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Improving the topical delivery of antifungals by using nano-vesicular drug delivery systems: the case of novasomes

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Abstract

Topical delivery of antifungal is widely used for treating superficial and deep skin mycosis. However, conventional formulations have some limitations, including low skin penetration, short retention times at the site of application, and reduced therapeutic efficacy, as well as topical adverse effects such as irritation, erythema, burning, itching, sensation, stinging, and dryness at the application site. Furthermore, prolonged application may lead to contact dermatitis, scaling, or peeling. To overcome these limitations, novel drug delivery systems like novasomes have gained increasing attention. Novasomes are multilamellar nano-vesicular systems that consist of non-ionic surfactants, free fatty acid, in addition to cholesterol as a membrane stabilizing agent. The presence of free fatty acids (FFAs), such as stearic acid or oleic acid, in their structure acts as a permeability enhancer agent, making the novasomes more flexible and tissue permeation compared to the older niosomes or liposomes. Furthermore, the novasomes have more drug loading and stability in contrast to other nanovesicles. These characteristics make the novasomes a target for improving the topical and transdermal delivery of antifungals. When applied topically, the novasomes can interact with the stratum corneum, enhancing the skin permeation and improving the topical delivery. Several studies demonstrate that the novasomes have a prolog drug release profile, a higher cumulative drug release percent compared to conventional creams or gels. Additionally, the novasomes are formulated from biocompatible and skin-friendly components. Overall, the novasomal drug delivery systems represent a promising strategy for topical antifungals, offering safe, effective, and more patient adherence.

Keywords. Skin mycosis, Topical antifungals, Novasomes, Skin permeation enhancers, and dermal targeting.

Introduction

Skin mycoses are among the most common fungal infections worldwide [1]. The high prevalence of superficial mycotic infections, which are around 20-25% of the patients, is skin fungal infections [2]. In the last decade, there has been an increase in opportunistic fungal infections due to many reasons, like a high number of susceptible hosts, the use of immunosuppressive agents, and frequent use of antimicrobial agents that affect the body's native immunity [3]. The most common species of fungi that cause invasive and deadly superficial infections are Candida, Aspergillus, and Cryptococcus species. Aspergillus fungitaus remains the most common fungal infection in some populations [4] while infections caused by Candida species are the major causes for morbidity and mortality among inpatients. Furthermore, a wide range of clinical manifestations can be detected from superficial, mucosal to life-threatening cases [5]. The presence of dermatophytosis (tinea infection) on different skin areas, which makes it have diverse names according to its infection site, like tinea pedis (athletes' foot) on the feet, tinea unguium on the nails (onychomycosis), tinea capitis on the scalp, tinea cruris on the groin, and tinea corporis on the body. The most common dermatological infections in children are caused by superficial tinea [6].

Many reasons make the skin a target for dermatophytosis. Firstly, many types of enzymes or proteins produced by dermatophytes play an essential role in keratinous skin layers [7]. Secondly, the topical and sub-topical high temperature and humidity, as well as other predisposing factors for dermatophytosis [8]. Thirdly, patients living in low socioeconomic conditions are more prone to mycotic infections than those living in high to moderate socioeconomic conditions [9]. As well as, close contact with animals that are already infected with fungal infection increase the infection chance [10] etc...One of the most challenge during the management of superficial fungi is that dermatophytes attack the subcutaneous or keratinized structures of the skin in early phases [11] then penetrate to deeper layers of skin which is called "subcutaneous mycosis" via skin desquamation [1].

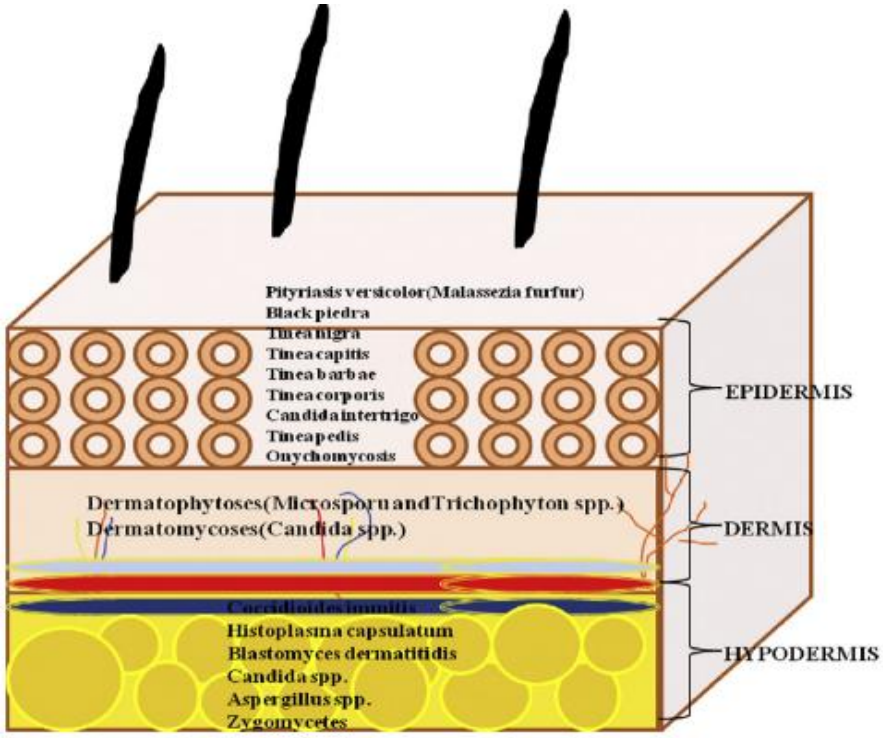

Figure 1. The schematic representation of the skin layer with different mycoses[2]

The strategies for treating skin dermatophytosis

Skin dermatophytes may be treated with a topical or systemic or both options[3]. The preferred option focuses on the use of topical antifungals that are classified as polyenes, imidazoles, and the allylamine/benzylamine drugs[4]. The management with topical antifungals is preferred for" localized" infections or those with limited spreading. Although the patient fulfillment is low, practically with the antifungals that need multiple frequencies during the day to remain at therapeutic levels [5].

Drawbacks associated with conventional topical formulations

The available traditional topical formulations include creams, ointments, powders, gels, etc. It was found that these formulations cause topical adverse effects like burning, redness, and swelling[6, 7]. Furthermore, less fungal sensitivity to the existing antibiotics, incomplete remission, and a high rate of recovery[8]. Besides, the duration of treatment for dermatophytosis is usually 2-4 weeks for complete remission with multi-daily use, which may impair patient adherence[9]. To overcome the drawbacks associated with conventional topical antifungals, novel drug delivery systems are developed for encapsulating the drugs.

Novel delivery systems for topical antifungals

In the last decades, the evolution of nanotechnology has occupied the pharmaceutical drug development owing to the nanoparticle that can be used as a drug carrier, which can improve the pharmacokinetic as well as the pharmacodynamic features of the drugs in many ways, like enhancing the drug solubility, permeability and stability,

reducing the side effect, decreasing the overall effective dose, and improving targeting[10]. The most common carriers used for this purpose are as follows:

Solid-lipid nanoparticles (SLNs)

Theyare nano-sized lipid carriers in which the active ingredient is dispersed in the lipid matrices core. It usually consists of solid lipid and may contain surfactants. These lipid particles are fabricated by hot homogenization or one of the microemulsion techniques[11, 12]. Actually, these delivery systems can protect the loaded APIs from chemical degradation, and provide controlled release for the drug, low risk of toxicity (biocompatible) as it is made from the same biological lipid [13]. Additionally, lipid carriers such as SLNs or nanostructured lipid carriers (NLCs) improve the topical delivery of the drugs by increasing the skin permeation[14]. In a research study on the development of controlled-release clotrimazole-loaded SLN and NLC, these formulations were fabricated using a high-pressure homogenizer technique. The study concluded that NLC has more encapsulation efficiency than SLN due to their liquid contents, at the same time faster release profile than SLN [15]. The main drawbacks include low stability and EE% compared to other nanoparticles.

Microemulsions

Microemulsions are colloidal systems that are optically transparent and thermodynamically stable, and are formed spontaneously by mixing of lipid, water, and surfactants or co-surfactants, with a droplet size of 0.1–1.0 μm. These preparations are either w/o or o/w; this mainly depends upon the type of emulsifier agent that is used[16]. These types of drug carriers have several advantages, such as improving the drug solubility, stability, permeability, low cost, and high biocompatibility. They can be used topically or transdermally due to the presence of oils and surfactants that facilitate drug penetration through the subcutaneous layer[17]. Voriconazole microemulsion was prepared for topical delivery for curing deep skin invasive fungal infections, where the permeation enhancer is used to improve the penetration of the drug, called oleic acid or sodium deoxycholate[18].

Nanoemulsions

Nanoemulsions are transparent, isotropic, thermodynamically stable dispersions with droplet sizes of 5-200 nm, also termed as ultrafine emulsions, submicron emulsions, or miniemulsions. [19]. Various properties make these pharmaceutical immiscible systems used in topical applications, like small droplet size with large surface area, good biological tissue adherence, and they can be utilized for hydrophilic and hydrophobic drug formulation[20]. Clotrimazole formulated as nano-emulsion by using (10% labrafac® lipophile, 60% labrasol®:capryol® 90 mixture (ratio 4:1), and 30% propylene glycol) to apply topically for treating candidiasis, where it was shown droplet size range is 153-186 nm, narrow polydispersity index (PDI), negative zeta potential (ZP), biocompatible pH values, and the antifungal activity is superior when compared to conventional products[21].

Microsponges

They are polymeric microspheres used to prolong the duration of action of topically applied drugs. These particles are porous, which can deliver the drug with a minimum dose, low side effects, high stability, and sometimes modify drug release. These pellet particles are 10-25 microns in diameter. Microsponges Delivery System (MDS) is applied in the cosmetic, over-the-counter

medications, and sunscreens[22-24]. A potent antifungal agent like oxiconazole nitrate is topically used as a cream or lotion for treating skin fungal infections like tinea corporis and tinea pedis. These traditional formulations have some undesirable side effects, like blistering, burning, erythema of the skin, soreness, swelling, and itching. This shows that patient compliance improvement supervenes by formulating APIs with novel delivery systems that provide formulations with minimal side effects, small doses, and low frequency. In fact, microsponges are selected as a novel carrier for encapsulating oxiconazole nitrate, which is then formulated as a gel dosage form. This formulation exhibited significant drug permeation to deep skin layers[25, 26].

Micelles

Micelles are self-assembled systems that are formed from aggregations of amphiphilic copolymers in aqueous media. The core of these micelles is hydrophobic, and the shell is hydrophilic. Polymeric micelles have been extensively studied since the 1990s for the delivery of various API classes, including cosmetic agents, medical agents, diagnostic agents for cancer, such as nucleic acids, and cytotoxic drugs[27, 28]. In a study for developing a polymeric micellar gel system for luliconazole antifungal to advance its topical activity against Candida infection. The properties of the optimized formulation involved a particle size within 226 nm, a PDI of 0.153, a ZP of 30 mV, and an entrapment efficiency (EE) of 88.38%. In addition, one of the formulations exhibited higher antifungal activity with minimum inhibitory concentration, more localization, and skin retention[29].

Nano-vesicular carriers as DDSs for topical antifungals

Liposomes

Liposomes are spherical vesicles developed by using amphiphilic lipids that are arranged as bilayers, where the core of these vesicles is hydrophilic and in between the two layers is hydrophobic. Both hydrophilic and hydrophobic moieties can be loaded within these nanocarriers. According to the number of bilayers involved in the structure, these carriers can be either unilamellar or multilamellar liposomes. Various types of active moieties can be considered as candidates for these lipid vesicles, such as small molecules, genes, peptides, and monoclonal antibodies[30-32]. Several antifungal drugs approved in the U.S. and European Union, such as Amphotericin B-liposome, was introduced in the 1990s as an attempt to replace the traditional formulation that had solubility problems [33, 34]. Liposomes are deliberately appropriate topical drug delivery systems as a result of their ability to adsorb on the top layer of skin or penetrate deep layers of skin. On the other hand, liposomes provide a controlled release profile, increase the drug residence time on the target site, and reduce the side effects associated with conventional formulations by minimizing the overall dose of APIs[35]. Liposomal gel of ketoconazole appears high retention time in the skin when compared with available conventional formulations, gel, cream[36].

Ethosomes

Ethosomes are vesicular nanocarrier structures that consist of phospholipids and 20 - 45 % of ethanol[37]. The presence of ethanol in their structure can fluidize the stratum corneum intercellular lipids and allow penetration of the antibiotic more deeply than conventional liposomes. Econazole nitrate-ethosomes loaded gel was developed to improve its antifungal activity [38].

Transethosomes

They are advanced vesicular systems where the edge activator would add to the ethosomes' structure. This modification makes them more permeable than corresponding ethosomes or transferosomes. Voriconazole-loaded transethosmal gel was fabricated to enhance the antifungal activity of the former drug[39]

Transferosomes

Transferosomes are also called deformable vesicles. Edge activator will add to the liposome structure to make them more permeable than general liposomes. Various materials can be used as edge activators, like sodium deoxycholate, tween 80, 60, 20, and span 80, 60, 65, etc.[40]. Clotrimazole and miconazole-loaded transferosomes were both developed to improve their topical activity[41].

Niosomes

Niosomes are nanocarrier drug delivery systems that consist of nonionic surfactant and cholesterol. Where these amphiphilic molecules arrange themselves in a vesicular, spherical shape called niosomes. In fact, liposomes were developed before the niosomes, but due to some disadvantages like toxicity, low stability, especially at different pH. So, the development of niosomes as an alternative is crucial. The presence of nonionic surfactants instead of phospholipids makes these vesicles more biocompatible, safe, and stable, and their similarity to liposomes is related to the type of loaded APIs, which can be hydrophilic or hydrophobic[42-44]. The Spans® (20, 40, 60, 80, and 85), Tweens® (20, 40, 60, and 80), and Brij® (30, 35, 52, 58, 72, and 76) are recurrently used as non-ionic surfactants in the fabrication of niosomes. The cholesterol used as a stabilizer agent provides rigid, stable vesicles[45]. Luliconazole is a topical antifungal used for treating Candida albicans, where it was formulated as a niosomal gel as a mode for improving its solubility and permeability, minimize its toxicity. The results of this study exhibited particle size within nanometers, EE within 88%, with a sustained release profile up to 24 h[46].

Proniosomes

They are dry surfactant-coated free-flowing vesicles. This surfactant can act as a permeation enhancer to improve its activity. Furthermore, these dry powders of niosomes make them more convenient for transportation, storage, processing, and packing[47]. Mahajan etal. Formulated and evaluated ciclopirox proniosomal gel for topical skin delivery. Span®, cholesterol, and lecithin are used for preparing ciclopirox-loaded Proniosomes[48]. The results showed the formulated nanovesicles had more skin permeation and residence time in comparison to marketed formulations.

Spanlastics

They are modified niosomes in which an edge activator is incorporated into the niosomal structure. Surfactants like spans®, in addition to edge activator tweens, are used in their structure. These novel nano-carriers were firstly developed by Kakkar and Kaur, where these vesicles were loaded with ketoconazole by utilizing spans and tween 80. Elsherif et al. developed terbinafine HCL-loaded spanlastics for the treatment of onychomycosis**.**

Biosomes

Biosomes are vesicular systems similar to niosomes except for bile salt incorporation. In fact, incorporating such additional material in their composition improves the flexibility of the vesicles, making them more permeable than corresponding conventional niosomes[49]. Sertaconazole-loaded bilosomes are developed by Eldemir et.al. The former showed superior activity against conventional Sertaconazole gel[50]

Cerosomes

They are niosomes coated with a ceramide lipid layer**.** The presence of this moiety makes the niosomes more permeable through the applied area. Furthermore, ceramides are more effective skin treatments when developed in a form that resembles the lipid bilayer of skin subcutaneous tissue[51]. Fenticonazole nitrate is an azole antibiotic that has activity against mixed mycotic and bacterial infections, so reported for the treatment of both skin and vaginal infections. PEGylated Cerosomes loaded with Fenticonazole were formulated to optimize their activity [52].

Terpesomes

Novel ultra-deformable liposomes that contain phospholipid and cholesterol, in addition to terpenes that act as a permeation enhancer. Furthermore, they can act as antifungal and antibacterial due to their accumulation in target tissue cells. In a study to developed formulation targeting vaginal candidiasis, Fenticonazole nitrate is loaded with terpenes in ultra-deformable liposomes[53]

Novasomes

Novasomes are a patent, novel technology of a vesicular delivery system that was developed by Novavax. IGI laboratories[54, 55]. Novasomes are a modified form of the liposome and niosome vesicles with a 2-7 bilayer wall [56], figure 2. narrow vesicular diameter 0.1-1 microns[57], and high nuclear capacity for more drug loading[58]. Furthermore, novasomes contain molecules that have a head group linked to a hydrophobic tail group. They consist of free fatty acid, nonionic surfactant, in addition to cholesterol[59]. In the novasomal description, the hydrophilic head group of the molecules points outward while the hydrophobic tails are found in between the layers, so that lipid-soluble molecules are found between the bilayer membrane and the water-soluble molecules found in the core of the novasomes[60]

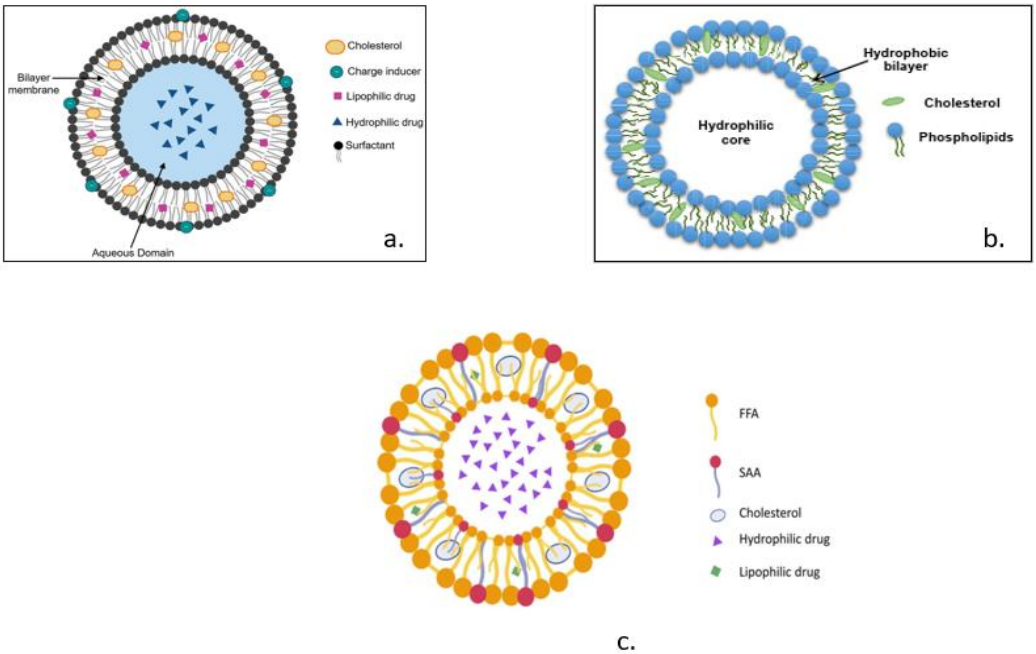

Figure 2. Graphical representations of the a) Niosomes[61], b) liposomes[62], and c) Novasomes[56]

Advantages of Novasomal Vesicles

A variety of characteristics make the novasomes a target for various types of drugs, such as their ability to load with hydrophilic and hydrophobic moieties. Furthermore, sometimes be filled with both types, similar to liposomes. Moreover, the presence of surface charge improves repulsion and stability. In addition to their ability to adsorb on the body surfaces like the skin, there is an increase in the retention time at the target site. At the same time, the novasomes' amorphous core can be loaded with up to 80-85% of APIs. A continuous or controlled release can be achieved for drug release. Subsequently, it prolongs the duration of action and reduces the frequency of administration [54, 63]. Regarding novasomes stability at a wide range of pH values (2-13) and a temperature range from liquid nitrogen to water boiling point, studies showed that compared with liposomes (which are prone to oxidation and hydrolysis of phospholipids), novasomes contain non-ionic surfactants and cholesterol, making them less sensitive to oxidation, more resistant to leakage during storage and this results in longer shelf life than conventional liposomes. The thicker and multiple bilayer membranes of novasomes provide slower drug diffusion and prolonged release profiles. This is superior to liposomes, which often show rapid drug leakage, and niosomes, which may have less rigid bilayers. Furthermore, novasomes can fluidize the stratum corneum lipids and improve drug penetration through the skin, which gives novasomes an advantage over liposomes and conventional niosomes in dermal delivery systems[64].

Composition

Novasomes can be considered as an innovative modified structure of the old liposome or noisome vesicular carriers. Where the liposomes consist of phospholipid and cholesterol, whereas niosomes consist of non-ionic surfactant and cholesterol. On the other hand, the novasomes contain fatty acid, surfactant, and cholesterol[58].

1. **Free Fatty acids (FFAs).** Incorporating FFAs in the novasomes structure considers the building unit and regards the novelty in liposome/niosome structure-modifying technology[57]. The main role of this agent is to enhance the fluidity of the skin layers, modify the skin phospholipids, and improve membrane permeation[65]. Usually, various types of FFAs, like stearic acid or oleic acid, and sometimes palmitic acid are used in the fabrication of novasomes. The selection of free fatty acid is a critical point as it controls the properties of the resultant novasomes. Oleic acid produces vesicle with small size, narrow PDI and high ZP, but more leakey and with low EE%. On the other hand, stearic acid incorporation can lead to larger heterogeneous vesicles but higher EE%. Although stearic acid and oleic acid are both long chains hydrocarbon with C-18 structure, stearic acid is a saturated FFA, while oleic acid is unsaturated. This difference in the structure of FFA has a significant impact on novasomes size, PDI, ZP, and EE% [66].
2. **Surfactants**. In fact, using the surfactants with free fatty acid makes the backbone in the novasomes formulations[58]. Amphiphilic non-ionic surfactants are more frequently utilized in the fabrication of vesicular carriers like niosomes, novasomes, etc. Actually, the

tendency of these surfactants to form bilayer membranes rather than micelles not only depended on their hydrophilic and hydrophobic balance (HLB) values,but also on their chemical structure[67]. In addition to their main function as membrane-forming agents, they share the same functions of FFAs[65]. Span 60, Span 80, Brij 57, and Brij 35 were utilized as surfactants. The selection of a specific type of surfactant depends mainly on the purpose and the quality of the engineered vesicles. Novasomes produced by Brij 35 were normally small, uniform, but more leaky and less stable. It was suggested that Brij 35 reduces the surface tension between the vesicles. The hydrophilic nature of the Brij 35 (HLB=16.9) makes it possible to prepare novasomes having a small size, but they are more leaky.[68].On the other hand, span 60 produces larger vesicles with wide PDI and higher EE%. The lipophilic nature (HLB=4.7) and packing carbon chain of span 60 is assumed to be responsible for these structural changes [66].

3. **Cholesterol.** Cholesterol is considered the membrane-stabilizing agent, and it is one of the components that is continuously used in vesicular systems. Someplace, it reinforces the bilayer membrane[67]. The concentration of cholesterol affected the EE % [69]. TarekM.Ibrahim et al. demonstrated a significant increase in the EE% was achieved as the cholesterol concentration increased, where the cholesterol intercalates between the molecules and produces more rigid bilayer vesicles[70]. Furthermore, increasing the cholesterol concentration significantly reduces the vesicle size as reported by Mai Ahmed Tawfik et al. [71].

Novasomes preparation

Recently, specific devices have been used in the fabrication of novasomes. Where the high share production is considered the main principle for these devices.

1) **Microfluidizer:** It is the most common device used for this purpose, where the selected materials are mixed, heated, and blended to form the lipophilic phase. Subsequently, mixed

with the aqueous phase under high shear. A specific procedure is used for pumping the mixture into the device to produce the novasomes within seconds. Examples, Controlled release products, sustained release fragrant and emollient oils allowed to be formed by this efficient technology[58].

2) **Thin film hydration method (TFH). This** method is mentioned in detail in zolmitriptan-loaded novasomes[55]. In this method, the surfactants are mixed with the active ingredient at specific ratios, then dissolved in a few volumes of a selected solvent, such as chloroform (10 mL), and transferred to a 250 mL round-bottom flask.

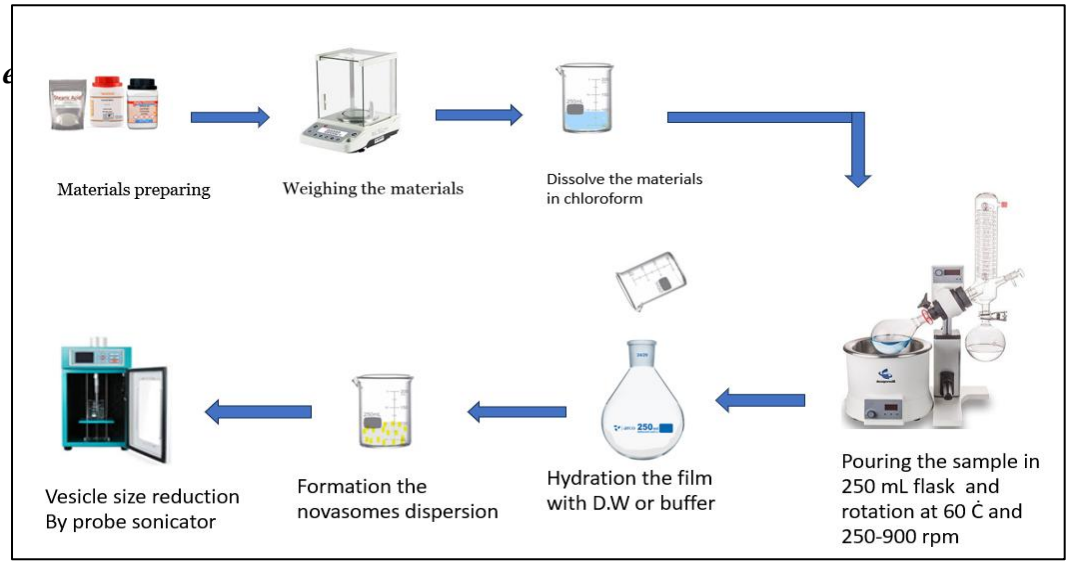

Figure 3. Schematic representations for the TFH method step by step.

Subsequently, the solvent allows for evaporation under low pressure and specific temperature (60 ˚C) to form a thin film on the flask. After that, the film is diluted with (10 mL) Phosphate buffer system or distilled water and continuously stirred for an appropriate time till the novasomal vesicles are formed. Finally, the nanosuspension that contains these novasomes is stored in a refrigerator. Posaconazole-loaded novasomes formulated by this method[72].

3) Solvent injection method (SIM). At a temperature of 60 ˚C, the surfactant, free fatty acid, cholesterol, and or the drug dissolve in diethyl ether or ethanol. After that, the resulting solution is injected in to aqueous solution of distilled water or buffer containing the drug or alone by using a needle of 14 gauge size. Then, solvent evaporation resulted in the formation of novasomes[58]. In the study o of terconazole-loaded novasomes, ethanol alcohol is utilized instead of ether[66], where Mosallam et al used this method that was adopted via Kakkar and Kaur. t[73] to formulate Terconazole-loaded novasomes. Another antifungal, like fluconazole[74] is developed by such a method as novasomal product.

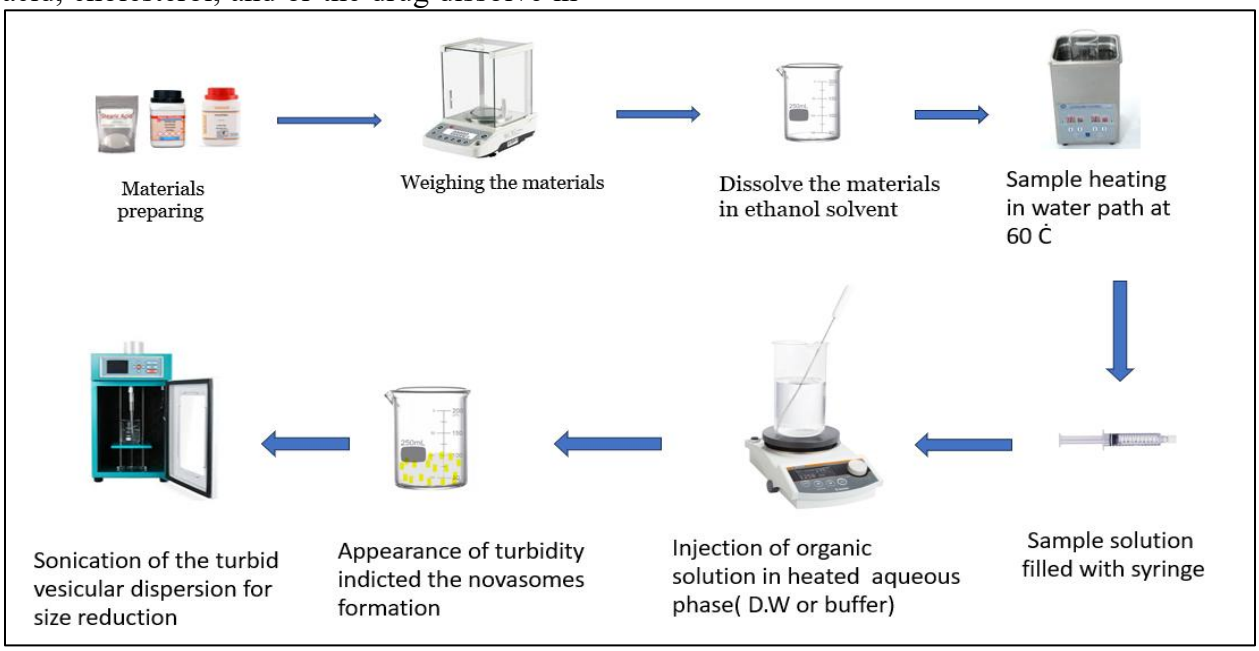

Figure 4. Schematic representation for EIM, step by step.

4) **Other methods** for nonspecific vesicular system preparations are mentioned in the published data in detail, like the hand shaking method, reverse phase evaporation technique, multiple membrane extrusion method, and sonication method [54].

Drug release mechanism

According to literature, the novasomes do not have a perfect array of bilayers, but instead their membranes contain lipoprotein channels (vacancies) for the passage of the active moiety. Where the loaded moieties move within and between the membranes by continuous jumping movement, resulting in lateral movement of voids in the bilayer. Furthermore, the novasomes' structural nature provides control or sustained release profile [54, 55].

Applications of novasomes. Several marketed preparations as novasomes, are available in the market.

1. Antifungal, humectant (1 % Miconazole Nitrate Novasomes).
2. Antibacterial, keratoplastic (2 % Chlorhexidine Gluconate, Sulfur, Salicylic Acid Novasomes).
3. Smallpox vaccine formulated as a target for Novasomes technology, Novasomes® [64].
4. AcneWorx consists of 2 % Salicylic Acid novasomes microvesicles for acne [54,64].

Table (1). The available scientific research about the novasomes is published data.

No.	Active moiety	Application(s)	Objective of the study	Reference	Publication Year
1	Mahonia aquifolium extract	Psoriasis, eczema, etc.	Improve its topical retention time & activity	[63]	2009
2	Influenza virus-like particles (VLPs) HA, NA, and M1 proteins	Avian influenza viruses	Novasomes adjuvant for safe and effective vaccines	[75]	2007
3	Placenta- extract	Hair	Improvement of hair growth	[76]	2023
4	Agomelatine	Depression	Improving transdermal and bioavailability	[65]	2021

5	Fluvoxamine	Depression	Improve its bioavailability through trans-nasal delivery	[77]	2023
6	Terbutaline sulfate	Asthma	Improve bioavailability and prove sustained release	[78]	2022
7	Zolmitriptan	Migraine headache	Improve nasal delivery to the brain bypass BBB	[55]	2016
8	Diacerein	Osteoarthritis	Improve skin permeation and sustained release.	[79]	2023
9	Quercetin & selenium	Anti-cancer	Improve bioavailability and synergize their activity	[68]	2022
10	Curcumin	Skin cancer	localized delivery, dose reduction, alleviated side effects	[80]	2023
11	Rasagiline mesylate	Parkinson disease	Transdermal delivery for bioavailability enhancement	[81]	2024

12	linagliptin	Alzheimer's disease	Improve its bioavailability through intranasal brain delivery	[82]	2025
13	Lornoxicam	Ulcerative colitis	Optimization and improvement the formulation	[83]	2025
14	Niflumic acid	Otitis media	Improve delivery through the tympanic membrane	[84]	2024
15	Fenticonazole nitrate	Fungal candidiasis	Potentiate the antifungal activity	[85]	2022
16	Fluconazole	Fungal candidiasis	Improve the topical activity against skin mycosis	[74]	2022
17	Terconazole	Skin candidiasis	Improve the topical activity against skin mycosis	[66]	2021
18	Posaconazole	Fungal candidiasis	Improving the topical use of such antifungal	[72]	2024
19	Nystatin	Fungal mycosis	Improve its topical application	[86]	2025

In this table, various medicinal moieties are used as candidates for a novasomal delivery system as an alternative to niosome or liposome, where the results showed the particles in nano-size with higher EE %, and more stability. Furthermore, the presence of the nonionic surfactant with fatty acid in their structure makes the novasomes act as a permeation enhancer. Therefore, the novasomes improve the permeability and bioavailability of the drug. Fluconazole and terconazole antifungals are studied as novasomal-loaded carriers for topically applied on the skin as a way for improving their local activity, increasing their residence time, skin targeting, and reducing the overall dose. In fact, other antifungals can be considered as a target for novasomal delivery system.

Novasomes characterization

Characterization of the novasomes is a critical step for evaluating their physicochemical properties, stability, and overall performance. Vesicle size, PDI, and the surface charge are considered the main preliminary parameters for selection. Further tests for confirming the vesicle morphology, EE, drug release profile, stability, and bioavailability. Novasomes appear to have more desirable parameters compared to the former liposomes. Fluconazole is an antifungal drug used for topical mycosis, where it was formulated as novasomes by

Iman Fatima et al. with vesicle size of 110 nm, 0.4 PDI, -24 ZP and 94.45% EE, while the liposomes developed by B. V. Mitkari et al with a 3.03 µm, -55 ZP and 57% EE. The difference in these parameters makes novasomes more skin-permeable, stable, with enhanced efficacy[74, 87].

Novasomes are designed to modulate drug release through their multilamellar vesicular structure, which acts as a barrier to rapid drug diffusion. This structural complexity allows for sustained and prolonged release of the encapsulated drug compared to conventional formulations. The release of the drug from novasomes generally occurs through diffusion across the lipid bilayers and, in some cases, through gradual erosion or destabilization of the vesicular membrane. The presence of cholesterol and FFAs within the novasomal structure enhances membrane rigidity, thereby reducing drug leakage and contributing to a controlled release profile. Hydrophilic drugs are mainly released from the aqueous compartments of the vesicles, while lipophilic drugs partition within the lipid bilayers and exhibit slower release rates. For terconazole-loaded novasomes, the cumulative drug release was 96% through 8 hours[66]. Overall, the controlled drug release characteristics of novasomes highlight their potential as efficient and reliable vesicular carriers for enhanced drug delivery.

Skin permeation studies are commonly conducted using Franz diffusion cells with excised animal or human skin. Parameters such as cumulative drug permeated, steady-state flux, and permeability coefficient are calculated to assess the efficiency of novasomal formulations. Compared to conventional formulations or non-vesicular systems, novasomes typically demonstrate significantly higher drug permeation and prolonged drug retention within the skin. The enhanced skin permeation of novasomes can be attributed to several mechanisms. First, the non-ionic surfactants present in novasomes act as penetration enhancers by fluidizing the lipid matrix of the stratum corneum. Second, the nanosized vesicles increase surface contact with the skin, promoting closer interaction and improved drug deposition. Additionally, FFAs within the formulation further disrupt the ordered lipid structure of the stratum corneum, increasing skin permeability. In the study of terconazole-loaded novasomes, the cumulated drug in skin was 2-fold compared to the terconazole suspension and 1.7-fold compared to the former niosomes formulation. The higher skin accumulation can be related to the high deformability of the novasomes compared to niosomes, that faciliting the passage through the stratum corneum and brings the drug to the deeper layer[66].

The clinical study is a very critical step to evaluate the efficacy and safety of the Novasomal formulation. In the study of the terconazole-loaded novasomes, two groups of patients were considered, where the first group was treated with the novasomal formulation, which showed complete remission within 10 days. On the other hand, the second group that received a placebo didn’t show any improvement and remained positive for Candida albicans infection[66].

Stability studies are essential to confirm that novasomes maintain their physicochemical properties and performance over time, which directly impacts their *in vivo* reliability and therapeutic efficacy. Monitoring vesicle size, PDI, and ZP ensures that novasomes resist aggregation or fusion during storage, which is critical for maintaining consistent *in vivo* behavior. Besides, evaluation of drug content and possible degradation confirms that the encapsulated drug remains chemically intact, ensuring a reliable dosing. Encapsulation efficiency, retention, and stability studies verify that the drug remains

entrapped within the vesicles, preventing premature leakage that could reduce *in vivo* effectiveness. In addition to thermal and storage stability, assessing novasomes under different storage conditions (e.g., refrigerated and room temperature) helps to predict shelf life and performance after storage and administration. Previous studies of drug-loaded novasomes stored at 4 °C and 25 °C for 3 months showed insignificant changes in vesicle size, PDI, ZP, and EE%[66].

Summary and future perspectives

In summary, this review shows that novasomes are potential drug delivery systems that can be fabricated using various types of drugs and excipients (hydrophilic, lipophilic, or even amphiphilic). Different routes of administration for novasomes are applicable, such as oral, transdermal, topical, pulmonary, and intranasal delivery. The novelty of novasomes as a modified niosome can be highlighted as they have more stability, tissue permeability, and even more entrapment efficiency when compared to liposomes or niosomes. The future development is expected to focus on more studies and approved products using these nanocarriers compared to the older nanovesicles. Add to that, new methods and characterization tools can be developed for optimizing the formulation parameters and selecting the most compatible and sustainable carriers for novasomes. Finally, the clinical studies are essential and crucial to support the formulated novasomal drug delivery systems as safe and effective pharmaceutical products.

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تحسين توصيل مضادات الفطريات إلى الموقعالمحدد باستخدام أنظمة توصيل الأدوية النانو الحويصلية: حالة النوفاسومات

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الملخص

يستخدم توصيل مضادات الفطريات الموضعية على نطاق واسع لعلاج الفطريات السطحية والعميقة للجلد. ومع ذلك، فإن التركيبات التقليدية لها بعض المحددات، منها انخفاض اختراق الجلد، وقصر أوقات الاحتفاظ في موقع التطبيق، وانخفاض الفعالية العلاجية، بالإضافة إلى الآثار الجانبية الموضعية مثل التهيج، والاحمرار، والحرقان، والحكة، والتحسس، واللسع، والجفاف في موضع التداوي. علاوة على ذلك، قد يؤدي وضع العلاج لفترة طويلة إلى التهاب الجلد التماسي أو التقشير. لتجاوز هذه السلبيات، حظيت أنظمة توصيل الأدوية الجديدة مثل النوفاسومات باهتمام متزايد. النوفاسومات هي أنظمة نانوية حويصلية متعددة الصفائح تتكون من مواد خافضة للتوتر السطحي غير أيوني، وحمض دهني حر، بالإضافة إلى الكوليسترول كعامل مثبت للغشاء. وجود الأحماض الدهنية الحرة، مثل حمض الستياريك أو حمض الأوليبك، في تركيبها يعمل كعامل معزز للنفاذية، مما يجعل النوفاسومات أكثر مرونة ونفاذا للأنسجة مقارنة بالنيوسومات أو الليبوزومات الأقدم. علاوة على ذلك، فإن النوفاسومات تتمتع بتحميل واستقرار أكبر للأدوية مقارنة بالحويصلات النانوية الأخرى. تجعل هذه الخصائص النوفاسومات هدفا لتحسين التوصيل الموضعي وعبر الجلد لمضادات الفطريات. عند استخدامها موضعيا، يمكن للنوفاسومات أن تتفاعل مع الطبقة المتقرنة للبشرة، مما يعزز نفاذ الجلد ويحسن التوصيل الموضعي. تظهر عدة دراسات أن النوفاسومات لها القدرة على تحرير العلاج لفترات مطولة، ونسبة تحرر دوائية تراكمية أعلى مقارنة بالكريمات أو الجل التقليدي. بالإضافة إلى ذلك، تم تصنيع النوفاسومات من مكونات متوافقة حيويا وصديقة للبشرة. بشكل عام، تمثل أنظمة توصيل الأدوية النوفاسومية استراتيجية واعدة لمضادات الفطريات الموضعية، حيث توفر التزاما آمنا وفعالا وأكثر للمرضى.

الكلمات المفتاحية. مضادات الفطريات الموضعية، عيوب التركيبات التقليدية، نوفاسومات، معززات نفاذ الجلد، واستهداف الجلد.