G, Kumar V, Mollik MS, Halakatti PK, Trivedi D, Vishvakarma P. Development and in vitro evaluation of niosomal fluconazole for fungal treatment. J Exp Zool India. 2024;27:1539-47. doi:10.51470/jez.2024.27.2.1539
7. Vishvakarma P, Mohapatra L, Kumar NN, Mandal S, Mandal S. An innovative approach on microemulsion: A review. European Chemical Bulletin. 2023;12(4):11710-33.
8. Margaret N, Mutimer CR, Hill JA, Murray E. Modern ointment base technology Comparative evaluation of bases. J American Pharm Association, 1956; 4:212-217.
9. Bhagchandani D, Shriyanshi, Begum F, Sushma RC, Akanda SR, Narayan S, Sonu K, Vishvakarma P. Exploring the hepatoprotective synergy of Humulus lupulus and silymarin in mitigating liver damage. Biochem Cell Arch. 2025;25(1):915-9. doi:10.51470/bca.2025.25.1.915
10. Kreilgaard M. Dermal pharmacokinetics of microemulsion formulations determined by in vivo microdialysis. Pharm Res. 2001; 18(3): 367–373.
11. Parida SK, Vishvakarma P, Landge AD, Khatoon Y, Sharma N, Dogra SK, Mehta FF, Sharma UK. Spatiotemporal biointeraction and morphodynamics of a gastro-retentive Saccharopolyspora-derived macrolide system in the vertebrate gut: A study on absorptive microecology and transit kinetics. J Exp Zool India. 2025;28:1743-51. doi:10.51470/jez.2025.28.2.1743
12. Fur JR. Fundamentals of immunology. In: Pharmaceutical Microbiology. London: Blackwell Scientific Publications 1992 305–31.
13. Khullar R, Saini S, Rana AC. Emulgels: a surrogate approach for topically used hydrophobic drugs. IJPBS, 2011; 1:117-128.
14. Kumar S, Manoyogambiga M, Attar S, Kaur K, Singh N, Shakya S, Sharma N, Vishvakarma P. Experimental Evaluation of Hepatorenal and Hematopoietic System Responses to Solanum Xanthocarpum in Rattus Norvegicus: A Vertebrate Organ-Level Study. Journal of Experimental Zoology India. 2025 Jul 1;28(2)
15. Ghannoum Ma, Hajjeh Ra, Scher R. A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol. 2000; 43(4): 641-648.
16. Suresh S, Tyagi N, Mandal S, Vishvakarma P, Reena K, Sarma SK, Ranjan R. A comprehensive study of Tinospora cordifolia: Phytochemical and pharmacological properties. Eur Chem Bull. 2023;12:2009-19.
17. Kasliwal N, Derle D, Negi J, Gohil J. Effect of permeation enhancers on the release and permeation kinetics of meloxicam gel formulations through rat skin. AJPS, 2008; 3:193-199.

18. Dhama P, Sutej BS, Alam MK, Juyal P, Gupta PS, Sahoo M, Islam R, Vishvakarma P. Synthesis and evaluation of piperic acid and 4-ethylpiperic acid amide derivatives as Nora efflux pump inhibitors against multidrug-resistant Staphylococcus aureus. Int J Environ Sci. 2025. doi:10.64252/w2y8gc49
19. Mukhrjee B, Mahapatra SK, Das S, Patra B. Sorbitan Monolaurate 20 as a potential skin permeation enhancer in transdermal patches. J Applied Res, 2005; 5: 96-107.
20. Mandal S, Raju D, Namdeo P, Patel A, Bhatt AK, Gupta JK, Haneef M, Vishvakarma P, Sharma UK. Development, characterization, and evaluation of Rosa alba L extract-loaded phytosomes. Eur Chem Bull. 2023;12:489-505
21. Bhatti M, Kumar J, Kareemulla S, Vishvakarma P, Deka P, Singh SP, Pujari NM, Singh S, Dixit CK. Exploring Marine-Derived Bioactive Compounds and Their Impact on Diverse Diseases. Biochemical & Cellular Archives. 2024 Apr 1;24(1)