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Review Article

A Review On Beyond Conventional: Itraconazole Niosomal Gel As A Novel Approach For Candida Albicans Management

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ABSTRACT

Candida albicans, a common pathogen responsible for mucocutaneous infections, has developed resistance to conventional antifungal agents. The current need for novel treatment strategies has been led to the development of nanotechnology-based drug delivery systems such as niosomes. Itraconazole, a triazole antifungal drug, is lipophilic and has limited aqueous solubility and bioavailability, but its encapsulation into niosomes may enhance its therapeutic efficacy. This literature review aims to present an overview of the current scenario on research on itraconazole-loaded niosomes and their probable potential as a treatment for Candida albicans infections. It discusses the preparation methods, characterization techniques, and in vitro and in vivo studies conducted with itraconazole-loaded niosomes. Additionally, the review highlights the advantages and limitations of niosomes as a drug delivery system and suggests areas for future research. Overall, itraconazole niosomal gel could be a promising alternative for the management of Candida albicans infections, pending further clinical trials to establish its safety and efficacy in humans.

INTRODUCTION

The delivery of medication molecules to their intended locations in biological systems has developed into a highly specialized and advanced field of pharmaceutical research. The role of a revolutionary drug delivery system extends beyond the convenience and ease of administration of drug packages; by delivering drug molecules to

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the target site in the most convenient way, it is also necessary to improve therapeutic efficacy and safety. These innovative carriers offer long-term, sustained medication release in the targeted tissue, improving therapeutic efficacy and reducing adverse effects [1]. The most prevalent places for superficial and moist Candida infections on the skin are these locations [2]. Any part of the body, including mucosal membranes, cuticles, vaginal regions, and moist skin folds, might experience its development [3]. Global concerns surround the health of women's reproductive systems, and one common type of acute fungal infection that causes inflammation of the vulva and vagina is called candidal vulvovaginitis (CV) [4]. Accompanied by several species of Candida (C. albicans, C. glabrata, C. tropicalis, and C. krusei) and, more recently, by the appearance of disease spectra that form biofilms attached to epithelium, it has gained the undeserved reputation of being a difficult drug target for scientists and clinicians [5]. Itraconazole belongs to the imidazole class of synthetic antifungal agents, which function by inhibiting the growth of infection-causing fungus. To treat fungal infections, it is utilized. Triazole medication targets the particular fungal production of lipids in membranes. Itraconazole selectively binds to fungal membranes, impairing their ability to function. 5-fluorocytosine targets DNA replication unique to fungi [6].

DISCUSSION

1. Niosomes –

When cholesterol and non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class are mixed together and then hydrated in aqueous conditions, microscopic lamellar structures known as niosomes or non-ionic surfactant vesicles are created. The same basic procedure is used for preparation: the lipid phase's aqueous phase hydrates the surfactant (which can be either pure or a combination of surfactant and cholesterol) [7]. When applied to topical drug delivery systems, niosomes improve penetration, function as a local drug storage facility for prolonged release, make poorly soluble pharmaceuticals more soluble, and operate as a rate-limiting membrane barrier for controlled administration systems. Numerous niosome–skin interaction mechanisms, including diffusion through skin, contact with skin lipids, and modification of stratum corneum structure to increase skin penetration, have been proposed in the literature for niosomes [8]. The surfactants act as an essential component of niosomes structure which act as permeation enhancers and direct fusion of vesicles with stratum corneum [9]. Niosomes are a better method than liposomes since they are comparatively more stable and cost-effective. Consequently, it is anticipated that using niosomes will enhance fusidic acid's skin penetration. Many nanosystems, such as nanoemulsions, solid lipid nanoparticles, liposomes, ethosomes, niosomes, polymeric nanoparticles, dendrimers, micellar systems, and carbon-based nanostructures, have previously been investigated for the treatment of wounds and related illnesses [10]. Because of their sturdy bilayer structure, niosomes increase the stability of the product by shielding the therapeutic ingredient inside from proteolytic enzymes, external pH changes, and osmotic agents. In contrast to liposomes, noisome has comparatively leaky vasculature. Despite their similar characteristics, niosomes have a few key advantages over liposomes. These include greater skin penetration, which makes them appropriate for the treatment of cutaneous and dermal mycosis, increased chemical stability, longer product shelf life, and reduced costs. Furthermore, a wide range of medicines can be entrapped by niosomes because of their special amphiphilic features. Niosomal preparation's additional shape, size, fluidity, and surface functionalization can be readily adjusted by modifying the formulation's composition and preparation technique. It was discovered that encasing ketoconazole in niosomes enhanced its antifungal effectiveness [11].

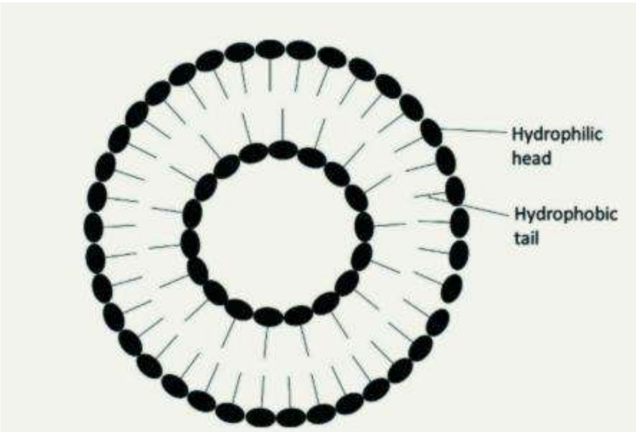

Fig 1. Structure of a Niosome

Formulation Components of Niosomes -

a. Non-ionic Surfactant

A non-ionic surface-active agent serves as the fundamental ingredient in the niosome preparation process. Amphiphilic in nature, non-ionic surface-active molecules have a non-polar tail and a polar head [12]. Compared to anionic, cationic, and amphoteric surfactants, these surfactants are less harmful, more stable, and compatible because they are charge-free. Less haemolysis and surface irritation are brought on by these surface-active compounds on cellular surfaces. These can be employed as emulsifiers, wetting agents, and to increase permeability and solubility. The ability of non-ionic surfactants to inhibit p-glycoprotein can improve absorption and targeting, which is a crucial characteristic [13]. Another significant component influencing the entrapment efficiency may be the phase transition temperature. As an illustration, span 60 shows a high entrapment efficiency, which could be related to a high transition temperature [12].

b. Cholesterol

An essential ingredient in the creation of niosomes is cholesterol. Although cholesterol per se is not necessary for the formation of niosomes, its presence influences numerous noisome characteristics. It may have an impact on the membrane's permeability and stiffness, entrapment effectiveness, stability, rehydration ease for freeze-dried niosomes, duration of storage, and toxicity. When cholesterol is combined with low HLB surfactants, the vesicle's stability can be increased. If the HLB value is more than 6, bilayer vesicles can be formed. When cholesterol is added, the preparation becomes more viscous and therefore harder [12].

c. Charge Inducer Molecule

The formulation of niosomes involves the use of certain chemicals that induce charges. By adding a charge to the surface and stabilizing the niosomes by electrostatic repulsion, these chemicals aid in delaying coalescence. Dicetylphosphate (negatively charged), phosphotidic acid (negatively charged), stearyamine (positively charged), and other compounds are a few instances of molecules that induce charge [12].

d. Hydration Medium

In addition to the components listed above, the hydration medium is another crucial element needed for the niosome preparation process. Phosphate buffer is typically employed as a hydration medium. However, the solubility of the medicine contained determines the pH of the buffer [14]. Zidovudine niosomes (stable vesicles) were generated using the film hydration process in phosphate buffer saline at pH 7.4. Drug leakage increased along with the hydration medium volume, but entrapment efficiency increased when the hydration period was extended from 20 to 45 minutes [15].

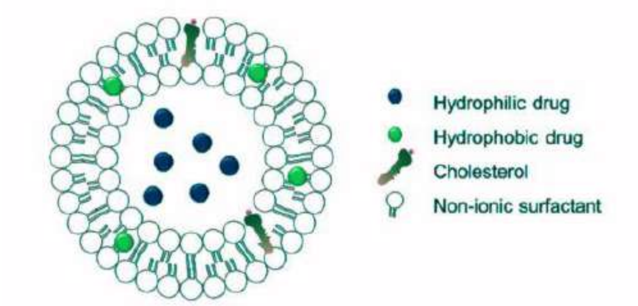

Fig 2. A Schematic Diagram of Niosomes showing a Non-ionic Surfactant-based Bilayer Vesicle. Cholesterol and Ionic Amphiphiles could be incorporated into the bilayers for additional Stability.

METHODS OF PREPARATION –

Niosome preparation starts with the hydration of a lipid mixture and surfactant at high temperatures. Optional niosome size reduction is then performed to produce a colloidal suspension [16]. Niosome preparation can be done using a number of well-researched conventional techniques. Among the techniques are sonication, microfluidization, ether injection, and thin-film hydration [17]. Then, using centrifugation, gel filtration, or dialysis, the unentrapped drug is removed from the entrapped drug [18].

a. Ether Injection Method

The dissolution of surfactant in diethyl ether is the initial stage in the niosome manufacturing process by ether injection. After that, the solution is injected using a 14-gauge needle into a drug aqueous solution that is kept at 60°C. Ether vaporization causes singlelayer vesicles to develop, which have sizes ranging from 50 to 1000 nm [19].

b. Thin-film Hydration Technique

The hand-shaking approach, sometimes referred to as the thin-film hydration technique, involves dissolving cholesterol and surfactant in a volatile organic solvent before moving the mixture to a rotary evaporator. A thin layer of the solid mixture is left on the flask wall following evaporation. The target medication is then hydrated into the dry layer using an aqueous phase. This procedure can be completed with mild stirring at room temperature [19].

c. Sonication

Another method for making niosomes is to sonicate a solution containing the medication, cholesterol, and surfactant for three minutes at 60°C. The vesicles created with this technique are often uniformly tiny in size [19].

d. microfluidization

Another repeatable method for achieving this size homogeneity is microfluidization. In operation, two fluidized streams pass through a precisely defined microchannel at a very high speed while interacting with one another [19].

e. Multiple Membrane Extrusion Method

Since then, many techniques for niosome preparation have been established. Using the multiple membrane extrusion approach, a thin film is created by evaporating a mixture of surfactant, cholesterol, and dicetyl phosphate in chloroform. After hydrating the film with an aqueous drug solution, the suspension is extruded through a succession of polycarbonate membranes that can accommodate up to eight passageways [19].

f. Reverse-phase Evaporation Technique

In addition to ether and chloroform, the reverse-phase evaporation method uses a combination that includes cholesterol and surfactant in a 1:1 ratio. The combination is mixed with an aqueous phase containing the target medication, and then it is sonicated at a temperature of 4-5°C. After a little amount of phosphate-buffered saline is added to the mixture, sonication is carried out once again. The residual suspension is diluted with phosphate-buffered saline after the organic solvent is extracted at 40°C under light pressure. The mixture is heated to 60°C for 10 minutes to produce the final product, niosomes [19].

g. bubble Method

The "bubble" approach can be used to generate niosomes without the use of organic solvents. A round-bottomed flask with three necks submerged in water makes up a "bubbling unit." The first and second necks of the flask are filled with a thermometer and a water-cooled reflux condenser, respectively, while the third neck is used to supply nitrogen. Using a "bubbling unit," cholesterol and surfactant combined at 70°C in a buffer are homogenized and "bubbled" at that temperature [20].

h. Emulsion Method

Another way for making niosomes is the emulsion approach, which makes use of an oil-in-water emulsion made from an organic solution of cholesterol, surfactant, and medication in an aqueous solution. The finished product is obtained by evaporating the organic solvent. In contrast, the lipid injection method involves melting and injecting a mixture of lipids and surfactant into a heated aqueous phase that contains the medication [19].

Problems faced during Formulation

- Aggregation, fusion, and leakage are common issues throughout the niosome manufacturing process. These issues are influenced by the physiochemical characteristics of vesicles, such as their size, charge, lamellarity, elasticity, and thermodynamic phase. The afore mentioned restrictions may be circumvented by preparing proniosomes, a dry form of niosomes that hydrate instantly before usage to produce an aqueous niosome dispersion [20].
- The charge and rigidity of the niosome's bilayer structure are indirectly influenced by the interactions that encapsulated medicines often have with the surfactant's head group. In general, hydrophobic medications increase the stability of niosomes, whereas hydrophobic medications decrease it. It's interesting to note that amphiphilic medications don't visibly alter the bilayer structure of niosomes [21].
- The creation of niosomes' size and shape as well as the assembly of surfactants into vesicles are both influenced by the temperature of hydration. The temperature selected should ideally be higher than the gel-to-liquid phase transition temperature [22].
- Niosome size grows in direct proportion to the rise in surfactant hydrophilic–lipophilic balance (HLB). It is deemed that the niosome vesicle formation is relatively steady and optimal if the HLB value is between 4 and 8 [23].
- The surfactant employed in the niosome production process must have a hydrophilic head and a hydrophobic tail. For the preparation of niosomes, surfactants having hydrophobic tails and alkyl (chain length from C12 to C18), perfluoroalkyl, or steroidal groups are often appropriate [24].

2. Niosomal Gel –

It is possible to load drugs into niosomal vesicles, which can then be combined with the right gel base to create niosomal gel. Novel gel compositions may offer the following benefits: delivery of drugs at a certain location, staying away from first-pass metabolism removal of gastrointestinal discomfort brought on by specific medications, reduced frequency of dosage and maintenance of a controlled and prolonged drug level Self-administration and direct distribution to the intended site of action avoid drug-related side effects and hasten the end of the drug's action. Comparing niosomal gel to normal carbopol gel, another study showed that the former shows approximately 6.5 times higher drug localization in the skin, suggesting improved niosomal gel target accumulation. To improve the stability of the vesicles, charge inducers like cationic (cetyl pyridinium chloride and sterylamine) or anionic (diacetyl phosphate and lipoamine acid) components are frequently added to the formulation. It functions by preventing vesicles from aggregating because of net repulsive forces [26]. Niosomes' special properties enable application via a variety of topical routes, including ophthalmic, mucosal, and vaginal. Ning and colleagues looked at the clotrimazole-loaded niosomal gel's antifungal properties. The findings showed a regulated and prolonged release pattern in rats that was well tolerated at the tissue level for appropriate local vaginal treatment [27]. In comparison to standard niosomal formulations, negatively charged niosomes integrated into hydroxyethyl cellulose gel exhibit superior physical and chemical stability [28].

The following is the mechanism of niosomal gel absorption:

Lipophilic drugs penetrate the stratum corneum by way of niosomes, which diffuse from the stratum corneum layer of skin overall. Niosomes interact with the stratum corneum through aggregation, fusion, and adhesion to the cell surface, resulting in a high thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface. The structure of the stratum corneum may be altered by niosomes, which would result in a looser and more permeable intercellular lipid barrier [29].

3. Itraconazole –

Itraconazole is an orally active triazole antifungal agent, that demonstrates broad spectrum activity against a number of fungal species which includes dermatophytes, Malassezia furfur, Candida species, and Histoplasmacapsulatum [30]. It is also recommended for systemic infections in cases where other antifungal medications are inappropriate or ineffective, such as aspergillosis, candidiasis, and cryptococcosis. Itraconazole acts by preventing the synthesis of ergosterol, which is a crucial part of the fungal cell membrane [31]. Because of its somewhat acidic pKa of 3.7, this salt can only be ionized at extremely low pH levels. Its aqueous solubility is also low, being slightly greater than 4 ng/ml at pH 1 and nearly equal to 1 ng/ml at pH 7. Accordingly, it falls into class II of the Biopharmaceutical Classification System, which includes compounds with poor solubility and high permeability for which the dissolution rate is the factor limiting absorption. It is therefore categorized as a highly lipophilic molecule. Itraconazole is not well absorbed following oral administration, similar to other medications with low water solubility. This results in a wide range of absorption extent and rates, which in turn causes variations in blood levels and Area Under the Curve (AUC) values. Since P-glycoprotein controls the pre-systemic first pass effect, its role in the oral absorption of itraconazole may also contribute to the substantial variability in the drug's bioavailability. Owing to Itraconazole's limited bioavailability (maximum of 55% when taken with a full meal), transdermal administration is the favoured alternate mode of administration. The stratum corneum is the primary barrier to drug delivery via the skin, and several strategies have been proposed to overcome it [32]. Itraconazole uses a variety of methods to carry out its mission. It prevents the formation of fungal-mediated ergosterol by inhibiting lanosterol 14α-demethylase [33]. It is distinct in that it suppresses angiogenesis and the hedgehog signaling pathway, which connects it to the suppression of trafficking, glycosylation, phosphorylation of VEGFR2, and cholesterol production [34]. Owing to its efficacy, Itraconazole is used in a number of systemic oral marketed treatments, including Fungitraxx® and Sporanox® [35].

4. Candida albicans

Globally, systemic infections are primarily caused by Candida albicans and other newly discovered NAC species, including as Candida glabrata, Candida krusei, Candida tropicalis, and Candida parapsilosis. These microbes are the most frequent cause of mucosal or superficial vaginal infections. In certain cases, they can also penetrate the bloodstream and cause deep-tissue infections [36]. As a diploid polymorphic yeast of mucosal surfaces, Candida albicans is a frequent microflora member found in the human gastrointestinal (GI), respiratory, and genitourinary systems. Normally benign, this commensal fungus has the ability to transform into an opportunistic pathogen in people with weakened immune systems or immunodeficiency. This microbe can interact with a range of host cells, including Th17 cells, over the course of illness symptoms [37]. Within the damage response framework, the results of C. albicans infections can be categorized into six groups based on the host immune response, the anatomical site of infection, the virulence of Candida, and the morphology of hyphae and hyphae-specific gene expression as important virulence factors [38].

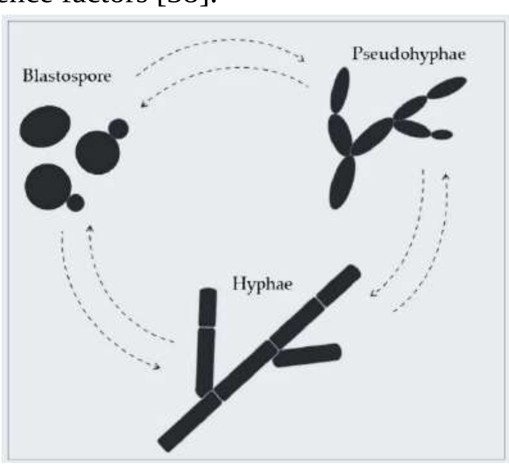

Fig. 3 The morphological switches and transitions of Candida Albicans during the infection process

There are various morphological forms of Candida albicans, including hyphae, pseudohyphae, and blastospores (Fig 3). By budding, bacterospores divide asexually [39]. On the surface of the blastospore, new cell material forms during that process. The new bud, which starts the growth phase, develops from a tiny, carefully chosen blastospore and is typically found away from the location of a birth scar. Following the completion of the growth phase, the cells divide, causing the daughter to create a partition that divides it from the parent cell [39]. Pseudohyphae are characterized by elongated yeast cell chains, while hyphae are characterized by branched tubular cell chains that do not narrow at the sites of septation [40]. Higher than 37 °C, an alkaline pH, serum, and high CO2 concentrations all promote filamentation [41]. Similar to this, it is also improved when N-acetylglucosamine (GlcNAc) is present but nitrogen and carbon are absent [40]. When a blastospore turns into a hypha, a complex regulatory network of signal pathways, including numerous transcription factors, is activated [41]. The hypha wall contains somewhat more chitin than the yeast wall, which is the primary compositional difference between the two [42]. The vital component of the cell membrane that gives it stiffness, stability, and resistance to external stresses is sterol [42]. The most prevalent type of sterol, ergosterol is found in fungal cell membranes. It is produced on lipid bodies and the endoplasmic reticulum [43]. There is a phospholipid bilayer in the cell membrane that contains proteins that function as receptors as well as those that are involved in signal transduction and transport [44]. Candida albicans employs amino acids as a supply of nitrogen and glucose as a source of carbon in its metabolism [45]. Chitin, protein, and glucan comprise the cell wall. Its function is to shield the cell from environmental stressors such osmotic shifts, dehydration, and temperature swings as well as from the host's immune system [46].

Table 1. Showcase studies that use alternative techniques to prepare itraconazole loaded niosomes

Sr. No	Article	Journal	Authors	Abstract	Methods used
1	Itraconazole-Loaded Ufasomes: Evaluation, Characterization, and Anti-Fungal Activity against Candida albicans	Pharmaceutics	Sara M. Hashem, Mary K. Gad, Hend M. Anwar, Neveen M. Saleh, Rehab N. Shamma and Noha I. Elsherif	Ufasomes loaded with itraconazole (ITZ) were designed to improve its penetration power. The optimized ITZ-loaded ufasomes had high encapsulation efficiency and showed promising anti-fungal activity against Candida albicans.	Thin Film Hydration Technique.
2	The Unique Carboxymethyl Fenugreek Gum Gel Loaded Itraconazole Self-Emulsifying Nanovesicles for Topical Onychomycosis Treatment	Polymers	Ali Alqahtani, Bhavana Raut, Shagufta Khan, Jamal Moideen Muthu Mohamed, Adel Al Fatease, Taha Alqahtani, Ali Alamri, Fazil Ahmad and Venkatesan Krishnaraju	The study developed a novel gel loaded with ITZ-nPEVs for topical onychomycosis treatment. The ITZ-nPEVs showed high drug content, good stability, and enhanced antifungal efficacy.	Thin Film Hydration Technique.
3	Novasomes as Nano-Vesicular Carriers to Enhance Topical Delivery of Fluconazole: A New Approach to Treat Fungal Infections	Molecules	Iman Fatima, Akhtar Rasul, Shahid Shah, Malik Saadullah, Nayyer Islam, Ahmed Khames, Ahmad Salawi,	Novasomes were used to encapsulate fluconazole for improved topical delivery. The best formulation	Ethanol Injection Technique.

			Muhammad and Masood Ahmed	showed high entrapment efficiency, small particle size, and effective antifungal activity.	
4	Assessment of antifungal efficacy of itraconazole loaded aspasomal cream: comparative clinical study	Drug Delivery	Caroline Lamie, Enas Elmowafy, Maha H. Ragaie, Dalia A. Attia & Nahed D. Mortada	Topical delivery of antifungal agent itraconazole (ITZ) is effective. ITZ aspasomal cream showed better results compared to non-formulated ITZ.	Thin Film Hydration Technique.
5	Preparation and Optimization of Itraconazole Transferosomes-Loaded HPMC Hydrogel for Enhancing Its Antifungal Activity: 2^3 Full Factorial Design	Polymers	Eidah M. Alyahya, Knooz Alwabsi, Amal E. Aljohani, Rawan Albalawi, Mohamed El-Sherbiny Rehab Ahmed, Yasmin Mortagi, Mona Qushawy	Itraconazole transferosomes (ITZ-TFS) were prepared to enhance skin permeability. ITZ-TFS gel showed higher antifungal activity than free ITZ gel.	Thin Film Hydration Technique.
6	Enhanced corneal permeation and antimycotic activity of itraconazole against Candida albicans via a novel nanosystem vesicle.	Drug Delivery	Aliaa N. ElMeshad & Amira M. Mohsen	Spanlastics were used as an ophthalmic delivery system to improve corneal permeability and antimycotic activity of itraconazole. Spanlastics showed increased permeation of ITZ through cornea and	Ethanol Injection Technique.

				enhanced antimycotic activity against Candida albicans.	
7	Formulation Development and Evaluation of Niosomal Gel of Combined Anti-Fungal Agents	International Journal of Pharmacy	Irene Thomas, Beena P, Elessy Abraham	Niosomal gel of combined anti-fungal agents (Miconazole and Terbinafine) was formulated and evaluated. Niosomal gel showed higher drug release and anti-fungal activity compared to plain gel.	Thin Film Hydration Technique.
8	Itraconazole Niosomes Drug Delivery System and Its Antimycotic Activity against Candida albicans.	ISRN Pharmaceutics	Vijay D. Wagh and Onkar J. Deshmukh	Niosomes of Itraconazole were formulated and evaluated for drug delivery. Niosomes showed good skin permeation and antimycotic activity against Candida albicans.	Thin Film Hydration Technique.
9	Analysis of Molecular Resistance Mechanisms of Itraconazole in Candida Albicans Clinical Isolates from India Research Article	International Journal of Pharmaceutical Sciences Review and Research	Desh D. Singh, Vinod Singh	Study on resistance mechanisms in Itraconazole-resistant Candida albicans isolates from AIDS patients. Identified point mutations in ERG11 gene and overexpression of ERG11 and	Cells Cultured

				efflux pump genes.	
10	Development of Itraconazole-Loaded Polymeric Nanoparticle Dermal Gel for Enhanced Antifungal Efficacy	Journal of Nanomaterials	Hoang Nhan Ho, Thien Giap Le, Thi Thanh Tuyen Dao, Thi Ha Le, Thi Thanh Hai Dinh, Dang Hoa Nguyen, Trinh Cong Tran and Chien Ngoc Nguyen	Gel formulations are suitable for treating cutaneous fungal infections. Incorporation of ITZ-loaded nanosystem into gel enhances antifungal activity.	Evaporation Emulsion Method
11	Evaluation of efficacy and safety of itraconazole oral solution for the treatment of oropharyngeal candidiasis in AIDS patients	Brazilian Journal of infectious diseases	Flávio Queiroz-Telles, Nanci Silva, Miriam M. Carvalho, Clinical Hospital, Federal University of Paraná, Curtitiba; Ana Paula Alcântara,Daniel da Matta, Maria G. Barberino, Aliança Hospital, Salvador, Bahia, Special Mycology Sergio Bartczak and Arnaldo Lopes Colombo	Study evaluated efficacy and safety of itraconazole oral solution for oropharyngeal candidiasis in AIDS patients. Itraconazole oral solution was found to be well tolerated and effective in suppressing symptoms.	Non-comparative multicenter clinical trial
12	Microemulsion based bioadhesive gel of itraconazole using tamarind gum: in-vitro and ex-vivo evaluation	Marmara Pharmaceutical Journal	Kailas K Mali, Shashikant C Dhawale, Remeth J Dias	The study aimed to formulate and evaluate a bioadhesive gel containing microemulsion of itraconazole. Tamarind gum was investigated as a gelling agent	Pseudoternary phase diagram construction

				for the gel formulation	
13	High prevalence of itraconazole resistance among Candida parapsilosis isolated from Iran	Current Medical Mycology	Fozieh Hassanmoghada, Tahereh Shokohi Mohammad Taghi Hedayati, Narges Aslani, Iman Haghani, Mojtaba Nabili, Ensieh Lotfali, Amirhossein Davari, Maryam Moazeni	Study aimed to determine susceptibility of Iranian C. parapsilosis to azole antifungals Majority of isolates showed high MIC values against itraconazole	polymerase chain reaction (PCR) amplification of the secondary alcohol dehydrogenase-encoding gene (SADH)
14	Evaluation of fluconazole, itraconazole, and voriconazole activity on Candida albicans: A case control study	Annals of Medicine and Surgery	Agung Dewi Sekar Langit Partha a, Agung Dwi Wahyu Widodo b, Pepy Dwi Endraswari b	Azole antifungals (fluconazole, itraconazole, and voriconazole) were evaluated for their activity against Candida albicans. The antifungals showed fungistatic activity and effectively inhibited the growth of Candida albicans.	Case-control study with a post-test control group design
15	Itraconazole-resistant Candida auris with phospholipase, proteinase and hemolysin activity from a case of vulvovaginitis.	The Journal of Infection in developing countries	Dharmendra Kumar, Tuhina Banerjee, Chandra Bhan Pratap, Ragini Tilak	Case of vulvovaginitis caused by itraconazole-resistant Candida auris with virulence factors. Patient successfully treated with oral fluconazole, no	Molecular methods using internal transcribed spacer polymerase chain reaction (ITS PCR)

				invasive fungemia.	
16	Formulation and Evaluation of Itraconazole Niosomal Gel	Asian Journal of Pharmaceutical Research and Development	Kumar Ashish, Dua J.S.	Niosomal gel formulation of itraconazole was prepared to enhance antifungal activity. Niosomes were prepared using different ratios of drug, surfactant, and cholesterol.	Thin Film Hydration Technique.
17	Formulation and evaluation of topical antifungal gel containing itraconazole	International Journal of Current Pharmaceutical Research	Poonam Madhukar Kasar, Kalyanisund Arrao Kale, Dipti Ganesh Phadtare	Topical gel formulation of Itraconazole developed Formulation F3 showed best drug diffusion and rheological properties	Magnetic stirring Method
18	Novel itraconazole nano-spanlastics gel with enhanced penetration to treat topical fungal infection	Journal of Drug Delivery Science and Technology	Sumeet S. Dhakane, Ashlesha P. Pandit *	. Nano-spanlastics of itraconazole were optimized using a response surface method and further transformed into gel. A custom ‘response surface method’ was applied to optimize independent variables (Span 60 and Tween 80) at two levels to study effect on entrapment efficiency	Ethanol Injection Technique.

19	“Research on the "Engineering of Nano-gel for delivery of Mometasone and 2 Itraconazole on Scalp and Beard for the Treatment of Fungal Infection"	Journal of Advanced Zoology	Saumya Srivastava, Dr. Shikhar Verma1	This research was conducted to develop Itraconazole and Mometsone Anti-fungal Nano-Hydro-Gel that is effective in the treatment of fungal infections of the scalp and beard	Solvent Diffusion Method
20	Formulation and Evaluation of Antifungal Nanogel for Topical Drug Delivery System	Asian Journal of Pharmaceutical and Clinical research	Anasuya Patil, Pranoti Kontamwar	In this research work, antifungal nanogel formulated to reduce size of particle, improve in-vitro release and in-vivo release study.	Homogenization Technique

Characterization of Niosomes

1. **Size, morphology and size distribution of niosomes**

Numerous methods, including electron microscopic examination, photon correlation spectroscopy, light microscopy, coulter counters, and Scanning Electron Microscopes (SEM), Transmission Electron Microscope (TEM) [47], The size and morphology of niosomes can be ascertained using the freeze-fracture replicator, light scattering, zeta sizer and metasizer [12]. Because the two methods employ different measuring methodologies, the particle size determined by the transmission electron microscope is smaller than that determined by the dynamic light scattering (DLS) approach [48].

2. **Entrapment Efficiency**

It can be calculated by subtracting the amount of unloaded drug from the total amount of drug added [1]. Techniques such thorough dialysis, filtration, gel chromatography, or centrifugation can be used to determine the unloaded medication [49]. By dissolving niosome in 50% n-propanolol or 0.1% Triton X-100, the concentration of loaded medicines can be determined. The resulting solution can then be tested using any particular technique [50]. Following equation can be used to calculate the % entrapment efficiency [12] -

%Entrapment Efficiency = Quantity of drug-loaded in the niosome/ Total quantity of drug in the suspension X 100

3. **Charge on niosome and zeta potential**

The charge on niosomes makes them repel one another. Additionally, they remain stable because this electrostatic repulsion stops them from aggregating and fusing [51]. Zeta potential is used to determine the charge on a niosome. The DLS apparatus, high-performance capillary electrophoresis, microelectrophoresis, mastersizer, zeta potential analyzer, and pH-sensitive fluorophores are utilized to measure the zeta potential [52]. The equation used to calculate zeta potential is Henry's equation [53] –

$$£ = \mu E \pi \eta / \Sigma$$

Where £ = Zeta potential.

μE = Electrophoretic mobility

η = Viscosity of medium

Σ = Dielectric constant

4. Membrane rigidity

A fluorescent probe's mobility can be utilized to assess the stiffness of the membrane as a function of temperature [54]. Fluorescence polarization can be used to determine the membrane's microviscosity and gain an understanding of the niosomal membrane packing structure [55]. The fluorescence anisotropy (r) of the fluorescence observations (λ = 350–425 nm) obtained using a luminescence spectrometer can be calculated using the equation that follows [56]:

$$\text{Florescence Anisotropy}(r) = (IVV - GIVH) / (IVV + 2GIVH)$$

5. In-vitro release

Dialysis membrane technique is used to study in vitro release. This procedure involves placing niosomes in a dialysis bag, which is then placed in a container containing a buffer or other dissolving liquid. The entire assembly is maintained at a regulated temperature of 37 °C using a magnetic stirrer. A sample is obtained from the receptor compartment at predetermined intervals, and the drug concentration is measured using any technique described in the literature [57][58]. Agarwal et al. employed an alternative technique to investigate the dispersion of morusin from niosomes. They mixed 15 cc of phosphate buffer with a pH of 4.5 and 7.4 to distribute 15 mg of the product. We collected this sample using fifteen eppendorf tubes. For nine days, these tubes were turned nonstop at a temperature of 37 °C at a speed of 130 rpm. The tube is removed at a prearranged interval and centrifuged at 15,000 rpm for 30 minutes. The amount of drug in the supernatant was determined using spectrophotometry [59].

6. Tissue distribution / In-vivo study

The method of distribution, drug concentration, action, and duration of drug presence in tissues such the liver, lung, spleen, and bone marrow all affect in-vivo niosome investigations [12]. Using animal models, the tissue distribution of a medication can be investigated. Animals must be sacrificed in order to remove various tissues, including the liver, kidney, heart, lungs, and spleen, which should then be homogenized, centrifuged, and cleaned with buffer in order to investigate the distribution pattern. The drug content of the supernatant is examined [59].

7. Stability studies

On storage, the drug may leak from the niosomes, because of aggregation and fusion [12]. Stability studies involve frequent evaluations of criteria such as entrapment efficiency, size, and shape [60]. Studying the impact of gastrointestinal enzymes on niosome stability was done by Bayindir and Yuskel [61]. In this investigation, the drug and drug-loaded niosomes were exposed to various gastrointestinal enzymes, including chymotrypsin, trypsin, and pepsin. It was discovered that the medication was shielded from gastrointestinal enzyme destruction by the niosomes.

Table 2. Showcase studies that use alternative Preformulation studies and Evaluation parameters after preparation of itraconazole loaded niosomal gel

Sr. No	Article	Journal	Authors	Preformulation Studies	Evaluation of ITZ loaded Gel
1	Itraconazole-Loaded Ufasomes: Evaluation, Characterization, and Anti-Fungal Activity against Candida albicans	Pharmaceutics	Sara M. Hashem, Mary K. Gad, Hend M. Anwar, Neveen M. Saleh, Rehab N. Shamma and Noha I. Elsherif	%EE, Particle Size, Polydispersity Index, Zeta Potential.	Morphological Examination by Transmission Electron Microscope (TEM), DSC, XRD, In Vitro Microbiology Evaluation on the Selected Formula on Candida albicans by - Strains Selection and Cultivation, Antifungal Activities Evaluation Using the Agar Well Diffusion Method, Evaluation of the Minimum Inhibitory Concentration (MIC) of ITZ, Proteinase Enzyme Secretion Assay, Phospholipase Enzyme Secretion Assay, Expression of Interleukin 1β, Flow Cytometry Analysis of TLR-4
2	The Unique Carboxymethyl Fenugreek Gum Gel Loaded Itraconazole Self-Emulsifying Nanovesicles for Topical Onychomycosis Treatment	Polymers	Ali Alqahtani, Bhavana Raut, Shagufta Khan, Jamal Moideen Muthu Mohamed, Adel Al Fatease, Taha Alqahtani, Ali Alamri, Fazil Ahmad and Venkatesan Krishnaraju	%EE, Particle Size and Polydispersity Index, Zeta Potential, Elasticity, Viscosity	Drug Content, %EE, Deformability index, DLS, In vitro drug release and kinetics, SEM, In Vitro ITZ Release, Nail Hydration/Transungual Drug Uptake of ITZ-nPEVs, Nail hydration study of various formulation, Stability Study
3	Novasomes as Nano-Vesicular Carriers to Enhance Topical Delivery of Fluconazole: A New Approach to Treat Fungal Infections	Molecules	Iman Fatima, Akhtar Rasul, Shahid Shah, Malik Saadullah, Nayyer Islam, Ahmed Khames, Ahmad Salawi, Muhammad and Masood Ahmed	%EE, Particle Size and Polydispersity Index, Zeta Potential, Release Kinetics, FTIR, DSC, TGA, SEM	Particle Size and Zeta Potential Analysis, %EE, In Vitro Drug Release, Release Kinetics, FTIR, DSC, TGA, SEM, Anti-fungal activity - Minimum Inhibitory Concentration (MIC)

					Assay via Resazurin Reduction Technique & Agar-Well Diffusion Method, Toxicity Studies of Novasomes, Effect of Storage Conditions on Novasomes.
4	Assessment of antifungal efficacy of itraconazole loaded aspasomal cream: comparative clinical study	Drug Delivery	Caroline Lamie, Enas Elmowafy, Maha H. Ragaie, Dalia A. Attia & Nahed D. Mortada	Utilization of placebos (void aspasomal cream and cream base)	Placebos (void aspasomal cream and cream base) were also utilized. The obtained results for diaper rash revealed that aspasomal cream (0.5% ITZ) was eminent with respect to complete cure andnegative candida culture after 10-day therapy relative to counterparts containing 0.1% ITZ aspasomes or non-formulated ITZ (0.1% and 0.5%). For tinea, the same trend was manifested in terms of 'cleared' clinical response in 90% of patients and absence of fungal elements after 4-week treatment
5	Preparation and Optimization of Itraconazole Transferosomes-Loaded HPMC Hydrogel for Enhancing Its Antifungal Activity: 2^3 Full Factorial Design	Polymers	Eidah M. Alyahya, Knooz Alwabsi, Amal E. Aljohani, Rawan Albalawi, Mohamed El-Sherbiny Rehab Ahmed, Yasmin Mortagi, Mona Qushawy		EE%, particle size, polydispersity index (PDI), Zeta Potential, homogeneity, drug content, spreadability, pH, and in vitro antifungal activity in comparison with the free ITZ gel.
6	Enhanced corneal permeation and antimycotic	Drug Delivery	Aliaa N. ElMeshad & Amira M. Mohsen		%EE, Vesicle size, Zeta Potential, Elasticity, DSC, In Vitro drug release,

	activity of itraconazole against Candida albicans via a novel nanosystem vesicle.				Corneal Permeability studies, In Vitro antimycotic study, n vivo eye toxicity Draize test.
7	Formulation Development and Evaluation of Niosomal Gel of Combined Anti-Fungal Agents	International Journal of Pharmacy	Irene Thomas, Beena P, Elessy Abraham	Organoleptic evaluations, FTIR, DSC	Five Niosomal formulations were prepared (N1- N5) and evaluated for surface morphology, particle size, PDI, Drug content, entrapment efficiency, Zeta potential, in vitro drug release and TEM analysis, physical properties, pH, Viscosity, Spreadability, Extrudability, Drug content and in vitro drug release
8	Itraconazole Niosomes Drug Delivery System and Its Antimycotic Activity against Candida albicans.	ISRN Pharmaceutics	Vijay D. Wagh and Onkar J. Deshmukh		Formulated niosomes were evaluated for vesicle size, entrapment efficiency, drug release, skin permeation, and antimycotic activity
9	Analysis of Molecular Resistance Mechanisms of Itraconazole in Candida Albicans Clinical Isolates from India Research Article	International Journal of Pharmaceutical Sciences Review and Research	Desh D. Singh, Vinod Singh	Real-time reverse transcriptase polymerase chain reaction (RT-PCR) PCR protocol for analyzing the MTL locus	Real-time RT-PCR assays were used to obtain more accurate data on gene expression in C. albicans.
10	Development of Itraconazole-Loaded Polymeric Nanoparticle Dermal Gel for Enhanced	Journal of Nanomaterials	Hoang Nhan Ho, Thien Giap Le, Thi Thanh Tuyen Dao, Thi Ha Le, Thi Thanh Hai Dinh, Dang Hoa Nguyen, Trinh	FTIR, XRD	Morphological Examination by Transmission Electron Microscope (TEM), DSC, XRD, Rheological Analysis, Ex vivo Permeation

	Antifungal Efficacy		Cong Tran and Chien Ngoc Nguyen		study, Anti-fungal Activity.
11	Evaluation of efficacy and safety of itraconazole oral solution for the treatment of oropharyngeal candidiasis in AIDS patients	Brazilian Journal of infectious diseases	Flávio Queiroz-Telles, Nanci Silva, Miriam M. Carvalho, Clinical Hospital, Federal University of Paraná, Curtitiba; Ana Paula Alcântara,Daniel da Matta, Maria G. Barberino, Aliança Hospital, Salvador, Bahia, Special Mycology Sergio Bartczak and Arnaldo Lopes Colombo	Patients, safety Analysis, Efficacy Analysis	Preliminary clinical studies in AIDS patients with severe oral candidiasis
12	Microemulsion based bioadhesive gel of itraconazole using tamarind gum: in-vitro and ex-vivo evaluation	Marmara Pharmaceutical Journal	Kailas K Mali, Shashikant C Dhawale, Remeth J Dias	Pseudoternary phase diagram construction Solubility determination of ITZ in various oils, surfactants, and cosurfactants	ITZ gels were evaluated for pH, drug content, viscosity, ex-vivo bioadhesion, spreadability and in vitro drug release. Furthermore, antifungal activity of the gels was performed by agar cup diffusion technique using cultures of Candida albicans.
13	High prevalence of itraconazole resistance among Candida parapsilosis isolated from Iran	Current Medical Mycology	Fozieh Hassanmoghada, Tahereh Shokohi Mohammad Taghi Hedayati, Narges Aslani, Iman Haghani, Mojtaba Nabili, Ensieh Lotfali, Amirhossein		Antifungal susceptibility testing using broth microdilution reference method Testing against fluconazole, itraconazole, voriconazole, luliconazole, and lanoconazole

			Davari, Maryam Moazeni		
14	Evaluation of fluconazole, itraconazole, and voriconazole activity on Candida albicans: A case control study	Annals of Medicine and Surgery	Agung Dewi Sekar Langit Partha a, Agung Dwi Wahyu Widodo b, Pepy Dwi Endraswari b	The time-kill curve of itraconazole against clinical isolates of Candida albicans	
15	Itraconazole-resistant Candida auris with phospholipase, proteinase and hemolysin activity from a case of vulvovaginitis.	The Journal of Infection in developing countries	Dharmendra Kumar, Tuhina Banerjee, Chandra Bhan Pratap, Ragini Tilak	PCR amplification product of Candida spp	
16	Formulation and Evaluation of Itraconazole Niosomal Gel	Asian Journal of Pharmaceutical Research and Development	Kumar Ashish, Dua J.S.	%EE, Particle Size Analysis, Drug Content Analysis	Physical Apperance, pH, Viscosity, Drug Content Uniformity, Entrapment Efficiency, In vitro Drug diffusion Study, Stability Study
17	Formulation and evaluation of topical antifungal gel containing itraconazole	International Journal of Current Pharmaceutical Research	Poonam Madhukar Kasar, Kalyanisund Arrao Kale, Dipti Ganesh Phadtare	% yield, Drug Content, Determination of pH, Spreadability	% yield, spreadability, extrudability, viscosity, In Vitro drug release, skin irritation, and stability
18	Novel itraconazole nano-spanlastics gel with enhanced penetration to treat topical fungal infection	Journal of Drug Delivery Science and Technology	Sumeet S. Dhakane, Ashlesha P. Pandit	Nanospanlastics (a) particle size and pdi, (b) zeta potential, SEM	In vitro diffusion study of nano-spanlastic gel, . Ex vivo diffusion study of nano-spanlastic gel, Texture profile analysis of (a) gel G2, (b) marketed gel; (c) stringiness of gel G2, Antifungal study (a) zone of inhibition for nano-spanlastic gel G2, (b) zone of inhibition for marketed gel, (c) graphical representation of zone of inhibition

19	"Research on the "Engineering of Nano-gel for delivery of Mometasone and 2 Itraconazole on Scalp and Beard for the Treatment of Fungal Infection"	Journal of Advanced Zoology	Saumya Srivastava, Dr. Shikhar Verma1	Melting point, solubility, pH, Viscosity, Spreadability, XRD, SEM, UV Spectroscopy of drug	homogeneity, drug content uniformity, spreadability, viscosity, Statistical analysis of experimental data by ANOVA using Excel, In-vitro-drug release study, release kinetic study, Particle size analysis, (SEM), FT-IR studies. In-Vitro Anti-fungal activity tested by using Nano-gel Franz diffusion cell (Make-Orchid scientific). Amount of drug released was determined using UV-spectrophotometer at 222 nm.
20	Formulation and Evaluation of Antifungal Nanogel for Topical Drug Delivery System	Asian Journal of Pharmaceutical and Clinical research	Anasuya Patil, Pranoti Kontamwar	Calibration Curve, Determination of melting-point, Saturation solubility studies, FTIR	In-vitro release profile of ciclopirox olamine nanogel, Release kinetics-models, DSC analysis, In-vivo study of antifungal nanogel

Table 3. Illustrate some of the research articles with their Conclusions and Practical Implications along with the keywords used

Sr No	Article	Journal	Authors	Conclusions	Practical implications	Keywords
1	Itraconazole-Loaded Ufasomes: Evaluation, Characterization, and Anti-Fungal Activity against Candida albicans	Pharmaceutics	Sara M. Hashem, Mary K. Gad, Hend M. Anwar, Neveen M. Saleh, Rehab N. Shamma and Noha I. Elsherif	Ufasomes loaded with itraconazole showed high encapsulation efficiency and small particle size. The optimized formula exhibited anti-fungal activity against Candida albicans.	Ufasomes loaded with itraconazole can improve its penetration power. The optimized formula showed promising anti-fungal activity against Candida albicans.	Itraconazole; ufasomes; oleic acid; Candida albicans; microbiology

2	The Unique Carboxymethyl Fenugreek Gum Gel Loaded Itraconazole Self-Emulsifying Nanovesicles for Topical Onychomycosis Treatment	Polymers	Ali Alqahtani, Bhavana Raut, Shagufta Khan, Jamal Moideen Muthu Mohamed, Adel Al Fatease, Taha Alqahtani, Ali Alamri, Fazil Ahmad and Venkatesan Krishnaraju	ITZ-nPEVs loaded in CMFG gel showed promising results for topical onychomycosis treatment. ITZ-nPEVs exhibited enhanced nail hydration, drug absorption, and antifungal efficiency.	The novel ITZ-nPEVs loaded in CMFG gel can be used for topical treatment of onychomycosis. ITZ-nPEVs showed improved nail hydration and antifungal efficacy compared to commercial gel	itraconazole; onychomycosis; self-emulsifying nanovesicles; transungual; anti-fungal
3	Novasomes as Nano-Vesicular Carriers to Enhance Topical Delivery of Fluconazole: A New Approach to Treat Fungal Infections	Molecules	Iman Fatima, Akhtar Rasul, Shahid Shah, Malik Saadullah, Nayyer Islam, Ahmed Khames, Ahmad Salawi, Muhammad and Masood Ahmed	Encapsulating fluconazole in novasomes improves topical delivery. The FN7 formulation shows high efficacy in inhibiting fungal growth.	Fungal infections are increasing, and conventional treatments are not effective for deep infections. This research aims to improve topical delivery of fluconazole using novasomes.	fluconazole; novasomes; ethanol injection technique; antifungal activity; toxicity study
4	Assessment of antifungal efficacy of itraconazole loaded aspasomal cream: comparative clinical study	Drug Delivery	Caroline Lamie, Enas Elmowafy, Maha H. Ragaie, Dalia A. Attia & Nahed D. Mortada	Aspasomal cream with 0.5% ITZ showed better results in treating diaper rash. ITZ aspasomal cream was effective in treating tinea infections.	Itraconazole aspasomal cream showed efficacy in treating diaper dermatitis and fungal infections. Lowering the concentration of ITZ in the cream may be beneficial.	Itraconazole; clinical study; candidiasis; tinea; aspasomes; cream

5	Preparation and Optimization of Itraconazole Transferosomes-Loaded HPMC Hydrogel for Enhancing Its Antifungal Activity: 2^3 Full Factorial Design	Polymers	Eidah M. Alyahya, Knooz Alwabsi, Amal E. Aljohani, Rawan Albalawi, Mohamed El-Sherbiny Rehab Ahmed, Yasmin Mortagi, Mona Qushawy	Itraconazole transferosomes (ITZ-TFS) showed higher antifungal activity than free ITZ gel. ITZ can be successfully delivered topically for its antifungal activities.	The study suggests that itraconazole transferosomes can enhance the antifungal activity of the drug when applied topically. The use of hydroxyl propyl methyl cellulose (HPMC) gel base can be a suitable formulation for delivering itraconazole transferosomes.	Itraconazole (ITZ), transferosome (TFS), antifungal activity, Candida albicans, optimization, stratum corneum
6	Enhanced corneal permeation and antimycotic activity of itraconazole against Candida albicans via a novel nanosystem vesicle.	Drug Delivery	Aliaa N. ElMeshad & Amira M. Mohsen	Spanlastics improved corneal permeability and antimycotic activity of itraconazole. In vivo Draize test showed no signs of acute ocular toxicity.	The paper investigates the potential of spanlastics as an ophthalmic delivery system for itraconazole. The spanlastics formulation showed enhanced corneal permeability and antimycotic activity against Candida albicans.	Candida albicans, elasticity, itraconazole, niosomes, spanlastics
7	Formulation Development and Evaluation of Niosomal Gel of Combined Anti-Fungal Agents	International Journal of Pharmacy	Irene Thomas, Beena P, Elessy Abraham	Niosomal gel containing combined antifungal drugs is more effective than plain gel. Niosomal gel improves topical formulation and increases	Combination of Miconazole and Terbinafine in niosomal gel form shows higher antifungal activity. Niosomal gel improves drug permeation and retention, reducing	Novel drug delivery, Niosomes, Anti-fungal agents, Miconazole, Terbinafine, Synergistic activity, Niosomal gel

				patient compliance	frequency of administration.	
8	Itraconazole Niosomes Drug Delivery System and Its Antimycotic Activity against Candida albicans.	ISRN Pharmaceutics	Vijay D. Wagh and Onkar J. Deshmukh	Formulated niosomes of Itraconazole showed larger zone of inhibition against Candida albicans compared to the marketed formulation. Niosomes may be a promising carrier for topical delivery of Itraconazole.	Niosomes may be a promising carrier for topical delivery of Itraconazole. Itraconazole niosomes showed larger zone of inhibition against Candida albicans.	Candida albicans, elasticity, itraconazole, niosomes, spanlastics
9	Analysis of Molecular Resistance Mechanisms of Itraconazole in Candida Albicans Clinical Isolates from India Research Article	International Journal of Pharmaceutical Sciences Review and Research	Desh D. Singh, Vinod Singh	Resistance mechanisms in Itraconazole-resistant isolates of Candida albicans were identified. Overexpression of ERG11 gene and efflux pump genes contribute to resistance.	Understanding resistance mechanisms can help in developing effective antifungal strategies. Identifying specific mutations can aid in targeted treatment of resistant strains.	Molecular resistance, Fungal infections, Candida albicans, Fluconazole, Itraconazole.
10	Development of Itraconazole-Loaded Polymeric Nanoparticle Dermal Gel for Enhanced Antifungal Efficacy	Journal of Nanomaterials	Hoang Nhan Ho, Thien Giap Le, Thi Thanh Tuyen Dao, Thi Ha Le, Thi Thanh Hai Dinh, Dang Hoa Nguyen, Trinh Cong Tran and Chien Ngoc Nguyen	ITZ NPs showed sustained release, good permeation through skin, and high drug content in skin.ITZ NP gel exhibited better in vitro antifungal activity compared to	Development of a gel formulation with enhanced antifungal activity. Potential for transdermal drug delivery to treat cutaneous fungal infections.	Itraconazole, Nanoparticles,Dermal Gel, Polymer, Nanotechnology

				conventional gel.		
11	Evaluation of efficacy and safety of itraconazole oral solution for the treatment of oropharyngeal candidiasis in AIDS patients	Brazilian Journal of infectious diseases	Flávio Queiroz-Telles, Nanci Silva, Miriam M. Carvalho, Clinical Hospital, Federal University of Paraná, Curtitiba; Ana Paula Alcântara, Daniel da Matta, Maria G. Barberino, Aliança Hospital, Salvador, Bahia, Special Mycology Sergio Bartczak and Arnaldo Lopes Colombo	Itraconazole oral solution is an effective treatment for oropharyngeal candidiasis in AIDS patients. Patients with severe immunosuppression may require frequent or long-term therapy.	Itraconazole oral solution is an effective treatment for oropharyngeal candidiasis in AIDS patients. Patients with severe immunosuppression may require frequent or long-term treatment.	AIDS, candidiasis, itraconazole
12	Microemulsion based bioadhesive gel of itraconazole using tamarind gum: in-vitro and ex-vivo evaluation	Marmara Pharmaceutical Journal	Kailas K Mali, Shashikant C Dhawale, Remeth J Dias	TG-containing ME gel showed complete drug release and greatest antifungal activity. TG can be used as a gelling agent in ME-based gels.	Tamarind gum-based microemulsion gel may be used for topical drug delivery.The gel showed fast and complete drug release and stability for three months.	Bioadhesion, itraconazole, microemulsion gel, tamarind gum, xanthan gum.
13	High prevalence of itraconazol	Current Medical Mycology	Fozieh Hassanmoghada, Tahereh	Majority of C. parapsilosis isolates showed high	High prevalence of itraconazole resistance among Candida	Azoles, Candida parapsilosis, Iranian isolates, Resistant

	e resistance among Candida parapsilosis isolated from Iran		Shokohi Mohammad Taghi Hedayati, Narges Aslani, Iman Haghani, Mojtaba Nabili, Ensieh Lotfali, Amirhossein Davari, Maryam Moazeni	MIC values against itraconazole. Choosing the appropriate antifungal is crucial for starting treatment.	parapsilosis in Iran Choosing appropriate antifungal treatment is crucial for starting treatment.	
14	Evaluation of fluconazole , itraconazole, and voriconazole activity on Candida albicans: A case control study	Annals of Medicine and Surgery	Agung Dewi Sekar Langit Partha a, Agung Dwi Wahyu Widodo b, Pepy Dwi Endraswari b	Fluconazole, itraconazole, and voriconazole effectively inhibit the growth of Candida albicans. Maximum inhibition of Candida albicans occurs after 12 hours of antifungal exposure.	Azole antifungals (fluconazole, itraconazole, and voriconazole) are effective against Candida albicans. Maximum inhibition of Candida albicans growth occurs after 12 hours of antifungal exposure.	Antifungal drug, Candida albicans, Infectious disease, Time-kill curve
15	Itraconazole-resistant Candida auris with phospholipase, proteinase and hemolysin activity from a case of vulvovaginitis.	The Journal of Infection in developing countries	Dharmendra Kumar, Tuhina Banerjee, Chandra Bhan Pratap, Ragini Tilak	Candida auris isolated from vulvovaginitis showed resistance to itraconazole. The isolate expressed virulence factors including phospholipase, proteinase, and hemolysin activity.	Candida auris is an emerging pathogen causing vulvovaginitis. The isolate in this case was resistant to itraconazole but responded to fluconazole treatment.	C. auris; non-albicans; resistance; phospholipase

16	Formulation and Evaluation of Itraconazole Niosomal Gel	Asian Journal of Pharmaceutical Research and Development	Kumar Ashish, Dua J.S.	Gel formulation containing niosomes loaded with Itraconazole showed prolonged action. Niosomal gel can improve the anti-fungal activity of Itraconazole.	Niosomal gel formulation with Itraconazole can enhance antifungal activity. Niosomal gel showed prolonged action compared to non-niosomal form	Niosome, Itraconazole, Cholesterol, Span 60/ Span 40, Diethyl Ether, Carbopol 940, Glycerol, Rotary Vacuum Evaporator
17	Formulation and evaluation of topical antifungal gel containing itraconazole	International Journal of Current Pharmaceutical Research	Poonam Madhukar Kasar, Kalyanisund Arrao Kale, Dipti Ganesh Phadtare	Formulation F3 was the best among the developed formulations. Formulation F3 should be further developed for industrial production.	Development of a topical gel formulation of Itraconazole for better patient compliance and reduced side effects. Formulation F3 showed the best drug diffusion and rheological properties.	traconazole, Carbopol 934p, HPMC
18	Novel itraconazole nano-spanlastics gel with enhanced penetration to treat topical fungal infection	Journal of Drug Delivery Science and Technology	Sumeet S. Dhakane, Ashlesha P. Pandit	nano-spanlastics, a promising non-ionic surfactant-based vesicles, were successfully prepared, by ethanol injection method using Span 60 and Tween 80.	Nano-spanlastics can be a potential nanocarrier for improved penetration and for targeting topical fungal infections, thus providing new opportunities for dermal treatment.	Nano-spanlastic Itraconazole Spanlastics Ethanol injection method
19	“Research on the "Engineering of Nano-gel for delivery of Mometasone and 2	Journal of Advanced Zoology	Saumya Srivastava, Dr. Shikhar Verma1	A modified emulsification-diffusion process was used to successfully create a topical Nano gel 361 that was	The physicochemical characteristics of Nano gel demonstrated its suitability for topical application. The produced Nano	Nanogel; Antifungal; Scalp and Beard; Mometasone; Itraconazole

	Itraconazole on Scalp and Beard for the Treatment of Fungal Infection"			loaded with Itaconazole & Mometasone.	gel's antifungal efficacy was demonstrated in vitro, slowing the growth of Candida albicans.	
20	Formulation and Evaluation of Antifungal Nanogel for Topical Drug Delivery System	Asian Journal of Pharmaceutical and Clinical research	Anasuya Patil, Pranoti Kontamwar	It would be concluded that the best formulation-F6 which elicited better in-vitro drug release and enhanced dermatitis scoring.	The test sample was found to be more potent than the marketed formulation because the dermatitis score was less in the test sample than the marketed formulation.	Ciclopirox-olamine, Eudragit-S100, Glycerol, Dermatitis, Carbopol-940, Cellophane membrane

APPLICATIONS

Transdermal Drug Delivery Systems (TDDS) encompass a wide array of therapeutic areas and have seen significant success in various medical applications:

1. Nicotine patches for smoking cessation, widely used in the United States and Europe.
2. Fentanyl CII (Duragesic) and buprenorphine CIII (BuTrans) patches for managing severe pain.
3. Hormonal patches including estrogen patches for menopausal symptoms and hormone replacement therapy, contraceptive patches (Ortho Evra or Evra), and testosterone patches for both men (Androderm) and women (Intrinsa).
4. Nitroglycerin patches for the treatment of angina.
5. Transdermal scopolamine for motion sickness.
6. Clonidine patches for hypertension.
7. Emsam, a transdermal form of the MAOI selegiline, for antidepressant therapy.
8. Daytrana, the first methylphenidate transdermal delivery system for ADHD treatment.
9. Secuado, a transdermal form of the atypical antipsychotic asenapine.
10. Vitamin B12 and 5-Hydroxytryptophan (5-HTP) patches for transdermal administration.
11. Rivastigmine patches for Alzheimer's treatment.
12. Quantum dot dye technology developed by Robert S. Langer and his team for the subcutaneous storage of medical information, especially beneficial in developing nations.
13. Caffeine patches designed for transdermal delivery of caffeine.

These examples underscore the diverse and expanding applications of TDDS in the realm of modern medicine, catering to a range of therapeutic needs and patient requirements.[7]

ADVERSE EVENTS

Certain transdermal drug delivery systems have been reported over the years, leading to safety concerns and subsequent regulatory actions:

1. In 2005, the FDA launched an investigation into reports of fatalities and other serious adverse events associated with narcotic overdose in patients using Duragesic, the fentanyl transdermal patch for pain management. As a result, the Duragesic product label was updated in June 2005 to include additional safety information.
2. In 2007, manufacturers Shire and Noven Pharmaceuticals voluntarily recalled specific batches of the Daytrana ADHD patch due to issues related to the separation of the patch from its protective release liner. No further complications with the patch or its protective packaging were reported subsequently.
3. In 2008, two manufacturers of the fentanyl patch, ALZA Pharmaceuticals (a division of Johnson & Johnson) and Sandoz, recalled their versions of the patch due to a manufacturing defect leading to the rapid leakage of the gel containing the medication. This defect raised the risk of potential overdose and subsequent fatalities. Sandoz, now manufactured by ALZA, ceased using gel in its transdermal fentanyl patch, employing a matrix/adhesive suspension instead, similar to other fentanyl patch manufacturers such as Mylan and Janssen.
4. In 2009, the FDA issued a public health advisory highlighting the risk of burns during MRI scans associated with transdermal drug patches containing metallic backings. Patients were advised to remove any medicated patch before undergoing an MRI scan and replace it with a new patch after the scan.
5. In 2009, an article in the Europace journal documented cases of skin burns resulting from transdermal patches containing metal, commonly used as a backing material. These burns were attributed to shock therapy from external as well as internal cardioverter defibrillators (ICD).[9]

CONCLUTION

Drugs can be delivered in a controlled, consistent, and targeted manner using niosomes as a delivery method. Because niosomes can concurrently encapsulate hydrophilic and hydrophobic medications, there is growing interest in them. Natural medicine, enzymes, peptides, genes, vaccines, anti-cancer agents, and nearly every other type of medication can all be encapsulated using them. They provide freedom in the mode of administration in addition to the medication. Their non-toxic advantage over liposomes gives them a better option for drug delivery. Therefore, it appears that niosome research will continue and could result in effective market formulation for the pharmaceutical sector. From the data of table. 3, we can conclude that Niosomal gel formulation with Itraconazole can enhance antifungal activity, its efficacy was increased, improved drug permeation and retention, reducing frequency of administration and it showed prolonged action compared to non-niosomal form. The physicochemical characteristics of Nano gel demonstrated its suitability for topical application. Thus, can be a potential nanocarrier for improved penetration and for targeting topical fungal infections, thus providing new opportunities for dermal treatment. In summary, a major breakthrough in the treatment of Candida albicans infections has been made with the creation of itraconazole niosomal gel. We have shown that this new strategy results in better medication distribution, increased bioavailability, and extended drug release—all of which led to increased effectiveness and fewer adverse effects. A promising option for getting around the drawbacks of traditional therapies and dealing with the problems caused by Candida albicans infections is the synergistic combination of itraconazole and niosomal technology. We hope to see this formulation widely used in clinical settings as we continue to improve and optimize it, providing patients with a more convenient and effective treatment alternative. Beyond traditional approaches, the itraconazole niosomal gel is a shining example of innovation, demonstrating the ability of contemporary pharmaceutical research to completely transform the treatment of infectious diseases.

CONFLICT OF INTEREST

The Authors declare that this article has no conflict of interest.

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