© INTERNATIONAL JOURNAL FOR RESEARCH PUBLICATION & SEMINAR
ISSN: 2278-6848 | Volume: 13 Issue: 04 | July - September 2022
Paper is available at http://www.jrps.in | Email : info@jrps.in
Refereed & Peer Reviewed

STUDY ON ISOCONAZOLE PRONIOSOMAL GEL IN TREATING FUNGAL INFECTION

Preeti Sharma[1], Dr. Manoj Sharma[2]
Assistant Professor, SOS In Pharmaceutical Sciences, JIWAJI University, Gwalior
Associate Professor, SOS In Pharmaceutical Sciences, JIWAJI University, Gwalior

ABSTRACT
Fungal skin treatment is a major issue and is generally treated without any care. Fungal infections are an overall worldwide medical issue; influencing a huge number of patients every time of these roughly 1.5 million are dispersed or obtrusive fungal infections (IFS), requiring propelled treatment and hospitalization. Unfortunately, this high number of infections is related with high death rates, with some fungal infections having death rates nearing 90% - 95%. Toxicities related with the utilization of some antifungal specialists can be restrictive toward utilize or should be acknowledged keeping in mind the end goal to successfully treat the patient. In this review, isoconazole proniosomal gel has been reviewed to treat fungal infections. Past literature has been studied with the aim to develop a medicine for treating fungal infections.
Keywords: proniosomal gel, isoconazole, fungal infection, antifungal.

INTRODUCTION
A fungal infection, also called mycosis, is a skin disease caused by a fungus.
There are millions of species of fungi. They live in the dirt, on plants, on household surfaces, and on your skin. Sometimes, they can lead to skin problems like rashes or bumps.

Fungal Infection Symptoms
A fungal skin infection might cause:

- Irritation
- Scaly skin
- Redness
- Itching
- Swelling
- Blisters

1.1. Types of Fungal Infections
Fungal skin infections can happen anywhere on your body. Some of the most common are athlete's foot, jock itch, ringworm, and yeast infections. [1]

1. **Athlete's Foot**

Athlete's foot, also called tinea pedis, is a fungal infection of your foot.
The fungi grow best in warm, moist places such as shoes, socks, swimming pools, locker rooms, and public showers. They're often found in the summer and in hot, humid climates. It happens more often in people who wear tight shoes, who don't change their sweaty socks, and who use public baths and pools.

Athlete's foot causes
The fungi behind athlete's foot live on the dead tissue of your hair, toenails, and outer skin layers. At least four kinds of fungus can cause the infection. The most common is *Trichophyton rubrum*.

2. **Jock Itch**

© INTERNATIONAL JOURNAL FOR RESEARCH PUBLICATION & SEMINAR
ISSN: 2278-6848 | Volume: 13 Issue: 04 | July - September 2022
Paper is available at http://www.jrps.in | Email : info@jrps.in
Refereed & Peer Reviewed

A type of fungus called tinea causes jock itch. The infection is also known as tinea cruris. Tinea loves warm, moist areas like your genitals, inner thighs, and buttocks. Infections happen more often in the summer or in warm, wet climates.

Jock itch is a red, itchy rash that's often ring-shaped.

Is jock itch contagious?

It's only mildly contagious. It can spread from person to person through direct contact or indirectly through objects with the fungus on them.

3. **Jock itch symptoms**

Symptoms of jock itch include:

- Itching, chafing, or burning on your groin or thigh
- A red, circular, rash with raised edges
- Redness on your groin or thigh
- Flaking, peeling, or cracking skin

4. **Ringworm**

Ringworm, also called tinea corporis, isn't a worm but a fungal skin infection. It's named for its ring-shaped rash with a winding, worm-like edge.

Is ringworm contagious?

Ringworm can spread through direct contact with infected people or animals. You can also pick it up off clothing or furniture. Heat and humidity can help spread the infection.

Ringworm symptoms

Ringworm is a red, circular, flat sore that can happen along with scaly skin. The outer part of the sore might be raised while the skin in the middle appears normal. Patches or red rings may overlap.

5. **Yeast Infections**

Yeast infections of your skin are called cutaneous candidiasis. A type of fungus called candida causes these infections when it grows too much. Yeast infections aren't contagious.

The infections are most common in warm, moist, creased areas of your body, including your armpits and groin. They often happen in people who are obese or who have diabetes. People taking antibiotics are also at higher risk.

Yeast infection symptoms

Signs of a yeast infection on your skin include:

- Rash
- Patches that ooze clear fluid
- Pimple-like bumps
- Itching
- Burning

1.2. Antifungal

An antifungal medication, also known as an antimycotic medication, is a pharmaceutical fungicide or fungistatic used to treat and prevent mycosis such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. Such drugs are usually obtained by a doctor's prescription, but a few are available over the counter (OTC). [2]

1.2.1. Types of antifungals

© INTERNATIONAL JOURNAL FOR RESEARCH PUBLICATION & SEMINAR
ISSN: 2278-6848 | Volume: 13 Issue: 04 | July - September 2022
Paper is available at http://www.jrps.in | Email : info@jrps.in
Refereed & Peer Reviewed

There are two types of antifungals: local and systemic. Local antifungals are usually administered topically or vaginally, depending on the condition being treated. Systemic antifungals are administered orally or intravenously.

Of the clinically employed azole antifungals, only a handful are used systemically. These include ketoconazole, itraconazole, fluconazole, voriconazole, Posaconazole, and isoconazole. Examples of non-azole systemic antifungals include griseofulvin and terbinafine.

1.3. PRONIOSOME

Proniosomes are dry plans of surfactant-covered transporter, which can be allotted as required and rehydrated by brief tumult in hot water. These "proniosomes" limit issues of niosomes physical soundness, for example, aggregation, fusion and releasing and gave extra accommodation in transportation, distribution, storage and dosing. Proniosomes-determined niosomes are better than regular niosomes in accommodation of capacity, transport and dosing. Dependability of dry proniosomes is required to be steadier than a pre-fabricated niosomal definition. [3]

- **PRONIOSOMAL GEL**:

Proniosomal gel are made by dissolving the surfactant in an insignificant amount of a satisfactory dissolvable, (to be specific ethanol) and after that hydration with scarcest measure of water to frame a gel. Proniosomal hydrogels have likewise been portrayed for theirpotential use as transdermal medication conveyance vehicles [31,32].Proniosomes are otherwise called "dry niosomes" in light of the fact that theyrequire hydration to shape niosomal vessels before sedate discharge and saturation through the skin[34]. Not at all like niosomes, proniosomes are not independently arranged; be that as it may, the greater part of the planning steps, for example, the expansion of a surfactant and a gelling operator is all the while performed and they are scattered in a warm water shower. Along these lines, the scattering is chilled off at room temperature until the point that it changed over into proniosomal gel.[33] These structures are fluid crystalline thick niosomes half and halves that can be changed over into niosomes in a split second upon hydration or utilized all things considered in the topical/transdermal applications. Proniosomal gels are by and large present in straightforward, translucent or white semisolid gel surface, which makes them physically stable all through capacity and transport.

ADVANTAGE OF PRONIOSOMES:

- ✓ Proniosomes avoids the problems of physical stability like aggregation, fusion and leaking of drugs.
- ✓ Avoids hydrolysis of encapsulated drugs which limits the shelf life of the dispersion.
- ➢ Ease on storage and handling.

The storage makes proniosomes a versatile delivery system with potential and wide range of active.

© INTERNATIONAL JOURNAL FOR RESEARCH PUBLICATION & SEMINAR
ISSN: 2278-6848 | Volume: 13 Issue: 04 | July - September 2022
Paper is available at http://www.jrps.in | Email : info@jrps.in
Refereed & Peer Reviewed

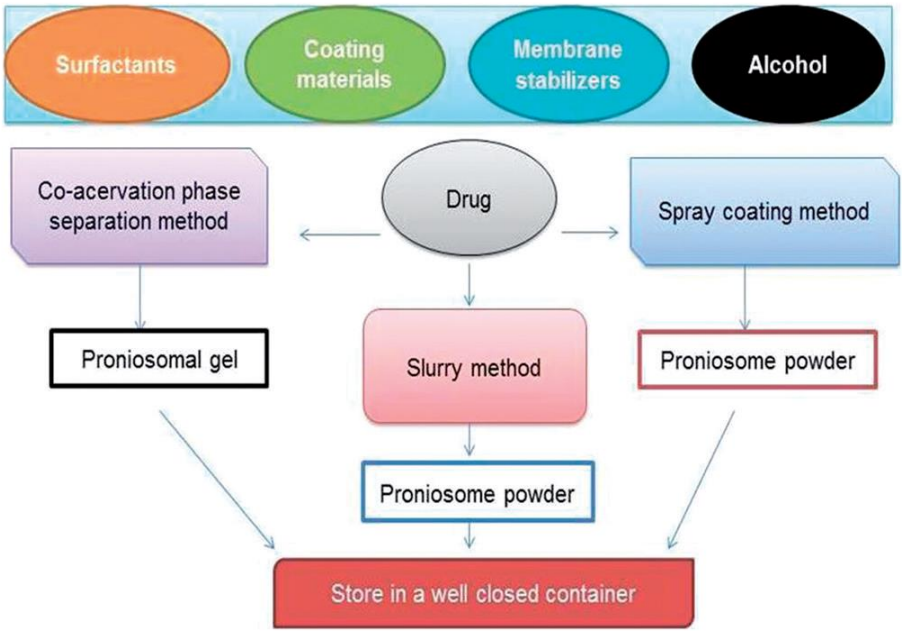

Figure: Method and materials

REVIEW OF LITERATURE

[4] Miconazole nitrate is a broad-spectrum antifungal agent, and it is used for the treatment of superficial fungal infections. It has low skin permeability. Therefore, the aim of this study was to prepare proniosomal 2% miconazole nitrate sustained release to a treat deep- seated fungal infections. The different batches of proniosomal 2% miconazole nitrate gel were prepared by the conservation phase separation method using different non-ionic surfactants and Cholesterol. Preliminary trial batches were formulated and evaluated for different evaluation parameters like pH, viscosity, % entrapment efficiency, % drug content, and in-vitro drug release study. A 32 full factorial design was used to check the effect of Span 60 (X1) and Cholesterol (X1) on % entrapment efficiency (EE) and % drug release at 20 h (Q20). Multiple linear regression analysis, ANOVA, and graphical representation of the influence factor by 3D response surface plots were performed using Design Expert 9. Checkpoint batch was prepared to validate the evolved model. Optimized batch was found to be stable, and it showed release 94.76% in 24 h. It followed the non-fickian diffusion and showed flux 289 µg/cm2/h in the ex-vivo study. SEM revealed that the noisome formed were spherical in shape. Therefore, proniosomal 2% miconazole nitrate gel has the ability to penetrate the skin and give the effect for a long time.

[5] Ketoconazole existing oral formulations suffer poor bioavailability since KTZ undergoes a marked first-pass effect and its absorption is dissolution rate-limited. In this study, a novel sustained release proniosomal system was designed using different non-ionic surfactants in which proniosomes were converted to niosomes upon skin water hydration following topical application under occlusive conditions. Different in vitro aspects (encapsulation efficiency, vesicle size and shape, in vitro release and stability) were studied leading to an optimized formula. All formulae exhibited high entrapment efficiencies, regardless of the surfactant HLB. Vesicle size analysis of promising formulation showed that all vesicles were in the quality range which favored efficient transdermal delivery. The entrapment efficiency of drug in optimized formulation (F3) containing Span 60 is high (94.93%) moreover, the extent of drug permeation through the membrane from

the optimized formula was also quite high (93.52%) after 24 hrs. Concentration of cholesterol and lipid also plays an imp role in the entrapment efficiency of formed proniosomes. The above results indicate that the proniosomal gel of KTZ could be formulated for sustained release using optimum concentration of cholesterol, lipid and suitable surfactant to deliver a desired concentration of drug at site of action and overcoming the side effects of oral route.

[6] Fluconazole is a synthetic antifungal drug, belonging to triazole group and mostly used to treat oral candidiasis caused by the yeast Candida albicans. Fluconazole commercially available in tablets that offer poor bioavailability, due to hepatic first pass effect and gastric instability leads to frequent dosing. Buccal drug delivery can bypass such problems of tablet and leads to increase in bioavailability. Due to low molecular weight, fluconazole can suitably be administered by buccal route, hence local and targeted action can achieve. The present study was conducted to develop proniosomal gel of fluconazole by coacervation phase separation method using Span 20, cholesterol, soya lecithin, ethanol and aqueous vehicle. Based on preliminary studies surfactant and aqueous vehicle was selected. The Box Behnken design was employed to optimized proniosomes by evaluating responses like entrapment efficiency, vesicle size and drug release. The optimized proniosomes were evaluated with entrapment efficiency (96.83%), vesicle size (2µm), in vitro drug release 85.66 % (3 h) and ex vivo mucosal permeation (85.67 %) with flux (394.09 µg/cm2h). The optimized proniosomes were incorporated into 2% w/w Carbopol gel 934 (1:1) to obtain proniosomal gel. This optimized proniosomal gel was found with good viscosity, good spreadability and adhesiveness, also it shows maximum drug release and permeation as compared to plain gel of fluconazole. In microbiological studies, optimized formulation shows the maximum inhibitory effect as compared to plain gel of drug, which concluded that optimized proniosomal gel exerted local and targeted buccal delivery with good fungistatic effect than plain gel of fluconazole against Candida albicans.

[7] The present research has been undertaken with the aim to develop a topical gel formulation of Itraconazole. Itraconazole is an imidazole derivative and used for the treatment of local and systemic fungal infection. The oral use of Itraconazole is not much recommended as it has many side effects. Commercially Itraconazole topical gel preparation are not available in the market, thus this formulation is made for better patient compliance and to reduce the dose of the drug and to avoid the side effects like liver damage and kidney damage. The gel was formulated by changing the polymer ratio. Various formulation (F1, F2, F3, F4, F5) were developed by using a suitable polymer (Carbopol 934p and HPMC). The formulation was evaluated for % yield, spreadability, extrudability, wash ability and viscosity in vitro drug release study, skin irritation study, stability testing. Viscosity studies of various formulations revealed that formulation F3 was better to compare to others. From among all the developed formulation, F3 shows better drug diffusion, did good Rheological properties. pH of the F3 formulation is sufficient enough to treat the skin infections. Results indicated that the concentration of carbopol-934 and HPMC K4M significantly affects drug release and rheological properties of the gels.

[8] Caused by a range of Epidermophyton, Microsporum and Trichophyton species, dermatomycoses manifest on glabrous skin as ringworm, an annular scaly lesion with a variable inflammatory component. Itch is the chief subjective symptom, particularly in tinea cruris. Unless lesions are extensive or resistant to local therapy, dermatomycoses of glabrous skin are treated

with topical antifungal agents, such as imidazoles and allylamines. Studies show, however, that the addition of a topical corticosteroid to imidazole therapy increases the bioavailability and prolongs the activity of the antimycotic, while rapidly reducing inflammatory symptoms. Travocort? is a combination of 1% isoconazole nitrate (ISN), a broad-spectrum imidazole with established antimicrobial activity and antimycotic efficacy, and 0.1% diflucortolone valerate (DFV), a potent topical corticosteroid with low systemic absorption and therefore a low risk of systemic glucocorticoid side-effects. In randomized, double-blind controlled clinical trials, Travocort? therapy showed a more rapid onset of action, faster relief of itch and other inflammatory symptoms, improved overall therapeutic benefits and better mycological cure rate during the first 2 weeks of treatment compared with ISN monotherapy. Travocort? is well tolerated and, because of prolonged ISN retention in the skin, provides antifungal protection against reinfection for some weeks after therapy.

[9] Voriconazole (VRC) is a triazole broad spectrum antifungal drug, used in the management of versatile fungal infections, particularly fungal keratitis. The obligatory use of niosomal delivery of VRC may reduce the frequency of dosing intervals resulting from its short biological half time and consequently improve patient compliance. VRC loaded proniosomes (VRC-PNs) were set by the coacervation technique and completely characterized. The developed formula was comprehensively assessed concerning in- vitro release behavior, kinetic investigation, and its conflict against refrigerated and room temperature conditions. A selected niosomal formula was incorporated into occusert (VRC- PNs) formulated by 1% w/w hydroxypropyl methyl cellulose HPMC and 0.1% w/w carbopol 940. Eventually, in vitro antifungal activity against Candida albicans and Aspergillus nidulans was assessed by the cup diffusion method.

[10] The aim of this study was to explore the potential of proniosomal gel for topical delivery of fluconazole, an antifungal drug used in fungal infections caused by pathogenic fungi. Fluconazole-loaded proniosomal gels were prepared by the coacervation phase separation method using different nonionic surfactants (spans and tweens). The prepared fluconazole proniosomal gels were evaluated for various parameters such as particle size (PS), drug entrapment efficiency percentage (EE%), and in vitro drug release. The experimental results showed that the EE% for the prepared formulae are acceptable (85.14%–97.66%) and they are nanosized (19.8–50.1 nm) and the diffusion from the gels gave the desired sustaining effect. F4, which was prepared from span 60, tween 80 (1:1), and cholesterol showed highest EE% and gave slow release (40.50% ± 1.50% after 6 h), was subjected to zeta potential (ZP) test, transmission electron microscopy as well as microbiological study.

[11] Global incidence of superficial fungal infections caused by dermatophytes is high and affects around 40 million people. It is the fourth most common cause of infection. Clotrimazole, a broad-spectrum imidazole antifungal agent is widely used to treat fungal infections. Conventional topical formulations of clotrimazole are intended to treat infections by effective penetration of drugs into the stratum corneum. However, drawbacks such as poor dermal bioavailability, poor penetration, and variable drug levels limit the efficiency. The present study aims to load clotrimazole into proniosomes and evaluate its topical bioavailability. Clotrimazole loaded proniosomes were prepared using cholesterol and sodium oleate by thin film hydration technique and evaluated for size, polydispersity index, and entrapment efficiency to obtain optimized formulation. Optimized

formulation was characterized using scanning electron microscopy (SEM), X-ray diffraction (XRD), and differential scanning calorimetry (DSC). Skin diffusion studies and tape-stripping were performed using human skin to determine the amount of clotrimazole accumulated in different layers of the skin.

[12] Azole derivative- based antifungal creams, liquids, or sprays are available to treat fungal infections; however, these formulations show various side effects on the application site. Over the past few years, herbal extracts and various essential oils have shown effective antifungal activity. Additionally, autoxidation and epimerization are significant problems with the direct use of herbal extracts. Hence, to overcome these obstacles, polysaccharide-based nanohydrogels embedded with natural plant extracts and oils have become the primary choice of pharmaceutical scientists. These gels protect plant-based bioactive compounds and are effective delivery agents because they release multiple bioactive compounds in the targeted area. Nanohydrogels can be applied to infected areas, and due to their contagious nature and penetration power, they get directly absorbed through the skin, quickly reaching the skin's third layer and effectively reducing the fungal infection. In this review, we explain various skin fungal infections, possible treatments, and the effective utilization of plant extract and oil-embedded polysaccharide-based nanohydrogels.

[13] Fungal skin infections are the most common global issue for skin health. Fungal infections are often treated by topical or systemic anti-fungal therapy. Topical fungal therapy is usually preferred because of their targeted therapy and fewer side effects. Advanced topical carriers because of their distinct structural and functional features, overcome biopharmaceutical challenges associated with conventional drug delivery systems like poor retention and low bioavailability. Literature evidence indicated topical nanocarriers loaded with anti-fungal agents display superior therapeutic response with minimum toxicity. Nanocarriers often used for topical anti- fungal medication includes Solid-Lipid nanoparticles, Microemulsions, Liposomes, Niosomes, Microsponge, Nanogel, Nanoemulsion, Micelles etc. This review summarizes recent advances in novel strategies employed in topical carriers to improve the therapeutic performance of anti-fungal drugs.

CONCLUSION

This review has showed that the fungal treatment needs proper care and treatment. There are various medicines in the market but not without flaws. The review showed that isoconazole proniosomal gel can be proven a better medicine than any medicine available with comparatively less flaws and more medicinal benefits. If prepared in proper composition, it can treat all types of fungal infections with ease. In discharge ponders proniosomes have all the earmarks of being equal to regular niosomes. Estimate disseminations of proniosomes-determined niosomes are fairly better that those of traditional niosomes so the discharge execution in more basic cases ends up being prevalent. Proniosomes avoids the problems of physical stability like aggregation, fusion and leaking of drugs. It can also avoid hydrolysis of encapsulated drugs which limits the shelf life of the dispersion. The storage benefits make proniosomes a versatile delivery system with potential and wide range of active.

REFERENCES

[1] B. D. Thimmaraju R, A. Nasir Kurnool, T. D. R α, and A. Nasir Kurnool σ, "Proniosomal Gel: Formulation and Charecterization of an Antifungal Drug (Butenafine Hcl) Loaded

Proniosomes for Topical Delivery," *Toxicol. Med.*, vol. 20, no. 5, 2020.

[2] G. Fetih, "Fluconazole-loaded niosomal gels as a topical ocular drug delivery system for corneal fungal infections," *J. Drug Deliv. Sci. Technol.*, vol. 35, pp. 8–15, 2016, doi: 10.1016/j.jddst.2016.06.002.

[3] M. M. Ahmed *et al.*, "Formulation and in vitro evaluation of topical nanosponge-based gel containing butenafine for the treatment of fungal skin infection," *Saudi Pharm. J.*, vol. 29, no. 5, pp. 467–477, 2021, doi: 10.1016/j.jsps.2021.04.010.

[4] N. Oza and S. Sagar, "a Statistical Approach To Development of Sustained Release Proniosomal," *Int. J. Pharm. Sci. Res.*, vol. 11, no. 11, pp. 5508–5517, 2020, doi: 10.13040/IJPSR.0975-8232.11(11).5508-17.

[5] G. Benipal, "Design, development and evaluation of proniosomal gel of an antifungal drug - Ketoconazole," *Int. J. Pharm. Sci. Rev. Res.*, vol. 31, no. 2, pp. 265–277, 2015.

[6] L. Lekshmi, S. Joseph, and P. Mathew, "Formulation and evaluation of antifungal lozenges for oral candidiasis," *Int. J. Pharm. Technol.*, vol. 8, no. 4, pp. 25245–25261, 2016.

[7] P. M. Kasar, K. Kale, and D. G. Phadtare, "Formulation and Evaluation of Topical Antifungal Gel Containing Itraconazole," *Int. J. Curr. Pharm. Res.*, vol. 10, no. 4, p. 71, 2018, doi: 10.22159/ijcpr.2018v10i4.28470.

[8] B. Havlickova and M. Friedrich, "The advantages of topical combination therapy in the treatment of inflammatory dermatomycoses," *Mycoses*, vol. 51, no. SUPPL.4, pp. 16–26, 2008, doi: 10.1111/j.1439-0507.2008.01615.x.

[9] G. A. El-Emam, G. N. S. Girgis, M. M. A. El Sokkary, O. A. El-Azeem Soliman, and A. E. G. H. Abd El Gawad, "Ocular inserts of voriconazole-loaded proniosomal gels: Formulation, evaluation and microbiological studies," *Int. J. Nanomedicine*, vol. 15, pp. 7825–7840, 2020, doi: 10.2147/IJN.S268208.

[10] A. S. M. Abu El-Enin, M. K. A. Khalifa, A. M. Dawaba, and H. M. Dawaba, "Proniosomal gel-mediated topical delivery of fluconazole: Development, in vitro characterization, and microbiological evaluation," *J. Adv. Pharm. Technol. Res.*, vol. 10, no. 1, pp. 20–26, 2019, doi: 10.4103/japtr.JAPTR-332-18.

[11] P. K. Bolla *et al.*, "Clotrimazole loaded ufosomes for topical delivery: Formulation development and in-vitro studies," *Molecules*, vol. 24, no. 17, 2019, doi: 10.3390/molecules24173139.

[12] N. Kaur, A. Bains, R. Kaushik, S. B. Dhull, F. Melinda, and P. Chawla, "A review on antifungal efficiency of plant extracts entrenched polysaccharide-based nanohydrogels," *Nutrients*, vol. 13, no. 6, pp. 1–26, 2021, doi: 10.3390/nu13062055.

[13] A. Garg, G. S. Sharma, A. K. Goyal, G. Ghosh, S. C. Si, and G. Rath, "Recent advances in topical carriers of anti-fungal agents," *Heliyon*, vol. 6, no. 8, p. e04663, 2020, doi: 10.1016/j.heliyon.2020.e04663.