American Journal of Psychiatric ehabilitation

Expert Opinion Article

Luliconazole-Loaded Niosomal Gel Formulation Strategies And Optimization And Evaluation Parameter

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Abstract

Objective: The objective of this review is to comprehensively evaluate recent advances in the formulation and characterization of luliconazole-loaded niosomes for topical antifungal therapy. The review highlights formulation strategies, critical material attributes, and performance outcomes, with a focus on improving drug solubility, skin permeability, and therapeutic efficacy.

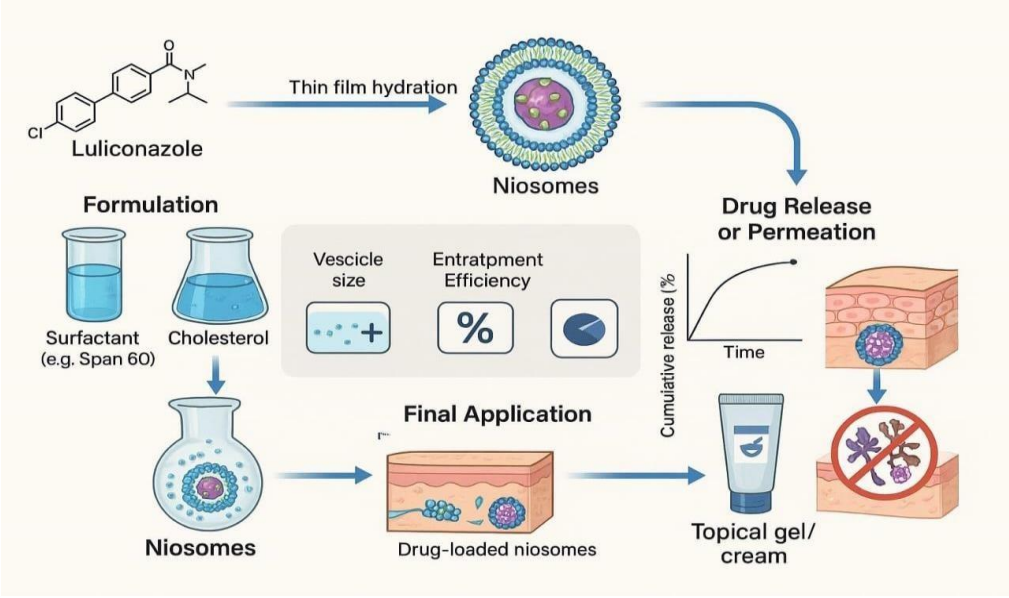
Significance of Review : Though highly effective against dermatophytes and Candida species, suffers from poor aqueous solubility and limited dermal retention, which reduce its therapeutic performance in conventional topical dosage forms. Niosomal drug delivery systems offer a promising alternative by enhancing drug stability, penetration, and controlled release. This review bridges the gap between lab-scale research and industrial application, providing insight into scalable, patient-compliant delivery platforms for antifungal therapy.

Key Findings : Niosomes consisting of non-ionic surfactants (e.g., Span 60, Tween 60) and cholesterol have demonstrated high drug entrapment efficiency (>80%) and nanoscale vesicle size (100-200 nm).- Luliconazole-loaded niosomes provide sustained drug release (up to 24 hours) and significantly improved antifungal activity compared to conventional formulations.- Characterization techniques including DLS, TEM, FTIR, and in vitro permeation studies are critical to evaluate the vesicle integrity, drug-excipient interactions, and skin delivery performance.- Incorporation into gel bases (niosomal gel) further improves patient acceptability and bioadhesion, making the system suitable for commercial topical applications.

Conclusion: Loaded niosomes are a potentially nanocarrier system for the effective handling of superficial fungal infections. The reviewed studies confirm their potential to enhance topical bioavailability, prolong drug release, and improve therapeutic outcomes. Further research should focus on in vivo evaluations, stability profiling, and scale-up processes to facilitate clinical translation and commercial development.

Keywords: Niosomes, Niosomal gel, Topical drug delivery, Antifungal therapy, Transdermal delivery, Controlled release, Dermatophytosis treatment.

Graphical abstract



1. Introduction :-

he drug distribution through the skin is the best route, ensuring its direct access and higher retention rate at the target. Topical delivery further contributes to reduced systemic toxicity and avoid pre-systemic metabolism (1).Topical pharmaceutical delivery systems benefit from first pass metabolism negotiation. Additionally, topical preparations are non-invasive and self administrable, patient compliance is higher. Some disadvantages of topical drug delivery techniques include low drug permeability via the skin, allergic reaction, skin irritation in contact dermatitis, and trouble absorbing large particle size drugs applied topically (2).

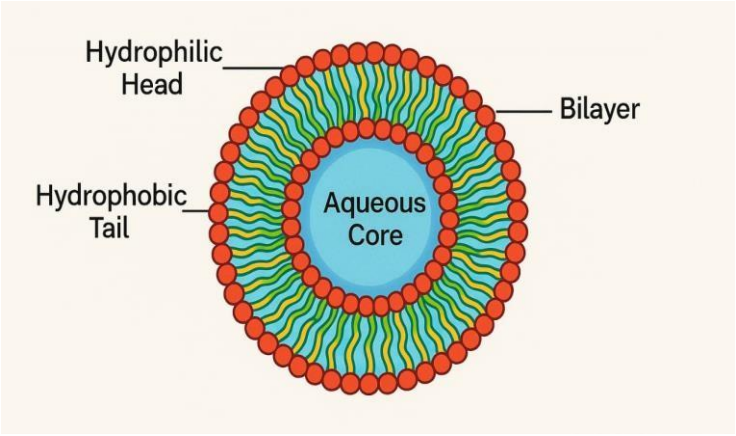


Figure 1 : Niosome

Novel drug delivery carriers have excellent potential for delivery through the skin they provide prolonged and sustained release of drug, so that required dose is decreased, and to avoid GI side effect and first pass hepatic metabolism (3). Among the most often utilized azole antifungal medications with broad spectrum action is Luliconazole. Fungal cytochrome P450 (CYP450) 14-a-demthylase is selectively inhibited by luliconazole, which has a distinct chemical structure. It prevents the production of fungal cell walls by interfering The transformation of lanosterol to ergosterol. Luliconazole belongs (BCS class II). It has a markedly poor aqueous solubility, which restricts its dermal accessibility. The toxicity of systemic dose forms and adverse medication reaction are major obstacles that limit the use of antifungal medicines (4). The study's goal was to develop Noisome, employed to alleviate the difficulty related to the traditional topical formulation. The aqueous phase is surrounded by a multitude of concentric bilayer membranes in niosomes, which are mostly composed of cholesterol and non-ionic surfactants. Niosomes have been shown to increase the solubility, bioavailability, and durability of several poorly soluble medicines, as well as their potential to provide sustained pharmacological activity. Surfactants improve total chemical penetration largely by absorption at interfaces, interactions with biological membranes, and changes in the SC's barrier function as a consequence of reversible lipid alteration (5). This study looks at the rationale, methodology, and results for developing luliconazole-loaded niosomal gels, with focus on contemporary research. This article aims to offer a complete overview of the recent advancements in the development and characterization of luliconazole-loaded niosomal gels.

2. Background :-

According to reports, Luliconazole works by preventing the fungus Cytochrome P450 ; that is, 14-α demethylase enzyme thus prevents the biosynthesis of ergosterol from lanosterol and interrupts cell wall synthesis within the fungi. When applied topically, Luliconazole's low solubility limits the drug's ability to penetrate the skin. However, traditional topical cream formulations have a number of disadvantages, including poor retention at the application site and low penetration from the stratum corneum. Novel delivery methods are desperately needed for better penetration and retention from the skin application site (6). Dermatophytes are aerobic fungi and the most common offenders in superficial fungal infections. According to their physiological makeup, these dermatophytes can develop and multiply in the epidermis' outermost layers by breaking down keratin. In clinical practice, therefore, keratin-rich body parts including the skin, hair, and nails are most commonly afflicted by dermatophytic infection. Embedded arthroconidia that survive for years in skin and hair scales frequently return or relapse. The dermatophytes that cause the problem are members of the three genera: Trichophyton, Microsporum, and Epidermophyton (7). Conventional dosage forms

(cream, powder, gels, etc.) available for the handling of superficial fungal infections are also reported to cure deep-seated fungal infections of the skin. Several adverse effects are associated with the usage of these formulations such as burning, redness, and swelling. Moreover, due to the immediate release of drug from these formulations, they can activate the immune system of body, stimulating various allergic reactions. Deep-seated fungal infections (invasive aspergillosis and invasive candidiasis) might be more complicated to treat with conventional topical formulation because the drug released from these cannot reach at the target site due to the low penetration ability. Thus, to overcome the problems of conventional therapy, a lot of work has been carried out to develop novel formulations delivering antifungal superficially (8). Luliconazole-loaded nisomes are a method that has been shown to meet the requirements. This is useful in sustaining the drug release (6). Drug targeting means to aim a therapeutic entity directly to a specific area where the action is desired, without any interaction of that entity with other surrounding tissues (9). Rationally developed drug delivery systems have the potential to deliver drugs at a predetermined rate and time, and this helps in improving drug efficacy by overcoming the existing limitations. Indeed, nonionic surfactant vesicles (niosomes) have demonstrated the ability to improve permeability and bioavailability of poorly water-soluble drugs and are promising for improvement of antifungal drug activity by enhancing the distribution of topical drugs (4).

3. Rationale for niosomal based delivery :-

The benefits of topical drug delivery include avoiding the hepatic first-pass metabolism of the drug and its associated adverse consequences. These have the drug's direct delivery and targetability to the skin's afflicted areas (10). This could be resolved with the usage of Noval drug delivery systems. Non-ionic surfactants give niosomes their name and make them nontoxic. They may comprise charged molecules and cholesterol or its derivatives in addition to non-ionic surfactants. Cholesterol makes the structure more stiff and the charged molecule keeps the preparation stable. Niosomes are formed when non-ionic surface-active chemicals self-assemble. Due to their structure, they may be used to load and distribute both hydrophilic and hydrophobic medicines(11). Compared to alternative drug delivery methods, niosomes have many benefits that make them extremely effective for a variety of applications. A noteworthy advantage of niosomes is their ability to encapsulate different medications, DNA, proteins, and vaccinations (12). Niosomes provide numerous benefits over traditional drug delivery methods, including the capacity to entrap both hydrophilic and hydrophobic medications and flexibility of drug delivery. Niosomes encapsulate solutes and API with varying solubilities and deliver them through a variety of delivery routes, including topical, parenteral, pulmonary, ophthalmic, and oral. (13). For the manufacture of noisome, surfactants with alkyl chain lengths between C12 and C18 are appropriate. Vesicles can be formed by span series surfactants with an HLB value between 4 and 8. Addition of cholesterol molecules to the niosomal system makes the membrane rigid and reduces leakage of drug from the noisome(14). Therapeutics performance can improve of drug molecules by protecting drug from environment which is biological results in better controlled drug delivery (15). Depending on the level of local humidity, niosomes may enter the stratum corneum intact or structurally change into smaller vesicles inside the skin. They may also interact directly with the stratum corneum through adsorption or fusion processes. Adsorption can occur via nonspecific physical interactions or through receptor-ligand binding, enabling direct drug transfer from the vesicle to the skin. In the case of fusion, the vesicle membrane integrates with the cellular membrane, allowing complete release of the niosomal contents into the cytoplasm (16). Niosome delivery improves skin penetration and increases active availability and minimizes irritant effects that conventional topical products commonly generate.The defensive functions of niosomes serve as beneficial (17). A nonionic surfactant like Span-60, which is typically stabilized by the addition of cholesterol and a little amount of nonionic surfactant like diacetyl phosphate, which also helps in stabilizing the vesicle (18). By altering the structural makeup and production process, niosomes' physicochemical characteristics, including their size, shape, and fluidity, can be readily adjusted (19).

4. Components of niosome:-

Niosomes are generally prepared using three major active components: non-ionic surfactants, suitable additives such as cholesterol, and charge-inducing agents (20).

Non-ionic Surfactant :

Non-ionic surfactants are the primary ingredients in niosomes formulation due to their amphiphilic structure with a polar head and a non-polar tail. Non-ionic surfactants are favored over other surfactant compounds (positive, negative, and amphoteric) because of their increased stability, low toxicity, biocompatibility, and lack of particular handling and storage requirements. (21).

Following non-ionic surfactants are commonly used in niosome manufacturing. 60, 40, 20, 85, and 80 spans, for example 20–40–60–80-year-old tweens (30, 35, 52, 58, 72, and 76) (22).

Cholesterol:
The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) values are important in determining which surfactant molecules to use over niosome synthesis (23). The needed amount of Cholesterol is indicated by the surfactants' HLB value. To counteract the effects of the larger head group on the critical packing parameter (CPP), the concentration of CHOL must be increased as the HLB value rinse over 10 (24). The niosome formulation uses cholesterol to give the niosomes stiffness, the right shape, and conformation. It makes the vesicles more stable (25). Non-ionic surfactants frequently contain a cholesterol, a waxy steroid metabolite, to provide stiffness and orientational order (23). Bilayers become stiffer due to cholesterol's inhibition and slowing of the encapsulated material's release. The distance between neighboring bilayers is increased by the charge seen in multilamellar vesicles , which subsequently increase the volume of the encapsulated material. Additionally, cholesterol can influence the structure of niosome vesicles. By forming hydrogen bonds between its hydroxyl groups and the alkyl chains of surfactant molecules. Cholesterol boosts the stability of bilayers (24).

Charged Inducers :
There are two varieties of charged inducers such as Positive and Negative charge inducers.
Through the induction of charge on the produced vesicles' surface, it improves their stability. It works by preventing vesicles with the same charge from fusing together and by supplying larger zeta potential values. The positive charge inducers that are frequently utilized are sterylamine and cetylpyridinium chloride and negative charge inducers are dicetyl phosphate, dihexadecyl phosphate and lipoamine acid (26). To manufacture niosomes, a variety of surfactants are used, including polyoxyethylene fatty acid esters, sorbitan fatty acid esters, and alkyl ethers and alkyl glyceryl ethers, and block copolymer (pluronic L64 and pluronic p105). Some input energy is needed to create these structures, such as heat or mechanical energy (such as stirring or sonicating) (27).

Components	**Type/Example**
Luliconazole	API (Active drug)
Non-ionic surfactant	Span 60 Span 40 Tween 40 Tween 80
Cholesterol	Lipid
Solvent	Chloroform
Hydration Medium	Phosphate Buffer Saline (PBS)
Charge inducer	Dicetyl phosphte Stearylamine
Preservative	Methylparaben Propyleparaben

5. Formulation Technique:-
Niosome preparation starts with hydrating a mixture of lipids and surfactants at high temperatures. Niosome size reduction is then optional to create a colloidal suspension. There are a number of established, thoroughly researched techniques for making niosomes (28). The different types of niosomes are as follows: Multi lamellar vesicles (MLV) Large unilamellar vesicles (LUV) Small unilamellar vesicles (SUV) (29).

Hand shaking method (Thin film hydration technique)
In a round-bottom flask, the mixture of vesicle-forming materials, such as cholesterol and surfactant, is dissolved in a volatile organic solvent (methanol, diethyl ether, or chloroform). Using a rotary evaporator, the organic solvent is eliminated at room temperature (20°C), leaving the flask wall covered in a thin coating of solid mixture. Rehydrating the dried surfactant film with an aqueous phase at 0–60°C with mild stirring is possible. This procedure creates normal multilamellar niosomes (30). Sometimes, sonication is combined with this method to create niosomes with a certain size distribution (31).

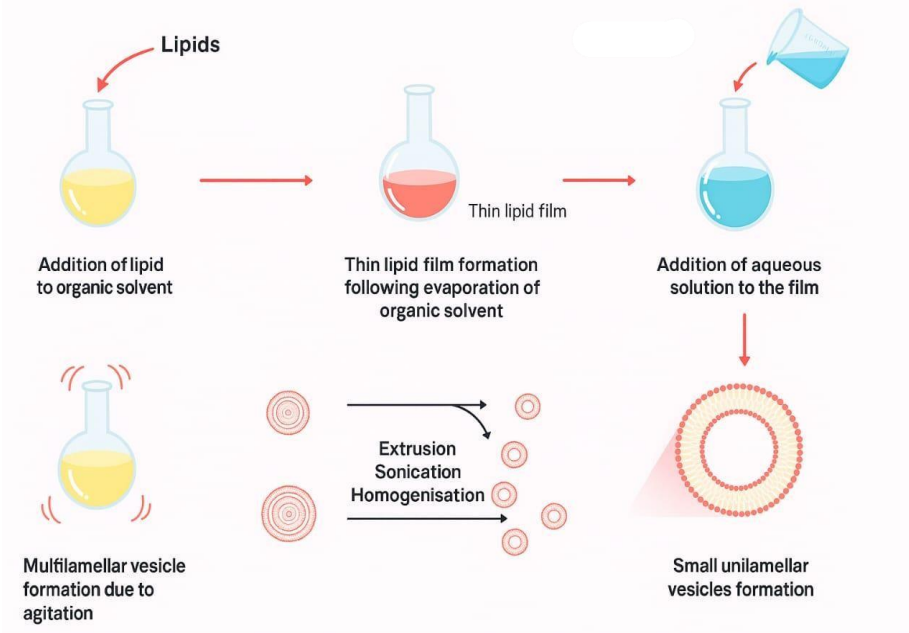


Figure 2: Hand Shaking Method (Thin Layer Hydration Method)

Ether Injection Technique

With the ether injection approach, niosomal components are gradually injected into a heated aqueous phase maintained at 60°C using a 14-gauge needle at a rate of roughly 0.25 ml/min. The formation of larger unilamellar vesicles is most likely due to the slow vaporisation of the solvent, It causes an ether gradient to stretch in the direction of the aqueous-nonaqueous interface. The former could be in charge of the formation of the bilayer structure. The disadvantages of this method incorporate the existence of a tiny amount of ether in the vesicle suspension, which is difficult to remove (32).

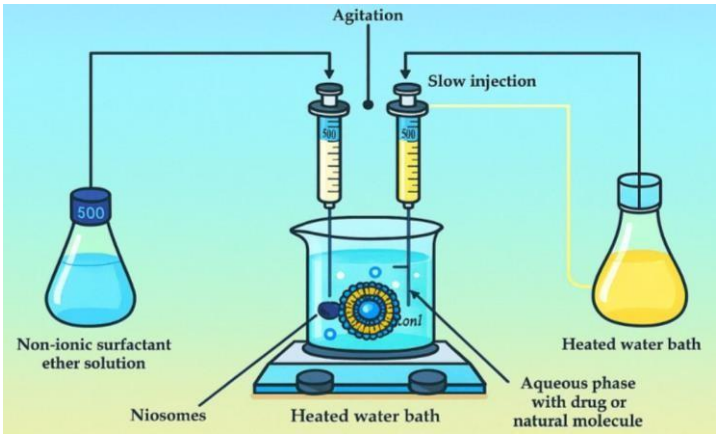


Figure 3 : Ether Injection Technique

Reverse Phase Evaporation Method

In this process, the solution of cholesterol and surfactant is produced in an ether and chloroform combination (1:1). To this, At 4 to 5°C, the drug's aqueous solution is added and sonicated. Phosphate buffer saline (PBS) is added to the resultant solution, which is then further sonicated to create a gel. The solvent is then removed by increasing the temperature to 40°C and lowering the pressure.The PBS is added again and heated on water bath at 60°C for 10 minutes to give niosomes (33).

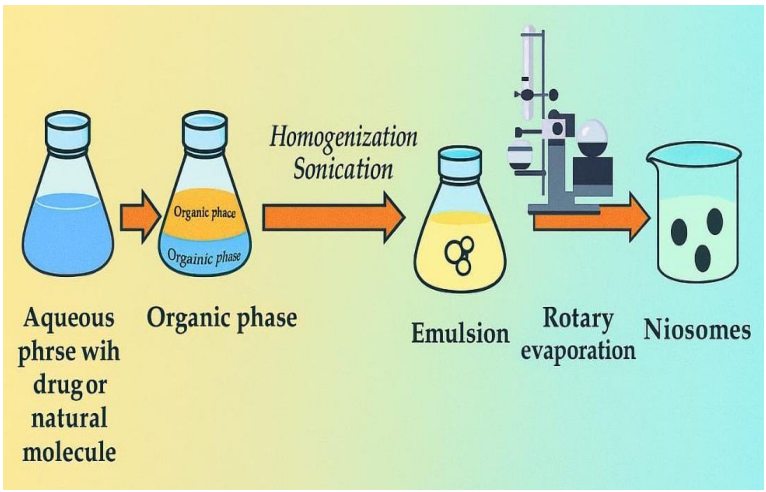


Figure 4: Reverse Phase Evaporation Method

Bubble Method

It's a creative method that removes the requirement for chemical solvents to simultaneously produce liposomes and niosomes. In water, it is immersed to regulate its temperature. It has three necks and a spherical bottom. The 1 It's a creative method that removes the necessity for chemical solvents to simultaneously produce niosomes. It is immersed in water to regulate its temperature. It has three necks and a spherical bottom. The 1st and 2nd necks are equipped with a thermometer and a cooled reflux, respectively, while the 3rd s supplied with nitrogen. At 70°C (pH 7.4), surfactant and cholesterol diffuse concurrently in this buffer. A constant stream of nitrogen containing gas bubble is added to the dispersion necks are equipped with a thermometer and a water-cooled reflux, respectively, while the 3 neck is supplied with nitrogen. At 70 surfactant and cholesterol diffuse concurrently in this buffer. A constant stream of nitrogen containing gas bubble is added to the dispersion to generate niosomes (34).

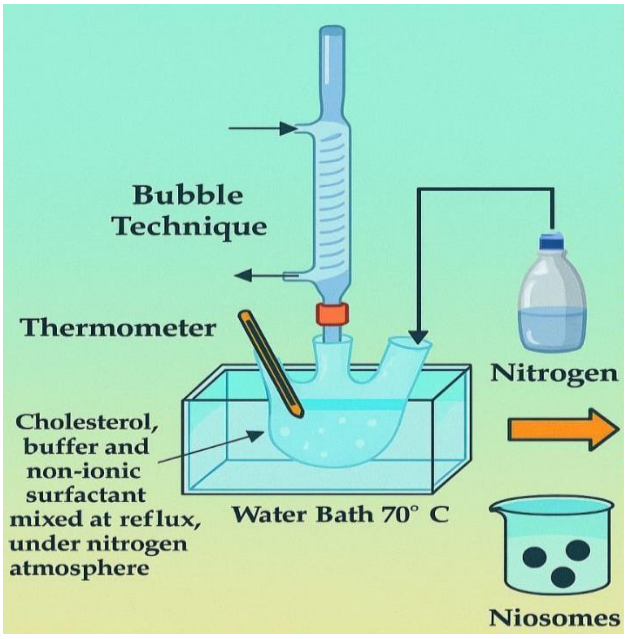


Figure 5: Bubble Method

6. Characterization Parameter :-

Several methodologies may be utilized to investigate niosome features, including as size, dispersion, zeta potential, shape, EE, and release behavior. (35).

• **Size and Morphology**: Dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), freeze fracture replication electron microscopy (FF-TEM)], and cryotransmission electron microscopy (cryo-TEM) are the most used methods for the determination of niosomes size and morphology. DLS provides simultaneously cumulative information of particle size and valuable information on the homogeneity of the solution. The existence of

a single population of scatterers is indicated by a single, strong peak in the DLS profile. In this regard, the PI is beneficial. For colloidal systems, it is less than 0.3, which indicates a homogeneous population. The microscopic approaches are generally employed to describe the morphology of the niosomes (36).

• **Encapsulation efficiency (EE):** EE may be calculated using the following formula and is defined as the ratio of drug molecules encapsulated into niosome nanoparticles to the total sum of drug utilized. EE = (Amount of trapped drug/Total amount of initially added- drug) × 100 % The unencapsulated drug molecules can be separated from the trapped ones using dialysis, filtration, gel chromatography, or centrifugation methods. Spectrophotometry and gel electrophoresis can be employed for determine the loaded drugs. Also, UV densitometry is applied for genetic materials and fluorescence markers are applicable for the biomarker
(35).

• **Membrane rigidity and homogeneity:** Probe fluorescence by using the function of temperature utilized to ascertain the membrane rigidity. Differential scanning calorimetric (DSC), P-NMR, FTIR, and fluorescence resonance energy transfer (FRET) are utilized to ascertain the membrane homogeneity (37).

• **Zeta potential analysis:** Using phase analysis light scattering with a Malvern Zetasizer Nano ZS (Malvern Instruments), zeta potential measurements of the stavudine niosomes were carried out. An appropriate amount of niosomal suspension (50100µL) was diluted with 5mL of filtered water (0.45µm) to achieve an appropriate concentration for analysis. This diluted sample was then injected in to the electrophoretic cell of the Zetasizer, where an electric potential of ± 150 mV was applied. The surface charge of the niosomes was evaluated by measuring the ensuing zeta potential, which gave important details on their stability and colloidal behavior in suspension (38).

• **Niosome stability:** The vesicular system's stability is a problem that affects not just its physical and chemical stability but also its biological stability. This essential metric is utilized to assess the niosomes' potential for both in vitro and in vivo applications. Stability is generally determined by monitoring 18 particle size and zeta potential over time, with variations in these two parameters indicating possible instability. Stability is often determined over three months in different conditions, such as 4C, 25C, 4C at 75% relative humidity, to assess the effect of temperature on stability (39).

• **Bilayer characterization:** Niosomes can be found in unilamellar or multilamellar structures, respectively.Nuclear magnetic resonance spectroscopy (NMR), AFM, and small angle X-ray scattering (SAXS) can all be used to count the number of lamellae. Niosomal bilayer thickness can be determined using energy-dispersive X-ray diffraction (EDXD) in conjunction with SAXS (40).

Evaluation of Niosome :-

• **Homogeneity:**
Niosoms gels placed in transparent beakers were examined visually to check for uniformity. Additionally, their appearance and the existence of any aggregates were examined.

• **Grittiness:**
Niosome gels were examined under a microscope to see whether any visible particles were present.

• **pH:**
The niosomal gels' pH was established by using digital pH meter which was previously calibrated by standard solution prepared by standard capsules of pH 4, 7 and 9.2 respectively. pH measurement of the gels was carried out by dipping the pH electrode of a digital pH meter completely into the gel formulation for 10 min prior to taking the readings in order to allow the pH values to stabilize. The measurement was carried out in triplicate, as well as the three averages readings was recorded.
The electrode was washed thoroughly between each reading .

• **Viscosity:**
The Brookfield viscometer with spindle number 64 was used to measure the viscosity of the niosomal gels. It was spun at 5 rpm for 5 minutes at 25 °C.

• **Spreadability:**
The spreadability of niosomal gels was determined on the basis of “maximum slip and minimum drag” principle, the excess quantity of gel formulation was placed in between two glass slides of length 7.5 cm each. For one minute, a 1000 g weight is left on the top slide to release air between the slides and ensure that the gel is distributed evenly. After removing the weight, extra gel that had stuck to the slides' edges was scraped off. The lower slide (immovable) was fixed on the wooden board.
The upper slide (movable) was attached with a string that was tied with a pan. The
string was passed over a pulley, and the pan was hung from the string. Thereafter 80 g weight was added to the pan, and the upper slide was subjected to pull with the help of string. Spreadability is measured by timing how long it takes to separate the two slides, or how long it takes for the top slide to glide over the lower slide. The tests were conducted three times. The following formula is used to calculate the spreadability. S = m × l t Where, S is the

Spreadability m is that the weight tied to the upper slide (g) l is the length of a glass slide (cm) t is the time taken to separate the slide completely from each other (s)

- **Extrudability:**

When pressure was applied, the amount of gel that extruded from the tube indicated the extrudability of niosomal gels. The formulation was put into a sterile lacquered collapsible aluminium tube of capacity 5 g with 5 mm orifice, and the tube is pressed firmly at the crimped end, and the clamp was used on prevent any rollback. The quantity of extruded gel was meticulously gathered and precisely weighed. The quantity of gel that extruded (in percentage) through the aperture when pressure was applied to the tube was then measured to ascertain extrudability. Three duplicates of the experiment were conducted (20, 21, 22, 24).

- **Drug Content Uniformity:**

To guarantee consistent drug distribution (entrapped in niosomes) in the gel, a predetermined number of gel samples were taken from the tube and weighed accurately 0.250 g of formulation and transferred in a 250 ml volumetric flask each and diluted with
100 ml methanol (as it also breaks the niosomal structure). The flask was sonicated for about 10 to 15 minutes to fully extract the medication after being aggressively agitated for 30 minutes on a mechanical shaker to distribute the gel. Then these solutions were filtered and were analyzed by UV-Vis spectrophotometer. Drug content was determined from the standard calibration curve of drug(41).

• Particle size:

Vesicle size determination can be carried out using an optical microscopy with a caliberated eyepiece micrometer. Approximately 200 niosomes were measured one at a time, average was taken, and their size range, mean diameter were
calculated(42).

7. Challenges and Limitation:-

Despite promise, several challenges exist in developing Luliconazole niosomal gels.

1. Achieving high drug entrapment efficiency for luliconazole within niosomes can be challenging due to its lipophilic nature and solubility limitation: Controlling vesicle size and ensuring uniformity in particle size distribution is crucial for consistent drug release and penetration but is technically demanding. Choosing the right surfactant, cholesterol ratio, and hydration medium is essential, and small changes can significantly affect the niosome properties.
2. Niosomes may undergo aggregation, fusion, or leakage of the encapsulated drug during storage, especially under temperature fluctuations. Luliconazole or surfactants used in niosomes may degrade over time, leading to loss of efficacy. Ensuring long-term stability and acceptable shelf-life is often more difficult compared to conventional formulations.
3. While niosomes are intended to enhance skin penetration, actual in vivo performance may vary based on formulation and skin conditions. Achieving a controlled and sustained drug release profile that matches the therapeutic needs without causing irritation can be difficult. Some surfactants used in niosomes may cause irritation or allergic reactions upon topical application.
4. Scaling up from lab to industrial production while maintaining uniform vesicle properties is a significant challenge. Manufacturing niosomal formulations involves more complex processes compared to conventional creams or gels, increasing cost.
5. Patient Compliance: The texture, feel, and application experience of niosomal formulations might not match conventional topical products, affecting patient compliance.

8. Conclusion :-

The development of luliconazole-loaded niosomes offers a novel and effective strategy for enhancing the topical delivery of antifungal agents. Niosomes, as non-ionic surfactantbased vesicular systems, provide several pharmaceutical advantages such as improved drug encapsulation efficiency, controlled release profiles, enhanced skin permeation, and reduced systemic exposure. The incorporation of luliconazole into niosomal carriers has demonstrated improved antifungal efficacy in various preclinical studies, demonstrating their capacity to get beyond the drawbacks of traditional topical formulations. This review has emphasized the role of formulation parameters—including surfactant type, cholesterol ratio, and preparation techniques—in influencing the physicochemical properties and performance of niosomes. Additionally, the existing body of research supports the use of niosomal systems for enhancing patient compliance through reduced dosing frequency and improved therapeutic outcomes. Despite these promising findings, further research, particularly in vivo evaluations and clinical trials, is essential to validate the long-term safety, stability, and therapeutic superiority of luliconazole-loaded niosomes. With continued advancements, this nanocarrier-based approach holds great promise for the development of more effective and patient-friendly antifungal therapies.

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