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A STUDY ON DEVELOPING ISOCONAZOLE PRONIOSOMAL GEL TO TREAT FUNGAL INFECTION

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ABSTRACT
Antifungal medicines treat fungal infections. Fungus in the soil, air and on your skin can cause yeast infections, ringworm, and nail and skin infections. Breathing in fungal spores can lead to respiratory illnesses. People who have weak immune systems are more prone to fungal infections that require antifungal medicine. Fungi grow as yeasts, molds or a combination of both. They reproduce through very tiny spores. These spores can exist in soil or become airborne. Proniosomal gel basically is a compact semi-solid liquid crystalline (gel) composed of non-ionic surfactants easily formed on dissolving the surfactant in a minimal amount of acceptable solvent and the least amount of aqueous phase and phosphate buffer. Proniosomal gels are typically present in transparent, translucent, or white semisolid gel texture, which makes them physically stable throughout storage and transport. This research work attempted to develop an isoconazole proniosomal gel to treat fungal infection. The research aimed to study the morphological shape and size of the developed drug to understand its effectiveness.
Keywords: proniosomal gel, isoconazole, fungal infection, antifungal.

1. INTRODUCTION
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%. Generally, IFIs are infections of immunocompromised hosts. The standard meaning of the immunocompromised host is growing from the customary arrangement of patients with AIDS, patients with tumor who are experiencing immunosuppressive chemotherapy or transplant patients whose resistant framework are smothered to forestall organ rejection. Additionally, IFIs are likewise seen in patients who are solid and obviously immunocompetent however who have hidden, asymptomatic condition that may adjust safe capacity and incline toward infections, for example, the nearness of against cytokines, for example, GM-CSF.
Anyway, these medications similarly as with any treatment with have constraints and provisos. For instance, 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.

1.1. TYPES OF FUNGAL INFECTIONS
There are more than 100 different types of fungal infections with different types and causes and treatment methods three of the most common types.

a. CUTANEOUS FUNGAL INFECTIONS
Superficial parasitic diseases (superficial mycoses) can be spread effectively however coordinate contact with tainted individuals, creatures, apparel, brushes and other object. The

fungi tend to grow in moist part of the body where the skin comes together such as between fingers, toes, breast and in genital area. For instance, foot growth fungus (tinea pedis), ring worm, candidiasis.[9]

b. SUB CUTANEOUS FUNGAL INFECTIONS

Affirmed by the exhibit of fungal grains in discharge or tissue biopsy culture is normally fundamental for species recognizable proof particular antibodies can as a rule be identified by precipitation for instance Actinomycetoma[9,10]

c. SYSTEMIC FUNGAL INFECTIONS

fungus in the blood and tissue (immunocompromised populace, generally life threating) powerless populace stomach medical procedure, cancer disease, chemotherapy, bone marrow transplant other immune compromising disease, for example histoplasmosis, Aspergillosis.

1.2. CAUSES OF FUNGAL INFECTIONS

Fungal infections are caused by microscopic organism that can invade the epithelial tissue. The fungal kingdom includes yeast, molds, rusts, and mushrooms. Fungi like animals hetrotropics, That is they obtain nutrients from the environment not from the endogeneous sources (like plants and photosynthesis). [8]

Disease caused by fungi included superficial infections of the skin by dermatophytes in the Microsporum, Trichophyton or Epidermophyton genera.

DERMOPHYTIC INFECTIONS	CAUSATIVE ORGANISM
Tinea corporis (ring worm)	*Microsporum canis, Tricophyton mentagrophytes*
Tinea pedis (athlete foot)	*T.rubrum,T.mentagrophyte,E.floccosum*
Tinea cruis (jock itch)	*T.rubrum,T.mentagrophyte,E.floccosum*
Tinea unguium(nails)	*T.rubrum,T.mentagrophyte,E.floccosum*
Tinea capis(scalp)	*M.canis,T.tonsurans*

Fundamental contaminations are caused by inward breath of spores and causes pneumonia. This pneumonia can't be transmitted from one human being to another. These contaminations can generally solid people. A significant number of the living being are that reason fundamental fungal contaminations which are limited to particular geographic areas because of positive atmospheres for their expansion.

SYSTEMIC INFECTION	CAUSATIVE ORGANISM
Coccidioidomycosis	*Cocidioides immitis*
Histoplasmosis	*Histoplasma capsulatam*
Brazillian Blastomycosis	*Paracoccidioies brasilliensis*
Blastomycosis	*Blastomyces dermatitidis*

1.3. MECHANISM OF ACTION OF ANTI FUNGAL DRUG

Cells of fungus are mind boggling living being that offer numerous biochemical focuses with their eukaryotic cells along these lines specialists that cooperate with contagious targets not found in eukaryotic cells are required the contagious cell divider is a one of a kind organelle that satisfies the criteria for particular poisonous quality. Albeit every life form has an alternate

biochemical synthesis their gross cell divider structure is comparative. There is general three general component of activity for antifungal specialists cell membrane interruption, restraint of cell division and hindrance of cell divider arrangement.

INHIBITION OF CELL WALL FORMATION

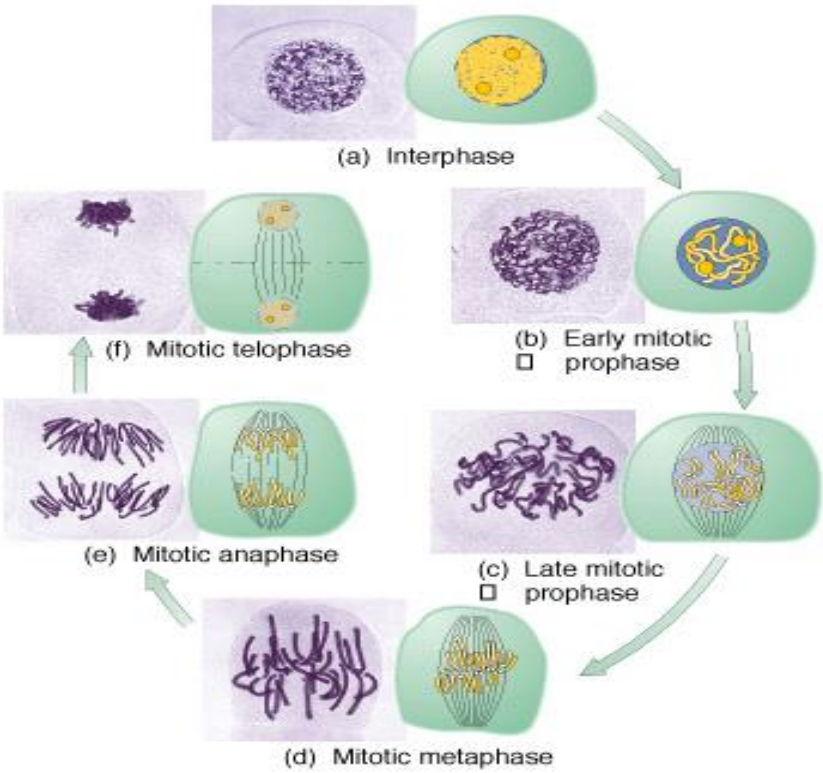
Obstruction with parasitic cell divider biosynthesis has not been as fruitful and successful as penicillin and cephalosporin against bacteria numerous synthetic compounds have been found that meddle with different strides in contagious cell divider synthesis with phenomenal antifungal action in vitro. Shockingly improvement of these specialists into helpful medications has demonstrated extremely troublesome. A significant number of these operators are produced to target B-glucagon synthesis.

I. CELL MEMBRANE DISRUPTION

Antifungal specialists that disturb the cell layer do as such by focusing on ergosterol either by authoritative to the sterol, shaping pores and making the film wind up cracked (as with polyene antifungals), or restraining ergosterol biosynthesis (as observed with azole antifungal agents). Ergosterol is like mammalian cholesterol, along these lines operators restricting ergosterol may have a cytotoxic impact in the host tissue. Ergosterol has two conjugated twofold bonds that are deficient in mammalian sterols.

II. INHIBITION OF CELL DIVISON

Nucleoside antifungal operators influence cell division by focusing on the microtubule impacts in shaping the mitotic axle:



Or by inhibiting DNA transcriptase

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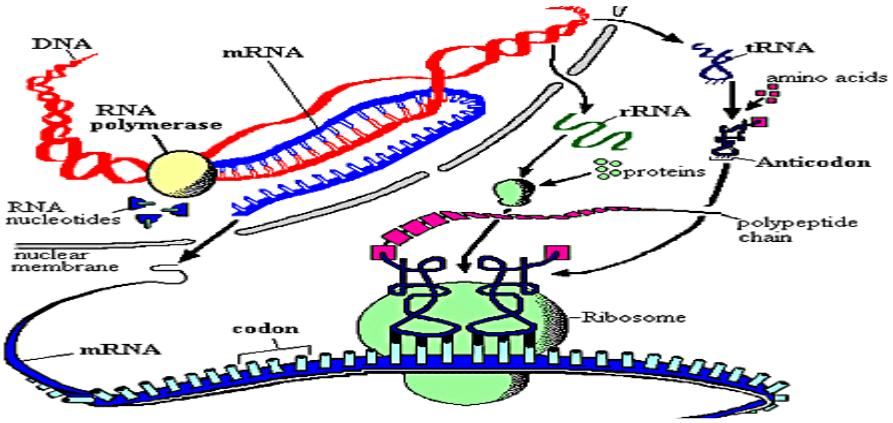

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NEWER APPROACHES FOR ANTI FUNGAL DRUG ACTION

The possibility of parasitic particular targets has been exceedingly alluring, because of the low potential for off-target impacts in the human host. Such has been the situation with the cell divider repressing echinocandins. Late research has investigated the trehalose biosynthesis pathway as a parasitic particular process required for destructiveness. Past investigations have demonstrated that trehalose generation is required for the destructiveness of a few parasitic animal types. For instance, interruption of both Candida albicans TPS1 and TPS2, the qualities encoding trehalose-6-phosphate synthase and trehalose-6-phosphate phosphatase, separately, prompts diminished development at high temperatures, and additionally a hyphal arrangement imperfection. In Aspergillus fumigatus, the homolog to TPS2, the second quality in the trehalose biosynthetic. Pathway is required for virulence, however has no impact on trehalose biosynthesis. Other specialists discovered that trehalose biosynthetic qualities are required for high temperature development and stress protection in both Cryptococcus neoformans and C. Gattii. Moreover, cancellation of the second quality engaged with trehalose biosynthesis, TPS2, prompted the accumulation of trehalose-6-phosphate and cell demise, proposing that blockade of biosynthesis now could give an intense effect to treatment because of middle of the road metabolite toxicity for the pathogen. The recent assurance of a crystal structure for C. albicans Tps2 takes into account further understanding and displaying of compound-catalyst interactions, taking into account the identification of potential inhibitors that specifically tie to this extraordinary focus for antifungal medication development. Additionally, another conserved protein being investigated as an antifungal medication target is the Hsp90 Heat shock protein. This Hsp90 molecular chaperone is associated with protein collapsing because of numerous cellular anxieties. Parasitic Hsp90 is remarkably associated with resistance to antifungals, including both azoles and echinocandins, in Candida albicans, C. glabrata and Aspergillus fumigatus. Hsp90 inhibitors apply intense activity in combination with different antifungals. For instance, the Hsp90 inhibitor geldanamycin has a powerful fungicidal effect against azole-safe A. fumigatus when utilized as a part of combination with caspofungin or the calcineurin inhibitor FK506.

DRUGS USED TO TREAT FUNGAL INFECTIONS

Drug	Indication
Polyene	
Amphotericin B	Life threating fungal infections including cryptococcal, meningitis, aspergillosis, blatomyosis, mucomyosis.

Azoles	
Fluconazole Itraconazole Voriconazole Posaconazole Isavuconazole	Invasive infection due to susceptible candida species; cryptococcus Aspergillosis Histoplasmosis, blastomycosis patients refractory to amphotericin B. Invasive aspergillosis, non-neutropenic candidiasis, serious Scedosporium or Fusarium infections refractory to other agents. Prevention o invasive fungal infection in neutropenic or HSC transplant recipient. Invasive yeast and mold infections.
Echinocandins	
Caspofungin Micafungin Anidulafugin	Candidemia,refractory aspergillosis. Candidiasis Candidiasis (adjunctive therapy with voriconazole for aspergillosis.)
Anti –metabolites	
Flucytosine	Adjunctive therapy in Cryptococcus neoformans meningitis and candida septicemia and endocarditis. (In combination with amphotericin B

1.4. 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. 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.

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 their potential use as transdermal medication conveyance vehicles. Proniosomes are otherwise called "dry niosomes" in light of the fact that the require hydration to shape niosomal vessels before sedate discharge and saturation through the skin. 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. 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.

2. LITERATURE REVIEWS

[1] 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

[2] 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.

[3] 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 ufosome and evaluate its topical bioavailability. Clotrimazole loaded ufosome 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.

[4] 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.

[5] 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.

[6] 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.

[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.

3. AIM AND OBJECTIVES

AIM: To formulate and evaluate isoconazole proniosomal transdermal gel.

Objectives:

- To develop isoconazole proniosomal gel.
- To perform morphological study for transdermal gel
- To carry out stability studies of the developed formulation.

4. MATERIAL AND INSTRUMMENTS

DRUG:

Isoconazole: Gift sample from BCC Chemicals Pvt Ltd, Mumbai, India.

MATERIAL AND CHEMICALS

Table: List of materials and chemicals

Sr .no	Name of materials	Manufacture supplies
1.	Span 60	Merck, India
2.	Cholesterol	Hi-media, India
3.	HPMC K-15	Colorcon, India
4.	Ethanol	
5.	Sodium Hydroxide	Merck, India
6.	Dialysis Membrane	Hi-media, India
7.	Potassium hydrogen di phosphate	Merck, India

5. RESEARCH METHODOLOGY

The framework of this research involved studying the characteristics of the drug. Following are aimed to find:

1. **Morphology shape and size**

FTIR investigation has been done to obtain infrared spectrum the morphological shape and size of the drug.

2. **Stability studies**
   a. At 40ºC ± 75% RH for 1 month
   b. Room temperature for 1 month

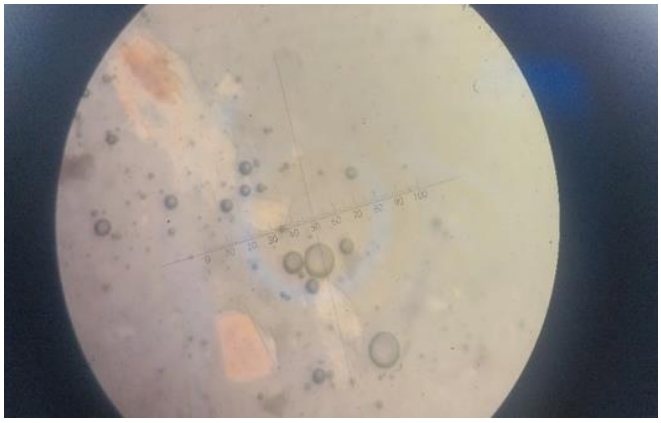
The drug was continuously studied at 40ºC ± 75% RH for 1 month and was also studied at room temperature for same time period.

6. RESULTS AND DISCUSSION

MORPHOLOGY AND SHAPE

(Optical microscopy)

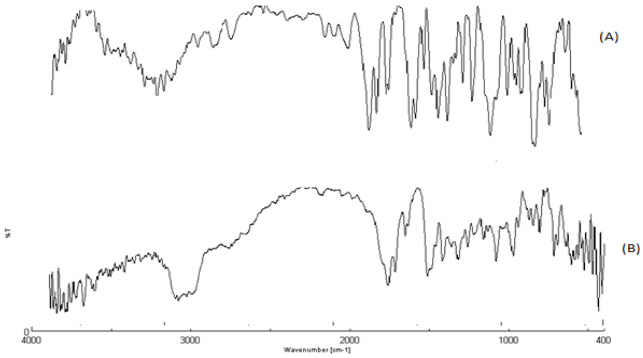
Proniosomal gel (10mg) was taken on the glass slide and evenly spread over the slide.it was observed under the optical microscopy with camera attached to it magnification of 40x and 100x.



Proniosomes observed optical microscopy.

Fourier Transform Infrared Spectroscopy

The FTIR spectrum for isoconazole shows a weak peak at 2983-2930 cm-1 due to the presence of a Aromatic C-H stretch carboxylic acid O-H stretch, at 1620- 1625 cm^{-1} due to the presence of C=O stretch, at 1595 cm^{-1} at Aromatic C=C stretch, at 1437 cm-1 due to presence of CH-CH 3 deformation, at 2891 cm-1 due to the presence of C-H stretch plus O-H deformation, At 1690 cm-1 due to presence of Carboxylic O-H. HPMC show characteristics peak at 3452 cm^{-1} O-H stretching, at 2926 cm-1 –CH stretching alkenes and 1118 cm-1 aliphatic C-O stretching. shifting of the C=O bond from 1620 cm-1 to 1612 cm-1 due to O-H stretching of HPMC notice peak at 2891, 1690,1595, 1437, cm-1 also appear in indomethacin Proniosomes transdermal batch indicating the no chemical interaction occurs.



IR spectra A) isoconazole B) Proniosomes transdermal Gel

6.1. DESIGN OF EXPERIMENT

The experimental design was carried out using the design expert software version 10.0 (state ease). depending on the data that obtained from performing the 9 batches graphical presentation was done. Response surface graph was plotted for both concentration of surfactant and concentration of cholesterol vs the particle size and the percent drug entrapment.

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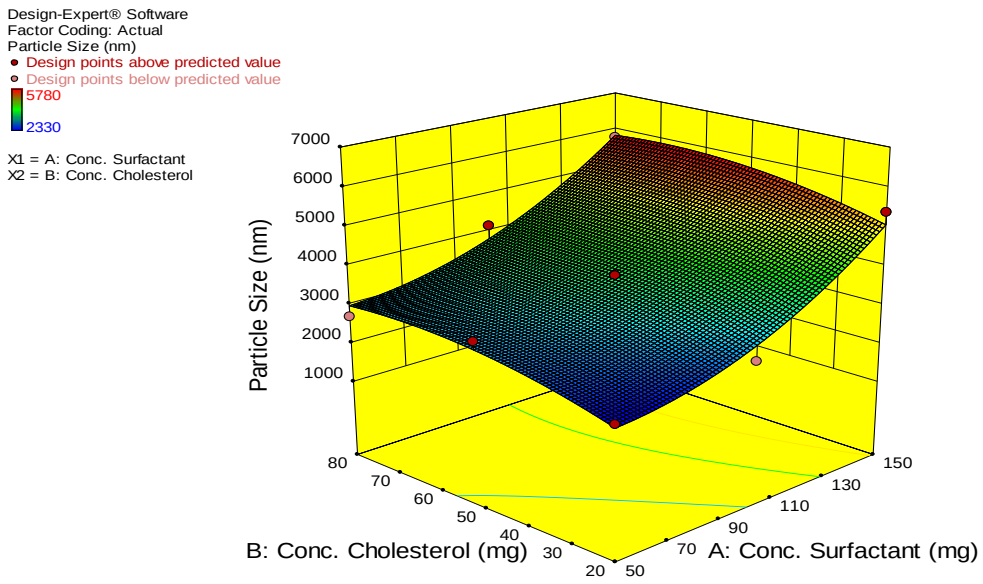
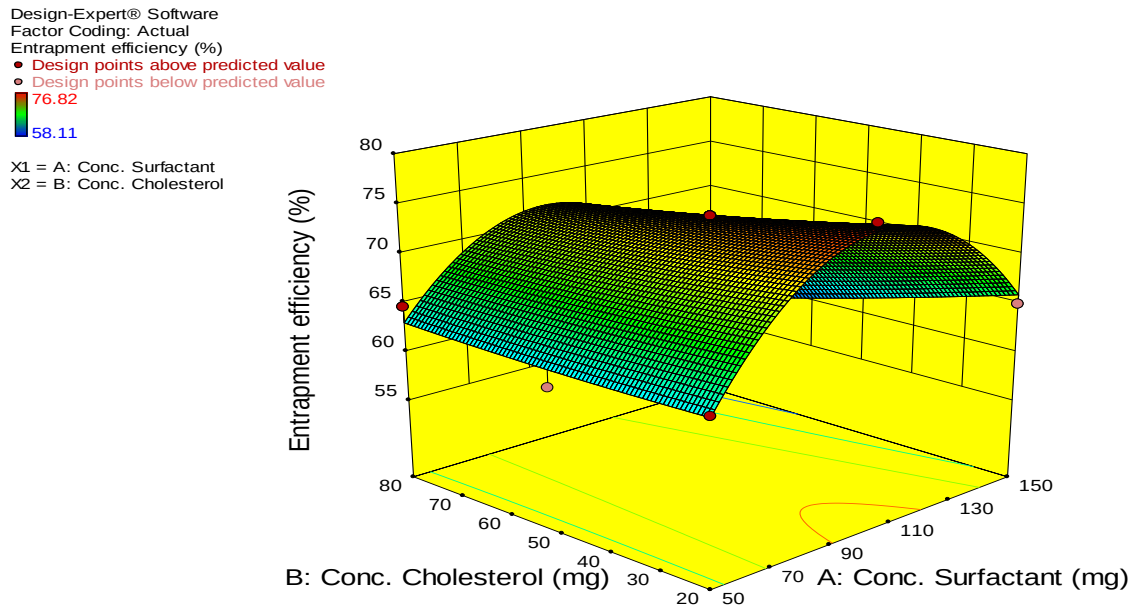


3D response surface graph showing effect of conc. Of surfactant and cholesterol on particle size As the 3D response surface graph shows concentration of surfactant goes on increasing the vesicle size goes on decreasing and as conc. Of the cholesterol increase vesicle size goes on increasing.



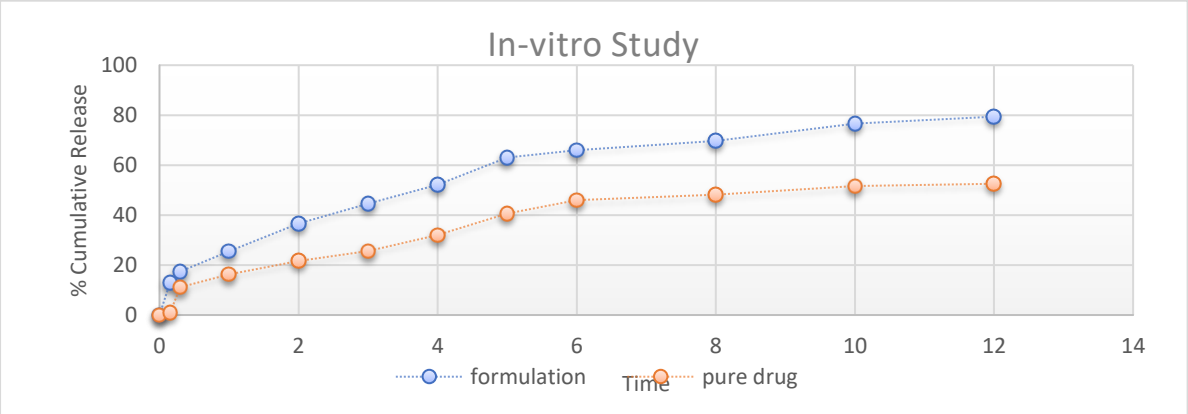
3D response surface graph showing effect of conc. of surfactant and cholesterol on entrapment efficiency.

3D response graph shows that the as concentration of surfactant increases entrapment efficiency of drug goes on increasing and as concentration of cholesterol increase entrapment efficiency goes on decreasing**.**

***IN-VITRO* DRUG DIFFUSION STUDY USING DIALYSIS MEMBRANE.**

To elucidate the mechanism of the active diffusion and diffusion of isoconazole from drug loaded proniosomes for transdermal administration, in vitro drug diffusion study using Franz diffusion cell have been performed. The temperature was controlled at 32ºC ± 1ºC.phospahte buffer (pH 7.4) was used as diffusion medium. Optimized batch showed a steady state diffusion through 12 hours. this slow diffusion rate will maintain the concentration of indomethacin drug up to 12 hours. The batch show the release of 76.39%. It is clear that the gel showed optimum drug release up to 12hrs. The permeation data fitted in zero order drug release indicating controlled release of the indomethacin from the formulations.it is observed that smaller vesicle size of the niosomes derived from proniosmes tend to fuse readily in the skin. Cholesterol content resulted in a more intact and ordered lipid bilayer as a barrier for drug release and helped as a controlled release and also decrease drug leakage.

Time (hrs)	Formulation	Pure Drug
0	0	0
0.15	12.86471	0.8412
0.3	17.38559	11.1641
1	25.42255	16.2206
2	36.58598	21.6198
3	44.52471	25.5973
4	52.08343	32.0628
5	63.07127	40.5772
6	66.01392	46.0163
8	69.69225	48.1044
10	76.57735	51.6402
12	79.39412	52.5389



In-vitro dissolution study of isoconazole.

STABILITY STUDIES

Stability study of optimized batch was carried out at different conditions of temperature and relative humidity i.e., 45ºc and 75% RH and at room temperature as per ICH guidelines. There is no significance change in the drug content at the end of the month.

7. CONCLUSION

This study has performed morphological study to know and understand the shape and size of transdermal gel. FTIR method was used to conduct this research. The obtained results showed a weak peak at 2983-2930 cm-1 due to the presence of an Aromatic C-H stretch carboxylic acid O-H stretch, at 1620- 1625 cm^{-1} due to the presence of C=O stretch, at 1595 cm^{-1} at Aromatic C=C stretch, at 1437 cm-1 due to presence of CH-CH 3 deformation, at 2891 cm-1 due to the presence of C-H stretch plus O-H deformation, At 1690 cm-1 due to presence of Carboxylic O-H. The gel showed optimum drug release up to 12hrs. The permeation data fitted in zero order drug release indicating controlled release of the indomethacin from the formulations.it is observed that smaller vesicle size of the niosomes derived from proniosmes tend to fuse readily in the skin. Cholesterol content resulted in a more intact and ordered lipid bilayer as a barrier for drug release and helped as a controlled release and also decrease drug leakage. Stability study of optimized batch showed no significant change in the drug content at the end of the month. This shows that developed drug is effective and can be manufactured for further experimentation to treat fungal infection.

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