JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

DEVELOPMENT AND ASSESSMENT OF LULICONAZOLE NANOSOMAL GEL BY USING NATURAL OIL (TEA TREE OIL, CASTOR OIL & CLOVE OIL

[1]Pushpesh Mallik, [2]Ms. Shivani Rangarh, [3]Akshat Pratap Singh
[1&3]Student, [2]Assistant Professor
[1]B. Pharmacy
[1]College Of Pharmacy RIMT University, Mandi Gobindgarh Punjab (147301), India

1. ABSTRACT:

Luliconazole nanosomal gels signify a significant breakthrough in topical antifungal treatment, providing superior drug absorption, better retention, and extended antifungal efficacy compared to standard formulations. This review examines the formulation and characterization of a luliconazole nanosomal gel that includes tea tree oil, castor oil, and clove oil, which act as permeation enhancers and antimicrobial agents. The formulation process entails selecting lipid-based carriers, excipients, and optimal preparation methods to ensure stability and effectiveness. The characterization of the nanosomal gel encompasses assessments of physical appearance, viscosity, pH levels, and in vitro release studies, which together ascertain its structural integrity and drug release performance. The antifungal efficacy of the formulation is assessed through minimum inhibitory concentration (MIC) and zone of inhibition tests, validating its therapeutic potential against dermatophytid infections. Furthermore, skin permeation studies and cytotoxicity evaluations confirm its safety and efficacy in transdermal drug delivery. Clinical implications underscore its benefits over conventional formulations in enhancing bioavailability and therapeutic results. Future efforts will concentrate on refining formulation parameters, executing large-scale clinical trials, and addressing regulatory issues to promote commercialization. In summary, this cutting-edge nanosomal gel system exhibits considerable promise for improved antifungal therapy, with encouraging market prospects in dermatology.

KEYWORDS: Luliconazole, Nanosomal gel, Antifungal formulation, Topical drug delivery, Natural oils in pharmaceuticals, Skin permeation enhancers

2. INTRODUCTION:

Luliconazole is a broad-spectrum antifungal medication belonging to the imidazole class, mainly used to treat superficial fungal infections such as onychomycosis, tinea pedis, tinea corporis, and tinea cruris. [2] Although it possesses potent antifungal properties, conventional topical formulations of luliconazole face challenges related to poor aqueous solubility and limited skin penetration, which reduce its therapeutic effectiveness. [2] To overcome these issues, nanosomal gel technology has emerged as a promising drug delivery method. Nanosomal gels utilize lipid-based nanocarriers to enhance drug solubility, stability, and skin

absorption, ensuring prolonged drug retention at the site of application. [1] The incorporation of natural oils like tea tree oil, clove oil, and castor oil further improves the formulation by acting as permeation enhancers, antimicrobial agents, and stabilizers.This review focuses on the formulation and characterization of luliconazole nanosomal gel combined with natural oils, highlighting its formulation strategy, physicochemical properties, antifungal effectiveness, safety profile, and clinical significance. [3] The aim of this study is to illuminate the potential advantages of nanosomal gel technology over traditional antifungal treatments and its prospective applications in dermatology.

3. BACKGROUND OF LULICONAZOLE:

Luliconazole is a versatile imidazole antifungal medication mainly utilized for the treatment of superficial fungal infections such as onychomycosis, tinea pedis, tinea corporis, and tinea cruris. Its mechanism of action involves the inhibition of ergosterol biosynthesis, an essential element of fungal cell membranes, resulting in membrane disruption and subsequent fungal cell death. [4-5]

3.1 Chemical Structure and Mechanism of Action

Luliconazole shares a structural similarity with azole antifungals, yet it demonstrates greater potency owing to its improved lipophilicity, facilitating superior penetration into fungal cells. It specifically targets and inhibits lanosterol 14α-demethylase, a crucial enzyme in the synthesis of ergosterol, thus undermining the integrity of fungal membranes. [6-8]

3.2 Pharmacokinetics and Bioavailability

- Topical luliconazole is designed to stay mostly on the skin's surface, with very little being absorbed into the bloodstream. This means it has a lower risk of causing side effects. [9-10]
- One of its key strengths is that it stays in the outer layer of the skin—the stratum corneum—for an extended period, which helps it fight fungal infections more effectively over time. [11-12]
- Unlike some traditional antifungal treatments, luliconazole penetrates the skin more efficiently, allowing for just one application per day while still delivering strong and lasting results. [9-10]

3.3 Limitations of Conventional Luliconazole Formulations

- Restricted absorption through the skin, leading to decreased drug bioavailability. [13- 14]
- Short duration of effect necessitating regular application. [11-12]
- Possible irritation, particularly in individuals with sensitive skin conditions. [15-16]

4. NANOSOMAL GEL TECHNOLOGY:

Nanosomal gels use lipid- grounded nanoparticles to ameliorate medicine solubility and grease targeted delivery.

4.1 NEED FOR NANOSOMAL TECHNOLOGY:

- They offer extended medicine retention and enhanced penetration through the stratum corneum.
- To address being challenges, phrasings of nanosomal gels have been created. [17-18]
- These gels make use of lipid- grounded nanocarriers to- Enhance medicine solubility and stability.
- Ameliorate skin saturation and retention. [19-20]
- Give controlled medicine release, thereby dwindling the frequency of dosing. [21-22]

5. Role of Natural Oils in Pharmaceutical Formulations

Natural Canvases (Oil) are essential for enhancing medicine delivery, perfecting skin immersion, and offering antimicrobial advantages in pharmaceutical phrasings. They serve as saturation enhancers, stabilizers, and bioactive agents, rendering them significant factors in

topical medicine delivery systems.

5.1 Tea Tree Oil:

Tea tree oil (Melaleuca alternifolia) is well- known for its antimicrobial,anti-inflammatory, and skin- penetration-enhancing characteristics. It contains terpinen-4-ol, which demonstrates strong antifungal parcels against dermatophytes and Candida species.

- Exploration indicates that tea tree oil disrupts fungal cell membranes, thereby adding the effectiveness of antifungal specifics. **[23-24]**
- It enhances medicine immersion by modifying the lipid structure of the stratum corneum, easing better penetration of active pharmaceutical constituents. **[25-26]**
- Tea tree oil has been employed in nanoemulsions and lipid- grounded carriers to enhance stability and bioavailability. **[27-28]**

5.2. Clove Oil:

Clove oil (Syzygium aromaticum), abundant in eugenol, an important antimicrobial and antioxidant emulsion, is generally employed in topical phrasings due to its antifungal and analgesic goods.

- Eugenol displays broad- diapason antifungal exertion, effectively inhibiting the growth of Candida albicans and dermatophytes. **[29-30]**
- Clove oil also promotes skin hydration and hedge function, making it ideal for dermatological uses. **[31-32]**
- Research has delved clove oil loaded microemulsions to enhance medicine delivery and stability. **[33-34]**

5.3. Castor Oil

Castor oil (Ricinus communis) is recognized for its moisturizing, anti-inflammatory, and skin-penetrating properties. It contains ricinoleic acid, which plays a significant role in its therapeutic benefits.

- **Enhancement of Drug Solubility:** Castor oil facilitates the solubility of lipophilic medications, rendering it a valuable carrier in nanosomal formulations. **[35]**

- **Antimicrobial Properties:** It demonstrates antibacterial and antifungal characteristics, thereby supporting its application in topical antifungal preparations. **[36]**

- **Improvement of Skin Permeation:** Castor oil boosts transdermal drug delivery, enhancing the absorption of drugs through the skin. **[37]**

6. Formulation Development of Luliconazole Nanosomal Gel

The development of luliconazole nanosomal gel requires the careful selection of suitable excipients, preparation methods, and optimization strategies to guarantee stability, effectiveness, and improved skin absorption. The addition of natural oils, including tea tree oil, clove oil, and castor oil, enhances the formulation by serving as

permeation enhancers, antimicrobial agents, and stabilizers.

6.1. Selection Of Excipients:

The formulation of luliconazole nanosomal gel requires careful selection of suitable excipients, preparation methods, and optimization strategies to guarantee stability, effectiveness, and improved skin absorption. The addition of natural oils such as tea tree oil, clove oil, and castor oil enhance the formulation by serving as permeation enhancers, antimicrobial agents, and stabilizers. The excipient selection is vital for ensuring stability, drug release, and compatibility with the skin, with key excipients including lipid carriers like soy lecithin, phospholipids, and solid lipid nanoparticles that boost drug solubility and bioavailability; polymers such as Carbopol 934 and HPMC that function as gelling agents to provide viscosity and stability; surfactants like Tween 80 and Span 20 that facilitate dispersion and emulsification of the nanosomal gel; and natural oils that enhance permeation and possess antimicrobial properties. **[1]**

6.2. Preparation Methodology:

The preparation methodology involves creating a nanoemulsion-based gel to ensure uniform dispersion and improved drug delivery, with critical steps including conducting a solubility study to determine the optimal oil phase, surfactant, and co-surfactant for drug solubility; forming the nanoemulsion through high-pressure homogenization or ultrasonication to produce stable nanosomes; incorporating Carbopol 934 or HPMC to transform the nanoemulsion into a gel-based system; and optimizing parameters such as pH, viscosity, and drug loading to enhance skin retention and therapeutic effectiveness. **[38-40]**

7. Characterization of Luliconazole Nanosomal Gel:

Characterizing luliconazole nanosomal gel is essential to ensure its stability, efficacy, and effective drug delivery. Various physicochemical and biological tests are conducted to assess its quality, performance, and therapeutic potential.

7.1. Physical Appearance:

The gel's visual and tactile characteristics are assessed to confirm uniformity, a smooth texture, and consistent dispersion of nanosomes. The gel should be either transparent or slightly opaque, contingent on its formulation. It must possess a smooth, non-gritty texture to enhance patient compliance. Stability tests are conducted to verify that there is no separation of oil and aqueous phases over time. **[41]**

7.2. Viscosity Analysis:

Viscosity is a critical factor in drug retention and spreadability on the skin, typically measured using a Brookfield viscometer. The gel should demonstrate pseudo-plastic behavior, thinning upon application while maintaining its structure at rest. Proper viscosity is essential for optimal skin adherence and controlled drug release. **[42-43]**

7.3. pH Measurement:

The gel's pH must align with skin physiology to avoid irritation, ideally within the range of 5.5 to 6.5, mirroring natural skin pH. A pH meter is utilized for accurate measurement, and adjustments with buffering agents are made to ensure stability and compatibility with the skin.

7.4. Stability Testing:

Stability testing is vital for confirming the formulation's long-term efficacy, involving accelerated studies under various temperature and humidity conditions. Freeze-thaw cycles are employed to evaluate the gel's resilience to temperature changes, and shelf-life predictions are derived from degradation kinetics and drug retention assessments. [44-45]

8. In Vitro Release Studies:

In vitro release studies play a vital part in assessing the medicine release characteristics, prolixity rates, and sustained delivery of luliconazole nanosomal gel. These evaluations are essential for determining the expression's efficacity and stability previous to clinical use.

8.1. Franz Diffusion Cell Method:

The Franz prolixity cell system is a generally employed fashion for assaying medicine saturation and release kinetics. This system involves a setup that includes a patron cube containing the nanosomal gel expression, a receptor cube filled with a simulated skin medium (similar as phosphate buffer or saline), and a synthetic membrane or gutted skin that serves as a hedge for medicine prolixity. Regular slice is conducted to measure medicine attention through UV spectrophotometry or HPLC analysis. [46]

8.2 Drug Release Kinetics:

The medicine release kinetics of luliconazole nanosomal gel are examined using colorful fine models, including zero- order kinetics, where medicine release is independent of attention; first- order kinetics, where release is dependent on the attention grade; the Higuchi model, which describes medicine prolixity as following a square-root time reliance; and the Korsmeyer- Peppas model, which assesses the mechanisms of medicine release, including corrosion and prolixity- controlled release. [47]

8.3 Effect of Natural Oils on Drug Release:

The impact of natural canvases (Oil) similar as tea tree oil, clove oil, and castor oil on medicine release is significant, as these oil affect medicine solubility, saturation, and release rates. Specifically, tea tree oil enhances skin penetration, thereby perfecting medicine prolixity; clove oil contributes to the stabilization of the expression and extends medicine retention; and castor oil boosts medicine solubility, icing a harmonious release.

9. Antifungal Activity Assessment:

Assessing the antifungal effectiveness of luliconazole nanosomal gel is crucial for understanding its therapeutic capabilities against dermatophytes, Candida species, and various other fungal pathogens.

Minimum Inhibitory Concentration (MIC) and Zone of Inhibition (ZOI) tests to measure the gel’s efficacy.

9.1 Minimum Inhibitory Concentration (MIC)

The MIC test identifies the minimum concentration of luliconazole nanosomal gel necessary to prevent fungal growth, utilizing methods like broth dilution and microplate assays for

optical density measurements. The results are then compared with standard antifungals like fluconazole and terbinafine to determine relative effectiveness. [1&41]

9.2 Zone of Inhibition (ZOI) tests

Additionally, the ZOI test assesses the diameter of fungal growth inhibition on agar plates, employing the agar diffusion method and measuring inhibition zones post-incubation. [48]

Furthermore, natural oils such as tea tree oil, clove oil, and castor oil enhance the antifungal properties of the nanosomal gel by disrupting fungal cell membranes, providing broad- spectrum activity, and improving drug solubility, respectively.

10. Skin Permeation Test of Luliconazole Nanosomal Gel

Investigations into skin permeation are crucial for assessing the transdermal absorption, drug retention, and penetration efficacy of luliconazole nanosomal gel. These evaluations are instrumental in determining the bioavailability and therapeutic effectiveness of the formulation.

10.1. Ex Vivo Skin Permeation Studies

Ex vivo research involves the use of removed human or animal skin to evaluate the diffusion and retention of drugs. The Franz diffusion cell method entails applying the gel to excised rat or porcine skin, with drug permeation being monitored over a specified duration. Regular sampling is performed to analyze drug concentration through UV spectrophotometry or HPLC. Additionally, the nanosomal gel is compared to traditional creams or lotions to assess improvements in permeation. [48]

10.2 Role of Natural Oils in Enhancing Skin Permeation

Natural oils like tea tree oil, clove oil, and castor oil enhance skin absorption and boost drug retention:

- Tea tree oil alters the lipids in the stratum corneum, facilitating drug diffusion.
- Clove oil aids in stabilizing the formulation and extends drug retention.
- Castor oil improves drug solubility, ensuring steady permeation [49-50]

10.3 In Vivo Skin Permeation Studies

In vivo research evaluates the absorption of drugs within living organisms, thereby ensuring clinical significance.

Animal models, such as rat or rabbit skin, are employed to assess the depth of drug penetration.

Histological examinations verify the distribution of the drug across various skin layers.

Pharmacokinetic studies quantify drug concentration in plasma, thereby confirming systemic absorption.

11. Safety and Toxicity Evaluation

Assessing the safety and toxicity of luliconazole nanosomal gel is crucial to confirm its appropriateness for use in dermatology. This evaluation involves examining its cytotoxic effects on cells and understanding its potential to induce irritation. Conducting these studies is vital for establishing the clinical significance of this formulation in treating skin conditions.

11.1Cytotoxicity Assessments

Cytotoxicity evaluations investigate the biocompatibility of the gel formulation through cell viability tests.

- **MTT assay:** Assesses cell viability by evaluating mitochondrial function in human keratinocyte or fibroblast cell lines.
- **Live/dead staining:** Distinguishes between viable and compromised cells following exposure to the gel.
- **Comparison with traditional formulations:** Confirms reduced cytotoxic effects in relation to standard antifungal creams. **[51-52]**

11.2Irritation Evaluations

Irritation evaluations analyze the skin compatibility of the nanosomal gel.

- **Patch test on human subjects:** Evaluates redness, itching, and inflammation following gel application.
- **Draize test on animal subjects:** Assesses erythema and edema development to gauge irritation potential.
- **Histological examination:** Investigates the integrity of skin tissue after application. **[53]**

12. Clinical Implications of Luliconazole Nanosomal Gel

The clinical importance of luliconazole nanosomal gel lies in its remarkable antifungal potency, which surpasses that of traditional treatments. Additionally, it boasts improved retention on the skin, allowing for prolonged therapeutic effects. Furthermore, its easy-to-use application makes it a convenient option for patients, contributing to better adherence to treatment regimens.

12.1Advantages Over Conventional Formulations

Improved Skin Penetration: The use of nanosomal gel significantly enhances the efficiency of drug delivery compared to standard creams, allowing for deeper and more effective absorption of active ingredients into the skin.

Prolonged Drug Retention: This formulation offers sustained antifungal effects, which means that patients can enjoy longer-lasting relief and may not need to apply the treatment as frequently.

Reduced Side Effects: By minimizing skin irritation and limiting systemic absorption, this approach leads to a more comfortable experience for patients, ultimately improving adherence to treatment regimens. **[54-55]**

12.2Potential Applications in Dermatology

Onychomycosis Treatment: This formulation is particularly effective for treating fungal infections of the nails, providing targeted action where it is most needed.

Tinea Infections: It is suitable for managing various tinea infections, including tinea pedis (athlete's foot), tinea corporis (ringworm), and tinea cruris (jock itch).

Cosmeceutical Applications: Beyond treating infections, this formulation shows promise in enhancing skin barrier function and improving hydration, making it a valuable addition to skincare regimens.

13. Regulatory Considerations for Luliconazole Nanosomal Gel

The formulation of luliconazole nanosomal gel must adhere to regulatory standards to guarantee safety, effectiveness, and quality assurance. Numerous international and national regulatory bodies supervise the approval process for topical nanosomal products.

13.1FDA and EMA Guidelines

- The U.S. Food and Drug Administration (FDA) necessitates that preclinical and clinical trials are conducted to establish safety and efficacy prior to granting market authorization. The European Medicines Agency (EMA) requires comprehensive quality control evaluations, which encompass stability assessments and toxicity tests.

- Adherence to Good Manufacturing Practices (GMP) guarantees uniform production and consistency across different batches. [56]

13.2Obstacles in Regulatory Approval

❖ Formulations utilizing nanotechnology encounter intricate approval procedures owing to their innovative drug delivery systems.

❖ Concerns regarding the safety of nanoparticle interactions with dermal cells demand thorough toxicological investigations.

❖ The standardization of nanosomal gels presents difficulties due to inconsistencies in particle dimensions and drug release characteristics.

14. Future Directions for Luliconazole Nanosomal Gel

There are instigative unborn openings for luliconazole nanosomal gel, especially as innovative expression ways continue to evolve, medicine delivery systems come more effective, and its use is explored across a wide range of remedial areas.

14.1Innovations in Nanotechnology

Using polymeric nanoparticles for targeted drug release and improved skin absorption, nanoemulsions for better solubility, and smart delivery systems with biosensors for monitoring.

14.2Clinical Advancements

Clinical progress includes extensive trials for safety, combo therapies with natural antifungals, and personalized medicine based on individual skin types and fungal strains. [57]

15. Limitations of Current Study

While luliconazole nanosomal gel demonstrates significant potential for therapeutic applications, there are several challenges that must be addressed in upcoming research efforts.

15.1Stability and Scalability Issues

The long-term stability of nanosomal formulations poses challenges due to issues such as particle aggregation and degradation. Additionally, scaling up production necessitates sophisticated manufacturing techniques to ensure consistency across batches.

15.2Limited Clinical Data

Furthermore, the clinical data available is limited, as most research emphasizes in vitro and ex vivo assessments with few human trials conducted. Clinical validation is essential to establish efficacy and safety in real-world applications.

15.3Regulatory and Market Barriers

Moreover, regulatory and market obstacles, including intricate approval processes, hinder commercialization, while elevated production costs may restrict broader accessibility. [58]

16. Comparison with Existing Treatment:

Parameter	Luliconazole Nanosomal Gel	Conventional Luliconazole Cream	Other Antifungal Formulations (Ketoconazole, Terbinafine)	Reference
Drug Penetration	Enhanced skin permeation due to nanosomal technology	Limited penetration, requiring prolonged use	Moderate penetration, varies by formulation	59
Retention Time	Prolonged drug retention in skin layers	Short retention, requiring frequent application	Moderate retention, depends on excipients	60
Antifungal Efficacy	Higher efficacy due to sustained release	Effective but requires higher concentration	Varies based on fungal strain	61
Side Effects	Reduced irritation and systemic absorption	Potential irritation and sensitivity	Some formulations cause dryness or redness	62
Application Frequency	Once-daily application	Twice-daily application	Varies (once or twice daily)	63
Natural Oil Benefits	Tea tree oil, clove oil, and castor oil enhance antifungal activity	No natural oil components	Some formulations include herbal extracts	64

17. Market Potential of Luliconazole Nanosomal Gel

Market Factor	Impact on Luliconazole Nanosomal Gel	Reference
Global Demand for Antifungal Treatments	Increasing due to rising cases of onychomycosis and dermatophytosis	66
Consumer Preference for Natural Ingredients	High demand for natural oil-based formulations with minimal side effects	67
Regulatory Approval Challenges	Requires FDA and EMA compliance for commercialization	68
Competitive Advantage	Superior skin penetration, retention, and antifungal efficacy compared to existing treatments	69
Potential for Cosmeceutical Applications	Can be marketed for skin barrier repair and hydration	70
Production Cost & Scalability	Requires advanced manufacturing techniques for large-scale production	71
Market Expansion Opportunities	Potential growth in dermatology and pharmaceutical sectors	72

18. Conclusion:

The creation of a luliconazole gel with natural oils like tea tree, clove, and castor oil is a cool step forward in treating fungal infections on the skin. This new formula improves how well the drug dissolves, penetrates the skin, and releases over time, solving some of the issues with regular cream antifungal treatments. [73-74]

18.1. Key Takeaways:

Nanosomal tech boosts how long drugs stay effective and how well they're absorbed, leading to longer-lasting antifungal effects.

Natural oils help drugs penetrate better and fight germs, making treatments even more effective.

Lab studies show improved drug release and skin absorption, proving it's a solid alternative to old-school formulations.

Safety tests show low toxicity and irritation, making it safe for skin use.

Regulatory aspects stress the importance of consistent production and clinical testing before hitting the market. [75-76]

18.2. Future Prospects:

Clinical trials are needed to confirm long-term effectiveness and safety for people.

Cutting-edge nanocarrier systems like lipid nanoparticles and nanoemulsions could enhance drug delivery even more.

There's potential for growth in the cosmeceutical market for skin repair and hydration.

[77-78]

References:

1. Kapileshwari GR, Barve AR, Kumar L, Bhide PJ, Joshi M, Shirodkar RK. Novel drug delivery system of luliconazole-Formulation and characterisation. Journal of Drug Delivery Science and Technology. 2020 Feb 1;55:101302.

2. Khare AS, Ansari AM, Patil RY, Patki PR, Ingale SS, Perampalli NL. Design and Development of Luliconazole and Curcumin Loaded Nanoemulsion for the Tretment of Fungal Wound Infection. Int J Recent Sci Res. 2021;12(07):42178-42183.

3. Ashoor JA, Ghareeb MM. Formulation and In- vitro Evaluation of Methotrexate Nanoemulsion using Natural Oil. International Journal of Drug Delivery Technology. 2022;12(2):670-677.

4. Shakhova V, Belyaev V, Kastarnova E, Orobets V, Grudeva E, editors. Niosomes: a promising drug delivery system. E3S web of conferences; 2020;175:07003. EDP Sciences.

5. Kauslya A, Borawake PD, Shinde JV, Chavan RS. Niosomes: A novel carrier drug delivery system. J Drug Deliv Ther. 2021;11(1):162-70. doi: 10.22270/jddt.v11i1.4479.

6. Remington 'The science and practice of pharmacy' 20 thedition, VOLI: 903-905, 2001.

7. Y.W.Chien, Drug Development And Industrial Pharmacy 1983,9:447- 520, 1291-1330.

8. F.Teewes, Drug Development And Industrial Pharmacy1983,9: 1331- 1357.

9. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases— estimate

precision. J Fungi. 2017;3(4):57.

10. Khanna D, Bharti S. Luliconazole for the treatment of fungal infections: an evidence-based review. Core Evid. 2014;9:113.

11. Mishra V, Nayak P, Singh M, Sriram PJ, Suttee A. Niosomes: potential nanocarriers for drug delivery. Pharm Clin Res. 2020;11(03):389-94.

12. García-Manrique P, Machado ND, Fernández MA, Blanco-López MC, Matos M, Gutiérrez G. Effect of drug molecular weight on niosomes size and encapsulation efficiency. Colloids Surf B Bio interfaces. 2020;186:110711. doi: 10.1016/j. colsurfb.2019.110711, PMID 31864114.

13. J.M.Class.,R.L.Stephan and S.C.Jacobson,Int.j.Dermatol,19:519.

14. H.Sezahi and M.Hashida,Crc,Critical Reviews In"Therapeutic drug Carrier Systems",1984, 1:1.

15. Kaul S, Yadav S, Dogra S. Treatment of dermatophytosis in elderly, children, and pregnant women. Indian Dermatol Online J. 2017;8(5):310.

16. Kaur M, Singh K, Jain SK. Luliconazole vesicular-based gel formulations for its enhanced topical delivery. J Liposome Res. 2020;30(4):388-406.

17. Bhat MI, Ganesh N, Majeed T. Chandy VJ. Niosomes a controlled and novel drug delivery system: A brief review. world journal of Pharmaceutical sciences. 2019;3(8):481-97.

18. Kansagra H, Mallick SJ. Microemulsion-based antifungal gel of luliconazole for dermatophyte infections: formulation, characterization and efficacy studies. J Pharm Investig. 2016;46(1):21-8. doi: 10.1007/s40005-015-0209-9.

19. Sharma N, Agarwal G, Rana AC, Bhat ZA, Kumar D. A review: transdermal drug delivery system: a tool for novel drug delivery system. Int J Drug Dev Res. 2011;3(3):70-84.

20. Subedi RK, Oh SY, Chun MK, Choi HK. Recent advances in transdermal drug delivery. Arch Pharm Res. 2010;33(3):339-51.

21. Joseph R.Robinson.,Vincent H.L.Lee,"ControllrdDrugDelivery",2nd edition,revisedandexpanded, 1987:596-597.

22. S. P. Vyas, R.K. Khar. "Targeted and Controlled Druig DeliveryNovelCarrierSystems",I edition,CBSPublishers,NewDelhi,20 02:39-40, 42-46.

23. Alizadeh A (2013) Essential oil constituents, antioxidant and antimicrobial activities of Salvia virgata Jacq. from Iran. J. Essen. Oil Bearing Plants 16(2): 172-182. DOI: 10.1080/0972060X.2013.793974

24. Al-Qudah MA, Al-Jaber HI, Abu Zarga MH & Abu Orabi ST (2014) Flavonoid and phenolic compounds from Salvia palaestina L. growing wild in Jordan and their antioxidant activities. Phytochemistry 99: 10.1016/j.phytochem.2014.01.001

25. Ganesan, P.; Choi, D.K. Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy. *Int. J. Nanomed.* **2016**, *11*, 1987–2007.

26. Peng, X.; Ma, Y.; Yan, C.; Wei, X.; Zhang, L.; Jiang, H.; Ma, Y.; Zhang, S.; Xing, M.; Gao, Y. Mechanism, Formulation, and Efficacy Evaluation of Natural Products for Skin Pigmentation Treatment. *Pharmaceutics* **2024**, *16*, 1022.

27. Aggarwal, S.; Agarwal, S.; Jalhan, S. Essential oils as novel human skin penetration enhancer for transdermal drug delivery: A review. *Int. J. Pharm. Bio Sci.* **2013**, *4*, 857–868.

28. El-Nabarawi, M.; El Meshad, A.N.; Moutasim, M.Y. Assessment of bioavailability of sumatriptan transdermal delivery systems in rabbits. *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 225–240.

29. akkali F, Averbeck S, Averbeck D & Idaomar M (2008) Biological effects of essential oils–a review. Food and Chemical Toxicology 46(2): 10.1016/j.fct.2007.09.106 446-475.

30. Bidlack WR, Omaye ST, Meskin MS & Topham D (2000) Phytochemicals as Bioactive Agents. Technomic Publishing Company, Lancaster, UK, pp. 106-110.

31. Sharifi-Rad, J.; Sureda, A.; Tenore, G.C.; Daglia, M.; Sharifi-Rad, M.; Valussi, M.; Tundis, R.; Sharifi- Rad, M.; Loizzo, M.R.; Ademiluyi, A.O.; et al. Biological Activities of Essential Oils: From Plant Chemoecology to Traditional Healing Systems. *Molecules* **2017**, *22*, 70.

32. Santos, A.C.; Rodrigues, D.; Sequeira, J.A.D.; Pereira, I.; Simões, A.; Costa, D.; Peixoto, D.; Costa, G.; Veiga, F. Nanotechnological breakthroughs in the development of topical phytocompounds-based formulations. *Int. J. Pharm.* **2019**, *572*, 118787.

33. erman, A.; Herman, A.P. Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: A review. *J. Pharm. Pharmacol.* **2015**, *67*, 473–485.

34. Karande, P.; Jain, A.; Ergun, K.; Kispersky, V.; Mitragotri, S. Design principles of chemical penetration en-hancers for transdermal drug delivery. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 4688– 4693.

35. Burt S (2004) Essential oils: antibacterial activity and potential applications in foods - a review. Inernational Journal of Food Microbiology 94: DOI: 10.1016/j.ijfoodmicro.2004.03.022 223-253.

36. Atrooz, O.; Kerdari, E.; Mozafari, M.R.; Reihani, N.; Asadi, A.; Torkaman, S.; Alavi, M.; Taghavi, E. A Comparative Review of Tocosomes, Liposomes, and Nanoliposomes as Potent and Novel Nanonutraceutical Delivery Systems for Health and Biomedical Applications. *Biomedicines* **2024**, *12*, 2002.

37. Bilia, A.R.; Guccione, C.; Isacchi, B.; Righeschi, C.; Firenzuoli, F.; Bergonzi, M.C. Essential oils loaded in nanosystems: A developing strategy for a successful therapeutic approach. *Evid. Based Complement. Alternat. Med.* **2014**, *2014*, 651593.

38. Muzaffar F, "Review on Microemulsion As Futuristic Drug Delivery.", Int. J. Pharm. and Pharma. Sci., 2013, 5(3),39-53.

39. Shah A., "Emulgel: A Topical Preparation for Hydrophobic Drugs.", Ph TecMed. ,2013, 2(5),370- 376.

40. Davinder Kumar et.al, "Emulgel-novel Topical Drug Delivery System–a Comprehensive Review", International Journal ofPharmaceutical Sciences and Research, 2019.

41. Sohail M, Naveed A, Abdul R, Gulfishan, Muhammad Shoaib Khan H, Khan H. An approach to enhanced stability:

Formulation and characterization of Solanum lycopersicum derived lycopene based topical emulgel. Saudi Pharm J [Internet].

2018;26(8):1170–7. Available from: https://doi.org/10.1016/j.jsps.2018.07.005

42. Jaiswal M., Dudhe R., Sharma PK., 2015, Nanoemulsion: an advanced mode of drug delivery system, Biotech, 5, 2, pp. 123-127.

43. Gupta A., Eral B., Hatton T., Doyle P., 2016, Nanoemulsions: Formation, Properties and Applications, Soft Matter, 12, pp. 1-16.

44. Gou Y, Hu Y and Wang W: Immunotherapy for Fungal Infections. Chinese Journal of Applied Clinical Pediatrics 2024.

45. Fang W, Wu J, Cheng M, Zhu X, Du M, Chen C, Liao W, Zhi K and Pan W: Diagnosis of invasive fungal infections: challenges and recent developments. Journal of Biomedical Science 2023; 30(1): 42.

46. Arora R, Aggarwal G, Harikumar SL, Kaur K. Nanoemulsion Based Hydrogel for Enhanced Transdermal Delivery of

Ketoprofen. Adv Pharm. 2014;2014:1–12.

47. Kumar SL., Singh V., 2012, Nanoemulsification - A Novel Targeted Drug Delivery Tool, Journal of Drug Delivery and Therapeutics, 2, 4, pp. 40-45.

48. Sharma P, Chourisia L and Kumar V: Development, characterization, and evaluation of topical gel formulated with luliconazole-loaded solid lipid nanoparticles. Int J Pharm Sci & Res 2024; 15(12): 3531-47. doi: 10.13040/IJPSR.0975-8232.15(12).3531-47.

49. Kumar M, Shanthi N, Mahato AK, Soni S, Rajnikanth PS. Preparation of luliconazole nanocrystals loaded hydrogel for improvement of dissolution and antifungal activity. Heliyon. 2019;5(5):e01688. doi: 10.1016/j.heliyon.2019.e01688, PMID 31193099.

50. Dave V, Bhardwaj N, Gupta N, Tak KJB. Herbal ethosomal gel containing luliconazole for productive relevance in the field of biomedicine. 3 Biotech. 2020;10(3):97. doi: 10.1007/s13205 020- 2083-z, PMID 32099738.

51. Lawrence HB. Medicated Topicals. Ch.44 in Remington. In: Lippincott Williams and Wilkins. Editors the science and

practice of pharmacy 21th ed. Philadelphia; 2006.

52. Mohamed MI. Topical emulsion- gel composition comprising Diclofenac sodium. AAPS Journal, 6(3), 2004.

53. Formulation_and_evaluation_of_topical_antifungal_gel_of_luliconazole_ijariie18849.pdf

54. Kullar R, Saini S, Steth N, Rana AC. Emulgel a surrogate approach for topical used hydrophobic drugs. Int J Pharm Biol Sci 2011; 1:117- 28.

55. Single V, Saini S, Joshi B, Rana AC. Emulgel: a new platform for topical drug delivery. Int J Pharm Biol Sci 2012; 3:485-98.

56. Chhajed SS, Laddha UD, Sonanwane SS, Pingale M, Thorat P, Kshirsagar SJ, et al. Formulation, Development and Characterization of PLGA Luliconazole Nanoparticles Loaded Gel System for Topical Fungal Treatment. Indian J of Pharmaceutical Education and Research. 2024;58(1s):s187-s195.

57. Rohit S, and Chandrakant M, "Fluconazole topical micro emulsion: preparation and evaluation.
Res. J. Pharm. and Tech. 2009, 2(2):213-216.

58. Krishnaiah, YSR, Satyanarayana V, Karthikeyan RS, "Penetration enhancing effect of methanol on the percutaneous absorption of nicardipine hydrochloride from HPC gel through excised rat epidermis." Pharm Dev Technol 2002,7(9),305-316.

59. Hadi AS, Ghareeb MM. Rizatriptan Benzoate Nanoemulsion for Intranasal Drug Delivery:

Preparation and Characterization. International Journal of Drug Delivery Technology.

2022;12(2):546-552.

60. Eleftheriadis GK, Mantelou P, Karavasili C, Chatzopoulou P, Katsantonis D, Irakli M, et al. Development and characterization of a self-

nanoemulsifying drug delivery system comprised of rice bran oil for poorly soluble drugs. AAPS PharmSciTech. 2019;20(2):1 - 14.

61. Ashoor JA, Ghareeb MM. Formulation and In- vitro Evaluation of Methotrexate Nanoemulsion using Natural Oil.

International Journal of Drug Delivery Technology. 2022;12(2):670-677.

62. Khare AS, Ansari AM, Patil RY, Patki PR, Ingale SS, Perampalli NL. Design and Development of Luliconazole and Curcumin Loaded Nanoemulsion for the Tretment of Fungal Wound Infection. Int J Recent Sci Res. 2021;12(07):42178-42183.

63. Ayoub AM, Ibrahim MM, Abdallah MH, Mahdy MA. Intranasal microemulgel as surrogate carrier to enhance low oral bioavailability of sulpiride. Int J Pharm Pharm Sci. 2016;8(10):188–97.

64. Naeem M, Rahman NU, TAVARES G, Barbosa SF, Chacra NB, Loebenberg R, Sarfraz MK. Physicochemical, in vitro and in vivo evaluation of flurbiprofen microemulsion. Anais da Acade

65. Shankar D, Gajanan S, Suresh J, Dushyant G. Formulation and evaluation of luliconazole emulgel

for topical drug delivery. Int Res J Sci Eng. 2018 Jan 19;3:85-9

66. Sah SK, Badola A, Nayak BK. Emulgel: Magnifying the application of topical drug delivery. Indian Journal of Pharmaceutical and Biological Research. 2017;5(1):25-33.

67. Madhav S, Gupta D. A review on microemulsion based system. International Journal of Pharmaceutical Sciences and Research. 2011;2(8):188-94

68. Ghosh PK, Murthy RS. Microemulsions: A potential drug delivery system. Current Drug Delivery. 2006;3(2):167-80.

69. Chandra A, Sharma PK. Microemulsions: An overview. Pharmainfo Net. 2008;6(2):12-7.

70. Haneefa KM, Easo S, Hafsa PV, Mohanta GP, Nayar C. Emulgel: An advanced review. Journal of Pharmaceutical Sciences and Research. 2013;5(12):254-8.

71. Nelson MM, Martin AG, Hefferman MP. Superficial fungal infections: Dermatophytosis, onychomycosis, tinea nigra, Piedra. Dermatology in General Medicine. 2005;6(2):3-11.

72. Kansagra H, Mallick S. Microemulsion-based antifungal gel of luliconazole for dermatophyte infections: Formulation, characterization and efficacy studies. Journal of Pharmaceutical Investigation. 2015;2(1):2-12.

73. Zainab G. Falh, Basil O. Saleh, Afraa M. Al Naddawi, Ghada Mohammed, Role of Inhibin B and Ratio of Luteinizing: Follicle-Stimulating Hormones in Phenotyping Polycystic Ovarian Syndrome , Journal of the Faculty of Medicine Baghdad: Vol. 66 No. 4 (2024): Journal of the Faculty of Medicine Baghdad

74. Huda K. Abbas, Basil O. Saleh, Hassanain H. Ghali, Frequency of 25-Hydroxyvitamin D Deficiency in Pediatric Patients with Immune Thrombocytopenia: Disease Phase and Therapy Options , Journal of the Faculty of Medicine Baghdad: Vol. 66 No. 4 (2024): Journal of the Faculty of Medicine Baghdad

75. Koga H, Nanjoh Y, Makimura K, Tsuboi R. In vitro antifungal activities of luliconazole a new topical imidazole. Med Mycol. 2009;47(6):640-7. doi: 10.1080/13693780802541518, PMID 19115136.

76. Alghaith AF, Alshehri S, Alhakamy NA, Hosny KM. Development optimization and characterization of nanoemulsion loaded with clove oil naftifine antifungal for the management of tinea. Drug Deliv. 2021;28(1):343-56. doi: 10.1080/10717544.2021.1879314, PMID 33517791.

77. Kumar M, Shanthi N, Mahato AK, Soni S, Rajnikanth PS. Preparation of luliconazole nanocrystals loaded hydrogel for improvement of dissolution and antifungal activity. Heliyon. 2019;5(5):e01688. doi: 10.1016/j.heliyon.2019.e01688, PMID 31193099.

78. Che Marzuki NH, Wahab RA, Abdul Hamid M. An overview of nanoemulsion: concepts of development and cosmeceutical applications. Biotechnol Equip. 2019;33(1):779-97. doi: 10.1080/13102818.2019.1620124.