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A RECENT UPDATES IN TOPICAL APPLICATIONS OF ANTIFUNGAL AGENTS: A REFERENCE TO LIPID-BASED FORMULATIONS

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Abstract:
Clinically available antifungals have a restricted range of efficacy, substantial toxicity, and emerging resistance. Because fungi and the humans who host them are both eukaryotic, it has been difficult to identify precise targets for antifungals. Novel antifungals include first-in-class compounds, new structures for a known target, formulation changes to antifungals already on the market, and repurposed medications. The authorized antifungal drugs, and 39; mechanisms of action, pharmacological profiles, and susceptibility to certain fungi were assessed. The field is paying more and more attention to membrane-interacting peptides and aromatherapy. Antifungal antibodies are making progress in clinical studies, making immunotherapy another intriguing therapeutic approach. New antifungal therapeutic targets are also being found, enabling the development of innovative, potentially effective drugs that could solve the resistance problem. Due to their unique structural and functional characteristics, advanced topical carriers get beyond biopharmaceutical issues with traditional drug delivery vehicles, such as poor retention and low bioavailability.
Topical nanocarriers containing anti-fungal pills have improved healing responses with little toxicity, in line with literature evidence. Topical antifungal medications are frequently delivered via nanocarriers such as solid- lipid nanoparticles, microemulsions, liposomes, niosomes, microsponges, nano gel, nanoemulsions, micelles, and so on. This review offers an overview of modern-day tendencies in new topical providers used to enhance the therapeutic efficacy of antifungal medicines.
Keywords: *antifungal, strong-lipid nanoparticles, microemulsions, liposomes, niosomes, microsponge, nanogel, nanoemulsions, micelles, and many others.*

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INTRODUCTION:

For many years, treating fungal infections has been a challenging medical problem. This phenomenon can be linked to the limited therapeutic window, significant toxicity, prolonged length of therapy, and widespread development of resistance to therapeutics. In the tragic COVID-19 epidemic, secondary life-threatening infections in intensive care units served as a reminder of how deadly fungal diseases may be.[1] Life-threatening human fungal infections are most frequently caused by Candida, Cryptococcus, and Aspergillus.[2] The fungus Candida auris is multi-drug resistant.[3] All clinically used antifungals are intrinsically resistant to Lomentosporaprolificans. Treatment-resistant Aspergillus fumigatus makes aspergillosis more challenging to cure; in rare cases, the fatality rate can reach 100% [4]

Millions of lives can be saved worldwide by early diagnosis and treatment of fungal meningitis and chronic pulmonary aspergillosis. Before it's too late, quick action is required to address the silent disaster that is fungal infections. To give the reader a thorough, up-to-date resource that will impact future synthetic efforts, we will highlight the most recent state-of-the-art advances in the antifungal pipeline, both in the clinical and preclinical stages, with a special focus on their chemistry. [5-6]

Fungal infection is one of the major burdens of skin disease worldwide. The informed frequency of fungal contamination is about 40 million people in evolving & undersized countries. Fungi usually attack the skin surface during the initial phase and later invade the deeper layer by desquamation. Candida species is one of the fungi which are the most superficial cutaneous infection. The most prevalent problem concerning skin health is fungus-related skin infections. Topical or systemic antifungal treatment is frequently used to treat fungal infections. Due to their tailored therapy and limited adverse effects, topical fungal therapies are typically favored.[7-9]

Additionally, standard formulations require frequent administration at high doses, which increases the risk of both local and systemic toxicity.[10] To decrease local side effects and improve therapeutic efficacy, innovative drug delivery systems are therefore being considered. The current review focuses on topical nano carrier techniques for the cutaneous application of anti-fungal drugs. One of the topics of topical formulation that has received the most attention in pharmaceutical research is novel drug delivery systems (NDDS). NDDS reduces dose frequency and improves clinical efficacy because of its exceptional capacity to control the release kinetics of encapsulated medications, encapsulate a broad range of pharmaceuticals, and boost disease-specific localization. However, to maintain enough effectiveness of an appropriate topical formulation, it is necessary to comprehend the precise mechanism of antifungal treatments.

A few examples of how various anti-fungal medications work include: Azoles (Ketoconazole, Itraconazole, Fluconazole, and Posaconazole) prevent the production of ergosterol. Lanosterol cannot be converted to ergosterol by anti-fungal drugs like morpholines, and terbinafines. Since squalene epoxidase is the therapeutic target, lipids in nanoparticles such as solid lipid nanoparticles, and liposomes will increase the drug's permeability to the intended tissues.[11] Amphotericin B and nystatin, two polyene antibiotics, interact with ergosterol to generate a complex that modifies the permeability of fungal cell membranes, causing leakage of cellular contents and eventual cell death. The main elements involved in maintaining the strength of the fungal cell wall are glucans. The glucans syntheses enzyme helps preserve the integrity of the fungal cell by adding glucose monomers to preexisting glucan. The recent updates in antifungal agents and their marketed status are depicted in Table No. 1.

Name of Antifungal Agents	Types of Dosage Forms	Mechanism of Action	Name of Company	Status
Amphotericin B	Amyfy Gel (zero.1p.CW/W)	It kills fungi by using destroying the fungal mobile membrane	Intas prescribed drugs LTD	to be had in the marketplace
	Amphonex injection (Lyophilized 50 mg)	Is polyene macrolide that binds to ergosterol of fungal cell membrane and bureaucracy pores that alters membrane balance and permit leakage of cell contents	Bharat Serum and Vaccine LTD	Available in market
Clotrimazole	Clotrimazole creamIP Candid cream	Interferes with the formationof the cell membrane	Glenmark pharmaceuticals LTD	Available in market

	Canesten cream	Interferes with the formationof the cell membrane	Bayer Pharmaceuticals PVT LTD	Available in market
Ketoconazole	Ketocross cream	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	PCD Pharma Franchise	Available in market
	Ketomac shampoo	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	ALKEM Labs	Available in market
Econazole	Oricon cream	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	Green Apple Life Science Ltd.	Available in market
Miconazole	Miconazole cream IP	Inhibit biosynthesis of triglycerides and phospholipids by fungi	Cipla LTD	Available in market
Bifonazole	Bifotosh cream	Azoles inhibit fungal cytochrome P450	SK Pharma	Available in market
Oxiconazole	Oxinaz cream	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	CAMBRO	Available in market
Tioconazole	Trosyd cream	Azoles inhibit fungal cytochrome P450	Weefsel Pharma	Available in market
Sertaconazole	Onabet cream	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	Glenmark	Available in market
Luliconazole	Ludra Soft cream	Azoles inhibit fungal cytochrome P450	Cipla	Available in market
Eberconazole	Ebergen cream	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway	PCD Pharma Franchise	Available in market

		that leads from Lanosterol to ergo sterol		
Sulconazole	Sulconazole nitrate cream 1.0 %	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	JG Pharma	Available in market
Fenticonazole	Fenza cream	Inhibition of cytochrome P450 14a-demethylase. this enzyme sterol biosynthesis pathway leads from Lanosterol to ergo sterol	Glenmark	Available in market
Fluconazole	Flucos Gel	Azoles inhibit fungal cytochrome P450 3-A dependent enzyme 14-alpha demethylase	Onknet Healthcare	Available in market
Efinaconazole	JUBLIA	Inhibition of 14-alpha-demethylase production of ergosterol inhibited the accumulation of toxic intermediate sterols	Valeant	Available in market
Terbinafine	Terbest cream	Terbinafine inhibits the fungal enzyme squalene epoxidase. this leads to accumulation of the sterol squalene, which is toxic to the organism	Systopic Laboratories Pvt Ltd	Available in market
Naftifine	Naftifast cream 2%	Inhibition of ergosterol+ Lanosterol synthesis	Zydus	Available in market
Butenafine	Fintop cream	Inhibition of ergosterol+ Lanosterol synthesis	Glenmark	Available in market
Amorolfine	Tefcros cream	Inhibition of ergosterol biosynthesis	White Eagle Laboratories	Available in market
Ciclopirox 8%	Ciclorite cream	CPX inhibition of m TORC-1 signaling is associated with the activation of AMPK-TSC and AMPK-raptor pathways	Edolf Healthcare private limited	Available in market
Tolnaftate	Tolnaftate 1% Antifungal cream	Squalene epoxidase inhibitors	Taro	Available in market
Tavaborole 5%	Tavaborole 5% Topical solution	Inhibition of fungal protein synthesis by binding to cytoplasmic leucyl-tRNA	Alembic	Available in market

Anti-fungal drug resistance and Biofilm formulation:

A Biofilm represents a structured microbial group attached to a substrate and present within a self-produced complex organic matter.[12] Biofilms constitute distinct protection against external threats.[13–15] Fungal Biofilm formation results from a series of biochemical events comprising cell adhesion to a suitable substrate, proliferation, production of matrix components, maturation, and dispersion. The cell density within the Biofilm matrix and the types of microorganisms are critical factors that influence antifungal resistance. Candida spp. is the most prevalent fungal species associated with Biofilm formation.[16–17] Apart from Candida, other filamentous fungi, including Malassezia, Saccharomyces, Histoplasm, and Trichosporon, are also suggested to develop Biofilm.[18–22] Some of these pathogens are ubiquitous, and it is assumed that Biofilm plays an important role in their survival under adverse conditions.[23–24] The microtiter plate model is frequently used to study fungal Biofilm. Biofilm formation in the case of C. albicans depends on morphogenetic conversions, growth conditions, cell density, and type of interactions with the extracellular matrix. As the Biofilm matures, the entire event is finely tuned and controlled by a complex regulatory network.[25-26] Current reports revealed liposomal formulations of Amphotericin B exhibit excellent anti-fungal performance against resistant strains of C. albicans 27.

Antifungal Agents and their basic features used in the dosage form designing:

Subsequently the nineteen fifty's, antifungal drug finding has identified 3 modules of natural goods (griseofulvin, polyenes, and echinocandins) and 4 modules of artificial compounds (allylamines, azoles, flucytosine, and phenyl morpho-lines) through clinical value against fungal infections. For life-threatening fungal diseases, polyene amphotericin B is still a common choice despite its toxic side effects. The azoles remain the most widely used group of antifungals active against a wide range of mycoses, benefiting from creative chemistry to boost their effectiveness. More recently, the echinocandins show great promise, with caspofungin licensed for clinical use in 2002 and two other molecules close to registration. New advances in molecular genetics afford the promise of revealing new antifungal targets, together with new agents to inhibit those targets specifically.[28] The summarized classification is presented in Figure no. 1

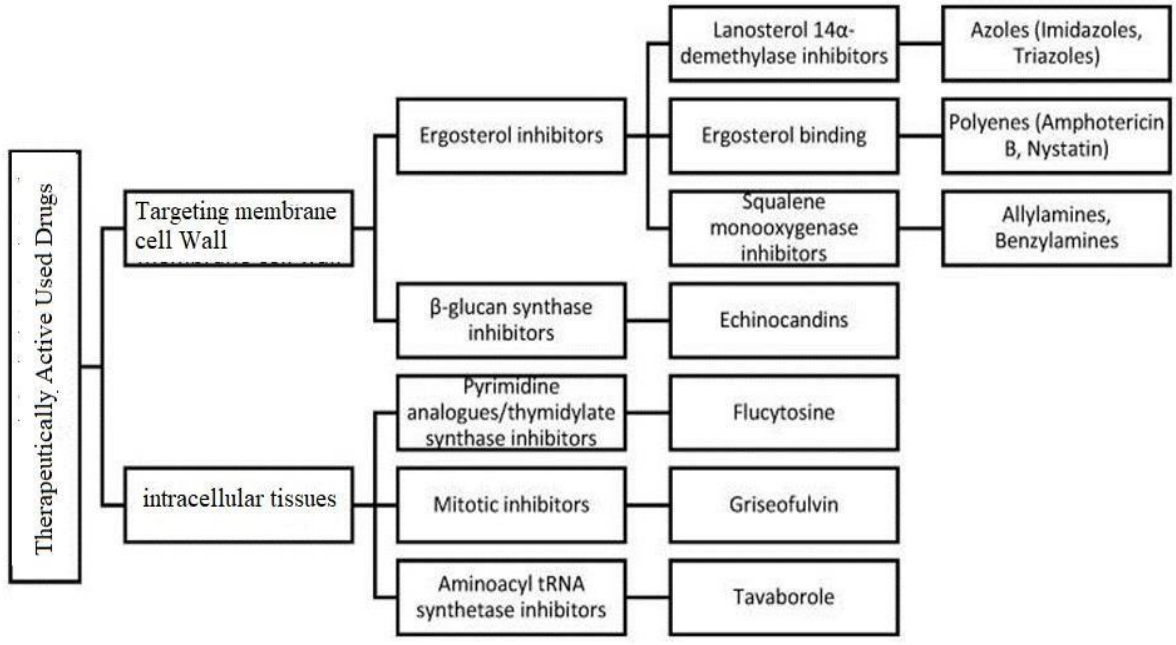

Fig-1: Schematic classification of Antifungal Agents with their basic chemical groups

Allylamines:
Each of the allylamines terbinafine and Naftifine is very effective against an extensive range of dermatophytes, and yeasts causing tinea corporis, tinea cruris, tinea pedis, cutaneous candidiasis, and pityriasis versicolor. Each is properly tolerated, not often causing destructive activities together with local infection or burning at the site of utility. 'Terbinafine' is theorized to act by constraining squalene epoxidase, therefore obstructive the biosynthesis of ergosterol, an important component of mycological cellular skins.[29]

Azoles:
The first topical imidazole antifungal agent, chlormidazole, was developed in 1959. Since that time, the number of agents in this class that are well tolerated has increased. The azoles can be subdivided into the imidazoles and the triazoles; all azoles work employing the same mechanism of action, that is, the inhibition of the cytochrome P450-dependent enzyme 14-a-demethylase, an essential enzyme in ergosterol synthesis. At the minimum inhibitory concentration, these agents are fungistatic, although at 5-10 times the minimum inhibitory concentration they do demonstrate fungicidal activity.[30]

Amorolfine:
Amorolfine is a morpholine derivative type of antifungal, unrelated to polyenes, azoles, or allylamines. At present, Amorolfine is not available in the US. It has activity against dermatophytes, yeasts, and filamentous fungi (molds). In the treatment of cutaneous dermatophyte or Candida species infection, Amorolfine 0.25% cream applied once daily is effective. The advantage of this medication has been as a topical therapy for onychomycosis. Amorolfine inhibits D14 reductase and D7-D8 isomerase, which depletes ergosterol and causes ergosterol to accumulate in the fungal cytoplasmic cell membranes.[31]

Ciclopirox:
Cicloprox has a wide spectrum of antifungal activity. It is applied topically as cream, solution, and powder for the treatment of cutaneous candidiasis and other fungal skin infections, namely dermatophytosis and pityriasis versicolor. Cicloprox is thought to act through significant activity against dermatophytes. The principal chelation of polyvalent metal cations, such as Fe3+ and Al3+. These cations inhibit many enzymes, including cytochromes, thus disrupting cellular activities such as mitochondrial electron transport processes and energy production.[32]

Mechanical methods to enhance drug delivery:
The penetration of antifungal agents can be enhanced by following methods
A. Chemical methods
B. Physical Methods

A. Chemical Methods:
Use of keratolytic, for example, forty percentage urea and ten percentage to forty percentage salicylic acid reasons become softer of the nail plate and organic avulsion of the nail, especially when useful under occlusion for one to two weeks, and will improve the preoccupation of up-to-date antifungals. One percent salicylic acid powder and Whitfield's ointment can also be used as adjuvants to topical therapy of tinea of glabrous skin as the keratolytic effect of salicylic acid can help in reduce the fungal burden. Still, carefulness is to be exercised because of possible skin irritation and salicylism, especially when used in extensive areas. The addition of propylene glycol, hydroxypropyl-β-cyclodextrin or two-n-nony one-one, and three-dioxolane to nail polishes improves infiltration of the antifungals in the nails. Ethylcellulose added to nail lacquers can give a sustained and slow release of the drug.
B. Physical Methods:
Following are the techniques used to enhance the penetration of topical antifungal agents
i) Ultraviolet-curable gel formulations,
ii) Iontophoresis,
iii) Microporation,
iv) Lasers etc.

New antifungal agents and their recent effective dosage forms:

Solid Lipid Nanoparticles (SLN) Based Antifungal Agents:
These are nano-lipid carriers where the active beneficial is discrete inside a lipid essential medium. These are nanoparticle-imprinted media self-possessed of lipids & surfactants. Solid lipid nanoparticles can be prepared using high homogenization or through the preparation of microemulsions.[33] SLN owing to their high lipid content shows increased drug payload, exhibiting slow and controlled drug release properties, particularly for azole drugs. SLNs comprising of Compritol and co-surfactant (PEG 600) prepared by using a hot high-pressure homogenization technique exhibits high encapsulation efficiency of Ketoconazole as high as 70%. However, the type of lipids, surfactants, their concentration, and method of preparation play pivotal roles in determining the efficacy of encapsulated therapeutics. Lipid nanoparticles with high molecular weight fatty alcohols and straight-chain primary alcohols show

poor drug loading capacity and delayed-release behavior due to their highly ordered crystalline structure of lipid matrix, leaving little space for therapeutic molecules. On the other hand, low melting point lipids, triglycerides, partial glycerides, and amphiphilic lipids considered suitable for SLNs, offer increased drug loading, improved skin penetration, and reduced drug leakage of topically applied anti-fungal drugs. Seeing proportional rewards, SLN give the impression to be a potential construction for the up-to-date delivery of anti-fungal chemotherapeutics. Souto and co-workers prepared SLNs and nano structured lipid carriers (NLCs) for the topical delivery of Clotrimazole.[34]

SLNs are w/o emulsion containing solids lipids as oil phase. The compensations of SLNs include a low dangerof toxicity (used lipids are physiologically the same), henceforth biocompatible. The smaller size of lipid particles allows close contact with the stratum corneum, and facilitates dermal penetration of the drug and controlled release of the drug. Their formulation generates a film on the skin and prevents water evaporation. As a result, the skin remains hydrated and barrier function remains intact. The lipid nanoparticles are spherical and hence have excellent lubrication behavior preventing skin irritation and allergy. They have high drug entrapping capacity and the release kinetics is well-modulated. The active constituents are endangered from deprivation finished encapsulation. The commercial sterilization procedure can be employed for a versatile range of preparations. The stability is excellent for the long term with bioavailability remaining high. However, SLNs suffer from a few limitations like limited numbers of drugs soluble and inappropriate lipids.[35]

Freshly lipid carriers based up-to-date gels were designed to overwhelmed potential limitations of lipid nano- carriers like poor preservation at the submission place, low drug shipment, poor storage stability, and the option of drug removal. Recently Shaimaa and co-workers studied the therapeutic potential of Fluconazole-loaded SLNs Cremophor RH 40 and Poloxamer 407 topical gel against Vesicular. The results showed entrapment efficiency between 55.49 to 83.04%. Clinical studies demonstrated a 1.4-fold greater clinical response againstmarketed cream.[36]

Notwithstanding rewards, SLNs have been suffering from a few limitations like low drug pay-load and uneven drug announcement. NLCs are second-generation nano-lipid carriers consisting of both solid and liquid lipids that can hold a wide variety of drugs. In a comparative study between NLC and SLNs on encapsulation performance for Ketoconazole, it is found 62.1 and 70.3 percent encapsulation for SLN and NLC respectively. Additional NLC has positively better-quality the light stability of Ketoconazole compared to SLNs.[37] Additional, the size of SLNs frolicked an significant title role in the action consequence of cutaneous mycosis. In a current study the impact of SLNs size on skin penetration was assessed by Zahra and co-workers, resultindicated that SLNs size in the range of 50–200 nm easily penetrate the cutaneous layer whereas sizes between 200 and 400 nm accumulate in the dermis, thereby recommended as appropriate regimens for treating fungal skin infections.[38] Although nano-lipid preparation has exhibited improved safety and higher therapeutic performance to treat critical fungal disorders. However poor storage stability, particle size, size distribution, poor drug payload, high manufacturing cost, and poor scalability remains a constant challenge for transition into the clinical set-up.

In addition to the drug, the anti-fungal efficacy of lipid Nanocarriers can be increased to a great extent using cationic lipids. Cationic lipids are known to modulate antifungal activity through various mechanisms including disruption of endosomal membranes, form complexes with DNA, and enhanced cell permeability. Recently Debora and co-workers suggested that cationic lipids like di octadecyl dimethylammonium bromide (DODAB) and hexadecyltrimethylammonium bromide (CTAB) show excellent anti-fungal activity against Candida albicans. Nonetheless, cationic lipids induce local toxicity over a therapeutic concentration.[39]

Niosomal-Based Antifungal Agents:

These are a kind of spherical lipids prepared by non-ionic surfactants.[40] They interact with the stratum corneum, resulting in the reduction of transepidermal water loss[41] its skin permeation depends on the types of surfactant, properties of the drug used, and morphological characteristics of Niosomal preparations.[42-43] the therapeutic activity of Ketoconazole was found to be increased in Niosomal preparations. Niosomes of Itraconazole and Miconazole were also found to be effective, proving themselves to be effective carrier systems for antifungal drugs. Fluconazole-loaded niosomes prepared using different surfactants (Span 40, Span 60, and Brij 72) revealed prolonged localized and sustained effects of Fluconazole[44] Another group has attempted to prepare and optimized a Niosomal gel containing Naftifine hydrochloride, in which drug loaded Niosomal preparation was incorporated into a

hydroxymethyl-cellulose gel to improve physical drug stability and drug loading[45] These are a kind of bilayer lipid structure with non-ionic surfactants.[46] They interact with the stratum corneum, resulting in the reduction of transepidermal water loss[47] The degree of skin permeation depends on the interaction between noisome and skin, the nature of the drug, composition, and morphology of noisome[48-49] Niosomes owing to their stable bilayer structure protects the encapsulated therapeutic agent from proteolytic enzymes, surrounding pH and osmotic agents, thereby increasing the product stability. However, noisome exhibits relatively leaky vasculature compared to liposomes. Irrespective of comparable features, niosomes provide several distinct merits over liposomes including higher skin permeation, making them suitable for the treatment of dermal and cutaneous mycosis, higher chemical stability increases product shelf life, and lower costs. Further niosomes due to their unique amphiphilic properties can entrap a wide variety of therapeutics. Further shape, size, fluidity, and surface functionalization of Niosomal preparation can be easily tailored by changing formulation composition and method of preparation. The antifungal activity of Ketoconazole was found to be increased by encapsulating it into niosomes. Niosomes of Itraconazole and Miconazole were also found to be effective in the treatment of fungal infections. Niosomal formulation containing Fluconazole prepared by using different surfactants (Span 40, Span 60, and Brij 72) showed enhanced skin permeation and drug accumulation following topical application.[50]

Similarly, another study demonstrated that Niosomal gel exhibits approx. 6.5 times higher drug localization in the skin when compared with plain carbopol gel indicating better target accumulation of Niosomal gel. Charge inducers such as anionic (diacetyl phosphate and lipoamide acid) or cationic (sterylamine and cetylpyridinium chloride) components are often incorporated in formulation to increase the stability of the vesicles. It acts by inhibiting the aggregation of vesicles due to net repulsive forces.[51] Negatively charged niosomes incorporated in hydroxymethyl cellulose gel show higher physical and chemical stability compared to plain Niosomal formulations.[52] Unique features of niosomes allow for usage through various topical routes like vaginal, mucosal, ocular, etc. Ning and co-workers investigated the antifungal activity of Clotrimazole-loaded Niosomal gel. Results indicated sustained and controlled release patterns with good tolerability on tissue level in rats for suitable local vaginal therapy.[53]

Liposomal-Based Antifungal Agents:

These are bilayer phospholipids spherical vesicles composed of amphiphilic lipids (phospholipids and cholesterol). They can quarter a wide diversity of drugs including both hydrophilic and lipophilic medications. They may trap hydrophilic molecules in their aqueous core and lipophilic drugs in their lipid bilayer.[54-55] The amphiphilic phospholipids and ultra-flexible character of liposomes protect the drug from degradation and increase skin permeability. Due to their ability to alter the bio-distribution profile of entrapped drugs, these are considered suitable for topical drug delivery. They can be either adsorbed on the outermost skin surface or penetrate deeper layers. Drug release profile, liposome morphology, and skin retention play a crucial role in deciding the therapeutic performance of the liposomal formulation. Amphotericin-B has a broad-spectrum antifungal activity but due to its ability to bind mammalian cell cholesterol produces unwanted toxicity. Liposomal Amphotericin B can reduce toxicity, due to its ability to form complex with Amphotericin. Liposomes with dissimilar surface properties and morphology have been examined for topical antifungal medication delivery including conservative, deformable, mucoadhesive liposomes. The liposomal gel of Ketoconazole shows higher drug retention in the skin as compared to the gel and cream formulations.[56] The therapeutic effects of two marketed Econazole formulations i.e. Econazole nitrate cream, and Econazole liposome gel have been investigated on both uninfected and infected reconstructed human epidermis. Toxicological findings suggested that a single application of the cream showed higher acute skin toxicity compared to the liposome gel. It was also observed that liposomal formulation eliminated Candida albicans- induced specific pathological alterations like hyperkeratosis, dyskeratosis, and parakeratosis.[57] Liposomes can be prepared from different techniques using a variety of phospholipids. Deformable or flexible liposomes characterize a new session of phospholipids vesicles designed to progress dermal and cutaneous antifungal drug distribution. Ultra-deformable liposomes prepared with Tween 80 as edge activator showed 1078 nm diameter, PDI of 0.078, and -3 0.2 mV zeta potential displayed 40 times higher accumulation of drugs compared to Am Bi some. In addition to lipid composition, liposome morphology, and surface properties also play a crucial role in determining drug permeability and dermal accumulation. Verma and co-workers reported liposomes with 120 nm size resulted from higher skin permeation compared to larger ones.[58] in an ongoing effort to improve antifungal activity; cationic

liposomes have been found advantageous. AmB-loaded cationic liposomes exhibited a size range of 400–500 nm and zeta potential between 40–60 mV, exhibiting higher antifungal activity compared to plain drugs. However, the clinical application of cationic liposomes is limited due to the toxicity of cationic components. Irrespective of advantages, major complications related to liposomal formulations include drug-drug-carrier compatibility complex, drug expulsion, scale-up procedures, and stability.

Microemulsions-based Antifungal Agents:

These are stable, translucent, and isotropic dispersions of oil in water stabilized by surfactants and co-surfactants for topical and transdermal administration of drugs with a droplet size of 0.1–1.0 µm. These have been reported as very promising delivery systems of anti-fungal agents due to their unique ability to enhance drug solubility. The antifungal variety of numerous azole drugs is negotiated due to their little aqueous solubility. A recent study by Ashara and co-workers determined the solubility of voriconazole in a microemulsions system developed by using Neem oil Acrysol™ K-150 and PEG as oil phase, surfactant, and co-surfactant respectively. Results indicated the solubility of voriconazole in Neem® oil microemulsions was found to be 7.51±0.14 mg/g against 2.7±0.12 mg/g of plain drug characterized by a significant increase in MIC values.[59] They offer the advantages like increasing drug solubility, high thermal stability, high permeability, easy manufacturing, optical clarity, and low cost. They show outstanding biocompatibility for the reason that microemulsions are the suitable distribution system for up-to-date and transdermal organizations. The presence of oils and surfactants in microemulsions formulation facilitates drug permeability across the stratum corneum.[60-63] A microemulsions gel containing Fluconazole seems to be effective for the treatment of invasive fungal infections.[64] Similarly, Radwan and co-workers in their study reported enhanced skin retention of Sertaconazole in 0.5% Carbopol 934 gel. Sertaconazole-loaded microemulsions Carbopol gel showed higher drug retention (1086.1µg/cm2) compared to the marketed formulation "Dermofix® cream" (270.3µg/cm2).[65] Microemulsions due to reduced interfacial tension and low particle size can be easily designed into a gel. Microemulsions topical gel not only improves stability but also enhances their antifungal activity, further gel formulation helps to reduce the local toxicity accounted due to the high content of surfactant in microemulsions. Accordingly, Kumari and Kesavan studied the antifungal effect of chitosan-coated microemulsions containing Clotrimazole. In vitro, anti-fungal study results demonstrated that chitosan-coated microemulsions revealed higher antifungal activity compared to plain microemulsions due to the controlled release behavior of encapsulated drug and intrinsic fungicidal activity of chitosan.[66] Several researchers further confirmed the ability of microemulsions to increase the percutaneous permeability of Fluconazole.[67-68] The same results were obtained with microemulsions formulae ofKetoconazole, Itraconazole, voriconazole, and Econazole. The microemulsions-based hydrogel containing Clotrimazole showed higher skin permeation, retention, and better in vitro antimicrobial activity against C. albicans compared to the reference cream.[69] Patel and co-workers investigated the therapeutic performance of Ketoconazole-loaded microemulsions prepared by using lauryl alcohol, Labrasol, and ethanol as oil phase, surfactant, and co-surfactant respectively. Experimental findings suggested that the developed microemulsions show superior percutaneous absorption of Ketoconazole. Further, it has been found that the skin permeation of Ketoconazole has increased with increasing the quantity of lauryl alcohol and with decreasing the surfactant/co-surfactant ratio in the microemulsions. The optimum formulation was chosen based on their activity against Candida albicans. The results indicated that microemulsions formulation shows a higher zone of inhibition compared to reference Ketoconazole cream. Histopathological analysis of the rat skin revealed no sign of toxicity.[70] Microemulsions formulations need a high concentration of surfactant and co-surfactants combination to cover a wider interface, complete emulsification of the ingredients, and long-term stability. However, the undesirable residues on the substrate may cause local skin toxicity on prolonged use, hence local toxicity must be taken into account, particularly when they are intended to be used for a longer period.

Micelles-Based Antifungal Agents:

Polymeric micelles, or aggregation colloids created in solution by the self-assembly of amphiphilic polymers, represent a novel way to address several problems with drug administration, Yogeshwar N. Kalia et.al. Developed an antifungal formulation using micelles and the ingredients Econazole (ECZ), terbinafine (TBF), and Amorolfine (AMF). For the simultaneous cutaneous delivery of three medications with complimentary modes of action using D-tocopheryl polyethylene glycol succinate (TPGS). Drug loading was ten times lower in the antifungal "tri-therapy" micelle-based formulation (Pevaryl®, 1% ECZ; Lamisil®, 1% TBF; Loceryl®, 0.25%

AMF) than in the "reference" commercial formulations.[71]

Nanogel-Based Antifungal Agents:

It has been proposed to use nanotechnologies to address penetration issues to overcome the drawbacks of these conventional topical treatments. Nishil Mohammed et.al. Formulated and characterized dermal administration of Terbinafine HCL (TBH) nano gels that are biodegradable, pH-responsive, chemically cross-linked, andcomposed of Pluronic F127 co-poly (acrylic acid) to boost its permeability and serve as a novel method for treating skin fungal infections. The rat skin ex-vivo skin retention investigations revealed that nanogel retained drugs more effectively than 1% Lamisil cream (a commercial product) furthermore, research on skin irritancy revealed that nanogel was not irritating. Bhalekar MR et.al., Developed a Miconazole nitrate lipid nanoparticle which was incorporated in the gel for simple topical treatment and their skin penetration was tested ex vivo.[72] In comparison to a conventional gel containing a free drug, gel with nanoparticulate dispersion allowed for better drug localization in the skin while allowing for less drug penetration into the receptor compartment.[72]

CONCLUSIONS:

The concentration attained in the target skin tissue has a significant impact on an antifungal agent's therapeutic effectiveness. The best way to reach therapeutic levels in the tissue is through frequent topical administration, although this is arduous and may have unpleasant side effects. A larger molecule size, however, may occasionally limit their inherent penetrability. As a result, the Novel Drug Delivery System provides new opportunities for the development of ophthalmic/cutaneous formulations of these antifungal drugs. It is possible to repackage and administer these medications more effectively using novel drug delivery systems, which will increase their bioavailability. They can be made more soluble and more likely to become trapped in niosomes, liposomes, and microspheres by using cyclodextrins, polymers, or other appropriate surfactants. The additional possibilities to increase permeability, reduce dosing frequency, and reduce side effects include SLNs, NLCs, microemulsions, and emulsions. This will increase the antifungal therapy's tolerance, affordability, and safety. Although the therapy may initially be expensive due to the expense of production, it may become profitable with less frequent use. The cost will also not be a concern for production companies that use more modern technologies for product development. For topical administration, the qualities of the chosen drug agent and the application site have an impact on the development of a good formulation. Since potency, deliverability, and effective therapeutic concentration at the target site must all be in balance.

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Conflict of Interest:

The authors declare no conflict of interest.

REFERENCES:

1. Du H., Bing J., Hu T.R., Ennis C.L., Nobile C.J., Huang G.H. Candida auris: Epidemiology, biology, antifungal resistance, and virulence. *PLoSPathog*. 2020; 16:e1008921.
2. Chowdhary A., Tarai B., Singh A., Sharma A. Multidrug-Resistant Candida auris Infections in Critically Ill Coronavirus Disease Patients, India, April–July 2020. *Emerg. Infect. Dis.* 2020; 26:2694– 2696.
3. Boral H., Metin B., Dogen A., Seyedmousavi S., Ilkit M. Overview of selected virulence attributes in Aspergillus fumigants, Candida albicans, Cryptococcus neoformans, Trichophytonrubrum, and Exophialadermatitidis. Fungal Genet. Biol. 2018; 111:92–107.
4. Magdum C, Naikwade N, Shah R. Preparation and Evaluation of Fluconazole Topical Microemulsion. Journal of Pharmacy Research, 3:557-561, 2009.
5. Banerjee M, Ghosh A, Basak S. Comparative evaluation of efficacy and safety of topical fluconazole angclotrimazolein the treatment of tineacorporis. Journal of Pakistan Association of Dermatologists, 22(4):342-349, 2012.
6. Gungor S, Erdal M, Aksu B. New formulation strategies in topical antifungal therapy. Journal of Cosmetics, Dermatological Sciences, and Applications, 3:56-65, 2013.
7. Silva H, Luz G, Satake C. Surfactant-based Transdermal System for Fluconazole Skin Delivery. J Nanomed Nanotechnol, 5(5):1- 10, 2014.
8. Naik A, Kalia Y N, Guy R H. Transdermal drug delivery: overcoming the skin's barrier function. Pharm SciTechnolo Today, 3:318-326, 2000.
9. Magdum C, Naikwade N, Shah R. Preparation and Evaluation of Fluconazole Topical Microemulsion. Journal of Pharmacy Research, 3:557-561, 2009.

10. .Percival SL, McCarty SM, Lipsky B. Biofilms and wounds: An overview of the evidence. Adv WoundCare. 2015; 4: 373–381.
11. Kravvas G, Veitch D, Al-Niaimi F. The increasing relevance of biofilms in common dermatological conditions. J Dermatolog Treat. 2018; 29: 202–207.
12. Van Dijck P, Sjollema J, Cammue BPA et al. Methodologies for in vitro and in vivo evaluation of efficacy of antifungal and antibiofilm agents and surface coatings against fungal biofilms. Microb Cell. 2018; 5: 300–326.
13. Flemming HC, Wingender J. The biofilm matrix. Nat Rev Microbiol. 2010; 8: 623–633.
14. Burkhart CN, Burkhart CG, Gupta AK. Dermatophytoma: Recalcitrance to treatment because of existence of fungal biofilm. J Am Acad Dermatol. 2002; 47: 629–631.
15. Kowalski CH, Kerkaert JD, Liu KW et al. Fungal biofilm morphology impacts hypoxia fitness and disease progression. Nat Microbiol. 2019; 4: 2430–2441.
16. Tragiannidis A, Bisping G, Koehler G, Groll AH. 2010. Mini review: *Malassezia* infections in immune compromised patients. Mycoses 53:187–195.
17. Samarei R, Gharebaghi N, Zayer S. 2017. Evaluation of 30 cases of mucormycosis at a university hospital in Iran. Mycoses.
18. Rojas FD, Sosa MDLA, Fernandez MS, Cattana ME, Cordoba SB, Giusiano GE. 2014. Antifungal susceptibility of *Malassezia furfur*, *Malasseziasympodialis*, and *Malasseziaglobosa* to azole drugs and amphotericin B evaluated using a broth microdilution method. Med Mycol 52:641–646.
19. Velegraki A, Alexopoulos EC, Kritikou S, Gaitanis G. 2004. Use of fatty acid RPMI 1640 media for testing susceptibilities of eight *Malassezia* species to the new triazole posaconazole and to six established antifungal agents by a modified NCCLS M27-A2 microdilution method and Etest. J ClinMicrobiol 42:3589–3593.
20. Miranda KC, de Araujo CR, Costa CR, Passos XS, de Fatima LisboaFernandes O, do Rosario Rodrigues Silva M. 2007. Antifungal activities of azole agents against the *Malassezia* species. Int J Antimicrob Agents 29:281–284.
21. Bellenberg S., Huynh D., Poetsch A., Sand W., Vera M. Proteomics reveal enhanced oxidative stress responses and metabolic adaptation in *Acidithiobacillusferrooxidans* biofilm cells on pyrite. Front. Microbiol. 2019; 10:592.
22. Aguilera A., Souza-Egipsy V., Martín-Uriz P.S., Amils R. Extracellular matrix assembly in extreme acidic eukaryotic biofilms and their possible implications in heavy metal adsorption. Aquat. Toxicol. 2008; 88:257–266.
23. Nobile CJ, Johnson AD. *Candida albicans* biofilms and human disease. Annu Rev Microbiol. 2015; 69:71–92.
24. Fox EP, Nobile CJ. A sticky situation: untangling the transcriptional network controlling biofilm development in Candida albicans. Transcription. 2012; 3:315–322.
25. Adler-Moore JP, Proffitt RT. Development, characterization, efficacy and mode of action of AmBisome, a unilamellar liposomal formulation of amphotericin B. J Liposome Res 1993; 3: 429–50.
26. Odds FC. Antifungal agents: their diversity and increasing sophistication. Mycologist. 2003 May 1;17(2):51-55.
27. Jones T. Treatment of dermatomycoses with topically applied allylamines: naftifine and terbinafine. J Dermatol Treat 1990; 1:29-32
28. Ernest JM. Topical antifungal agents. Obstet Gynecol Clin North Am 1992; 19:587-607.
29. Katz AS. Topical antifungal agents. Curr ProblDermatol2000; 12:226-229.
30. Bohn M, Kraemer K. The dermatopharmacologic profile of ciclopirox 8% nail lacquer. J Am Podiat Med Assn 2000; 90:491-494.
31. E.B. Souto, S.A. Wissing, C.M. Barbosa, R.H. Muller, Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery, Int. J. Pharm. 278 (1) (2004) 71–77.
32. S. El-Housiny, M.A. Shams Eldeen, Y.A. El-Attar, H.A. Salem, D. Attia, E.R. Bendas, M.A. El- Nabarawi, Fluconazole-loaded solid lipid nanoparticles topical gel for treatment of pityriasisvesicolor: formulation and clinical study, Drug Deliv. 25 (1) (2018 Jan 1) 78–90.
33. E.B. Souto, R.H. Müller, The use of SLN® and NLC® as topical particulate carriers for imidazole antifungal agents, Die Pharmazie-An Int J Pharmaceutical Sci 61 (5) (2006 May 1) 431–437.
34. Z. Karami, M. Hamidi, Cubosomes: remarkable drug delivery potential, Drug Discov. Today 21 (5) (2016 May 1) 789–801.
35. D.B. Vieira, A.M. Carmona-Ribeiro, Cationic lipids and surfactants as antifungal agents: mode of action, J. Antimicrob. Chemother. 58 (4) (2006 Aug 2) 760–767.
36. D.I.J. Morrow, P.A. McCarron, A.D. Woolfson, R.F. Donnely, Innovative strategies for enhancing topical and transdermal drug delivery, Open Drug Deliv. J. 1 (2007) 36–59.
37. H.E. Junginger, H.E. Hofland, J.A. Bouwstra,

Liposomes and niosomes interactions with human skin, Cosmet. Toilet. 106 (1991) 45–50.
38. F. Fernandez-Campos, B.C. Naveros, O.L. Serrano, Evaluation of novel nystatinnanoemulsion for skin candidosis infections, Mycoses 56 (1) (2013) 70–81.
39. M.J. Choi, H.I. Maibach, Liposomes and niosomes as drug delivery systems, Skin Pharmacol. Physiol.18 (No. 5) (2005) 209–219.
40. M. Gupta, B. Vaidya, N. Mishra, S.P. Vyas, Effect of surfactants on the characteristics of fluconazole niosomes for enhanced cutaneous delivery, Artif. Cells Blood Substit. Immobil. Biotechno. 36 (No. 6) (2011) 376–834.
41. H.S. Barakat, I.A. Darwish, L.K. El-Khordagui, N.M. Khalafallah, Development of naftifine hydrochloride alcohol-free niosomes gel, Drug Dev. Ind. Pharm. 35 (No. 5) (2009) 631–637.
42. D.I.J. Morrow, P.A. McCarron, A.D. Woolfson, R.F. Donnely, Innovative strategies for enhancing topical and transdermal drug delivery, Open Drug Deliv. J. 1 (2007) 36–59.
43. M. Gupta, B. Vaidya, N. Mishra, S.P. Vyas, Effect of surfactants on the characteristics of fluconazole niosomes for enhanced cutaneous delivery, Artif, Cells Blood Substit. Immobil. Biotechno. 36 (No. 6) (2011) 376–834.
44. H.S. Barakat, I.A. Darwish, L.K. El-Khordagui, N.M. Khalafallah, Development of naftifine hydrochloride alcohol-free niosome gel, Drug Dev. Ind. Pharm. 35 (5) (2009 May 1) 631–637.
45. H.S. Barakat, I.A. Darwish, L.K. El-Khordagui, N.M. Khalafallah, Development of naftifine hydrochloride alcohol-free niosomes gel, Drug Dev. Ind. Pharm. 35 (No. 5) (2009) 631–637.
46. D. Liu, P. Ning, R. Li, Establishing pairwise keys in distributed sensor networks, ACM Trans. Inf. Syst. Secur. 8 (1) (2005 Feb 1) 41–77.
47. M. Schafer-Korting, H.C. Korting, E. Ponce-Poschl, Liposomal tretinoin for uncomplicated acne vulgaris, Clin. Invest. 72 (12) (1994 Dec) 1086–1091.
48. M. Brisaert, M. Gabriel's, V. Matthijs, et al., Liposomes with tretinoin: a physical andchemical evaluation, J. Pharmaceut. Biomed. Anal. 26 (5-6) (2001 Dec) 909–917.
49. P.R. Patel, H.H. Patel, H.A. Baria, Formulation and evaluation of carbopol gel containing Liposomes of ketoconazole, Int J Drug Deliv Techno 1 (2009) 42–45.
50. M. Schaller, H. Preidel, E. Januschke, H.C. Korting, Light and electron microscopic findings in a model of human cutaneous candidosis based on reconstructed human epidermis following the topical application of different econazole formulations, Drug Target. 6 (No. 5) (1999) 361–372.
51. D.D. Verma, S. Verma, G. Blume, A. Fahr, Particle size of liposomes influences dermal delivery of substances into skin, International J Pharmaceutics 258 (1-2) (2003 Jun 4) 141–151.
52. K.C. Ashara, J.S. Paun, M.M. Soniwala, J.R. Chavda, Microemulgel of voriconazole: an unfathomable protection to counter fungal contagiousness, Folia Med. 59 (4) (2017 Dec 20) 461–471.
53. H.R. Neubert, Potentials of new nanocarriers for dermal and transdermal drug delivery, European J Pharmacy Biopharmacy 77 (No. 1) (2011) 1–2.
54. A. Kogan, N. Garti, Microemulsions as transdermal drug delivery vehicles, Adv. Colloid Interface Sci.123–126 (2006) 369–385.
55. M.R. Patel, R.B. Patel, J.R. Parikh, Effect of formulation components on the in-vitro permeation of microemulsion drug delivery system of fluconazole, AAPS PharmSciTech 10 (3) (2009) 917–923.
56. M. Kreilgaard, Influence of microemulsions on cutaneous drug delivery, Adv. Drug Deliv. Rev. 54 (Suppl 1) (2002) S77-98.
57. H.M. El Laithy, K.M. El- Shaboury, The development of cutinalipogels and gel microemulsion for topical administration of fluconazole, AAPS PharmSciTech 3(2002) E35.
58. S.A. Radwan, A.N. ElMeshad, R.A. Shoukri, Microemulsion loaded hydrogel as a promising vehicle for dermal delivery of the antifungal sertaconazole: design, optimization and ex vivo evaluation, Drug Dev. Ind. Pharm. 43 (8) (2017Aug3) 1351–1365.
59. B. Kumari, K. Kesavan, Effect of chitosan coating on microemulsion for effective dermal clotrimazole delivery, Pharmaceut. Dev. Technol. 22 (4) (2017 May 19) 617–626.
60. C. Salerno, A.M. Carlucci, C. Bregni, Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms, AAPS PharmSciTech 11 (2010) 986–993.
61. C. Salerno, A.M. Carlucci, C. Bregni, Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms, AAPS PharmSciTech 11 (2010) 986–993.
62. M.R. Patel, B.R. Patel, R.J. Parikh, K.K. Bhatt, B.A. Solanki, Investigating the effectof vehicle on in- vitro skin permeation of ketoconazole applied in O/W microemulsions, Acta Pharm Sci 52 (2010) 65– 87.
63. M.R. Patel, R.B. Patel, J.R. Parikh, A.B. Solanki, B.G. Patel, Investigating effect of microemulsion com- ponents: In vitro permeation of ketoconazole, Pharmaceut. Dev. Technol. 16 (No. 3) (2011) 250– 258.

64. E.A. Lee, P. Balakrishnan, C.K. Song, J.H. Choi, G.Y. Noh, G.C. Park, et al., Microemulsion-based hydrogel formulation of itraconazole for topical delivery, J Pharm Investig 40 (2010) 305–311.
65. A. Chudasama, V. Patel, M. Nivsarkar, K. Vasu, C. Shishoo, Investigation of microemulsion system for transdermal delivery of itraconazole, "J. Adv. Pharm.Technol. Research"" (JAPTR)" 2 (2011) 30– 38.
66. Shahid M, Hussain A, Khan AA, Ramzan M, Alaofi AL, Alanazi AM, Alanazi MM, Rauf MA. Ketoconazole-Loaded Cationic Nanoemulsion: *In Vitro-Ex Vivo-In Vivo* Evaluations to Control Cutaneous Fungal Infections. ACS Omega. 2022 May 30;7(23):20267-20279.
67. G.N. El- Hadidy, H.K. Ibrahim, M.I. Mohamed, M.F. El- Milligi, Microemulsions as vehicles for topical administration of voriconazole: formulation and in vitro evaluation, Drug Dev. Ind. Pharm. 38 (2012) 64–72.
68. Gou S, Monod M, Salomon D, Kalia YN. Simultaneous Delivery of Econazole, Terbinafine and Amorolfine with Improved Cutaneous Bioavailability: A Novel Micelle-Based Antifungal "Tri- Therapy". Pharmaceutics. 2022 Jan 24;14(2):271.
69. Bachhav YG, Mondon K, Kalia YN, Gurny R, Möller M. Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. Journal of controlled release. 2011 Jul 30;153(2):126-32.
70. Si Gou, Michel Monod, Denis Salomon, Yogeshvar N. Kalia. Simultaneous Delivery of Econazole, Terbinafine and Amorolfine with Improved Cutaneous Bioavailability: A Novel Micelle-Based Antifungal "Tri-Therapy".Pharmaceutics. 2022 Feb; 14(2): 271.
71. Bhalekar MR, Pokharkar V, Madgulkar A, Patil N, Patil N. Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS Pharm SciTech. 2009 Mar; 10:289- 96.
72. Hassan SU, Khalid I, Hussain L, Barkat K, Khan IU. Development and Evaluation of pH-Responsive Pluronic F 127 Co-Poly- (Acrylic Acid) Biodegradable Nanogels for Topical Delivery of Terbinafine HCL. Dose-Response. 2022 Apr 23; 20(2):15593258221095977.