



Advanced Vesicular Systems for Antifungal Drug Delivery

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Received: 12 February 2022 / Accepted: 6 July 2022 / Published online: 28 July 2022
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Abstract

Fungal infections are considered one of the most serious conditions as their occurrence has increased lately. Fungi like *Candida*, *Fusarium*, and *Aspergillus* species mostly affect immunocompromised patients as they are considered opportunistic pathogens. These infections can be superficial, cutaneous, subcutaneous, or systemic fungal infections that require specific treatment. There is a wide variety of antifungal drugs that can be used to cure fungal infections; however, most of them have many systemic side effects due to their physicochemical characteristics and high toxicity profile. Hence, the current review focuses on various advanced vesicular carriers with high biocompatibility that can encapsulate the antifungal drugs owing to increase their efficacy and limit the undesirable side effects. These advanced systems can manage stability, solubility, bioavailability, safety, and effectiveness issues present in conventional systems.

Keywords Antifungal drugs · Conventional systems · Advanced vesicular carriers · Fungal infections

Introduction

Fungal infections have undoubtedly increased lately and are stated as a serious emergent condition that threatens millions of lives in the world [1]. Fungi exist everywhere in houses, hospitals, hotels, gardens, playgrounds, skin, and mucous membranes. The most common isolated organisms are *Candida*, *Fusarium*, and *Aspergillus* species. Trauma, administration of immunosuppressive agents, and AIDs are the most prevalent risk factors [2]. The most common fungal diseases are superficial infections of the skin and nails which are mainly caused by dermatophytes, causing nails infection, ringworm of the scalp, and athlete's foot [3, 4]. Oral and genital tracts mucosal infections are also common, especially vulvovaginal candidiasis [5]. Invasive fungal infections have high mortality rates; however, they have a much lower incidence than superficial infections.

Antifungal drugs are classified as either fungistatic or fungicidal based on their mechanism of action. Fungistatic drugs inhibit the growth of the fungi while fungicidal drugs directly kill them [6]. They are divided according to their chemical structure into azole antifungals, polyene antifungals, echinocandin antifungals, allylamine antifungals, and others, as demonstrated in Fig. 1. The oldest antifungal drugs are polyenes. They have low rates of resistance, broad-spectrum activity, and established clinical records. Nystatin is a polyene antifungal drug that shows outstanding action against a wide range of yeast and fungi. Also, amphotericin-B is a polyene antifungal drug that has antifungal activity against *Candida* species [7].

Azole antifungals are synthetic drugs that act by inhibiting fungal cell membrane synthesis by inhibiting the enzyme which converts lanosterol to ergosterol. This in turn increases fungal membrane fluidity and permeability which inhibits fungal cell growth and replication. Examples of this group are clotrimazole, terconazole, isoconazole, miconazole, butoconazole, econazole, ketoconazole, fenticonazole, and sertaconazole [8]. Echinocandins are antifungal drugs that are effective against *Aspergillus* species. Rezafungin is a novel fungistatic echinocandin drug; however, it is used as secondary therapy with other antifungals [9].

Antifungal drugs have disadvantages in terms of the spectrum of activity, pharmacokinetics and pharmacodynamics, resistance mechanisms, drug-drug interactions, and

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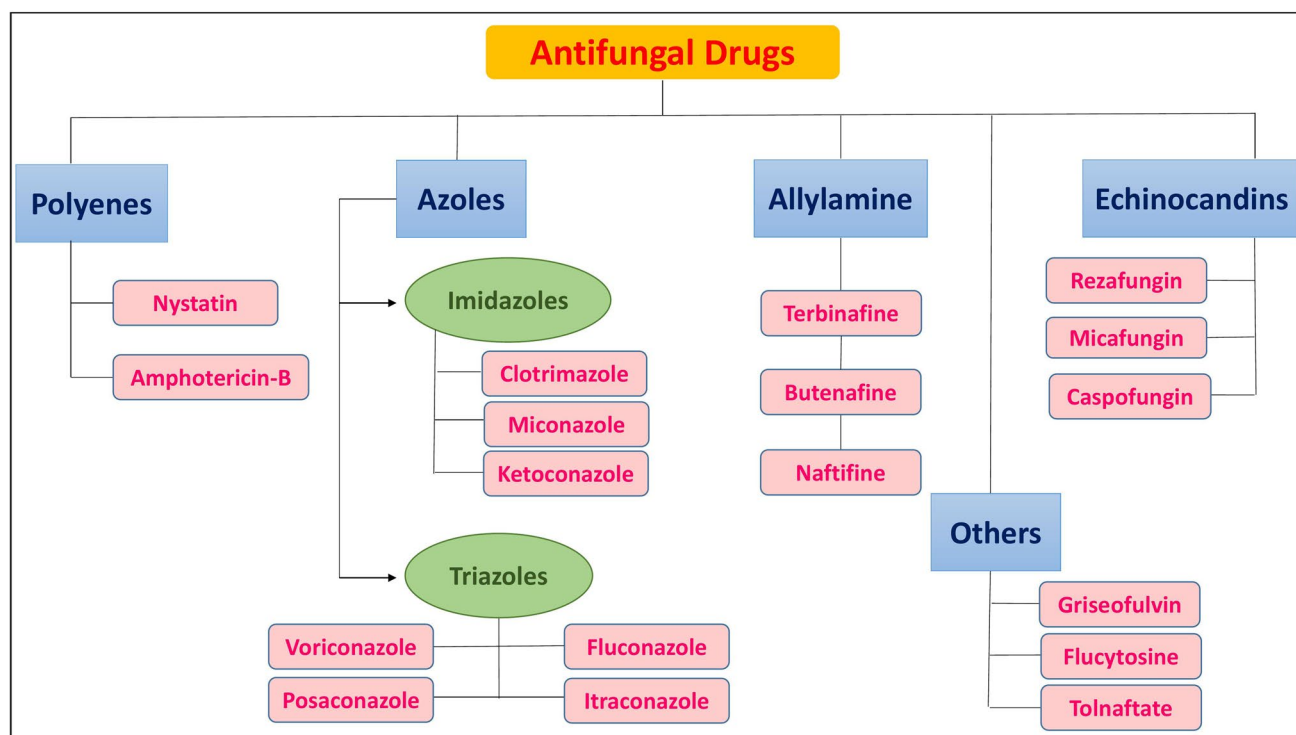


Fig. 1 Classification of antifungal drugs

compound toxicity. Moreover, they have some limitations regarding clinical efficiency due to their physicochemical characteristics such as their hydrophobic property that contributes to low aqueous solubility and also selectivity problems driving from the similarity between fungi and human cells [10]. This arouses the need to create a new delivery system for antifungal drugs owing to minimize or eliminate their drawbacks and improve their efficacy [11]. Hence, several advanced vesicular carriers with some of their applications in the treatment of fungal infections will be discussed in this review.

Vesicular Drug Delivery Systems

Vesicles are colloidal carriers formed using certain amphiphilic molecules such as phospholipids or surfactants surrounding an aqueous phase forming one or more concentric lipid bilayers [12]. Vesicles can entrap hydrophilic and lipophilic drugs in the aqueous compartment or the lipid bilayer [13]. They can reduce the risk of drug toxicity as they can deliver drugs to the targeted site of action hence lowering their concentration on other sites of the body [14]. Also, the entrapment of drugs in the vesicles increases the lifetime of drugs present in systemic circulation [15]. Furthermore, it was reported that vesicular systems can boost the penetration of antifungal drugs into the stratum corneum due to the

ability of their lipidic components to permeate and alter the intercellular lipid matrix of the stratum corneum [16].

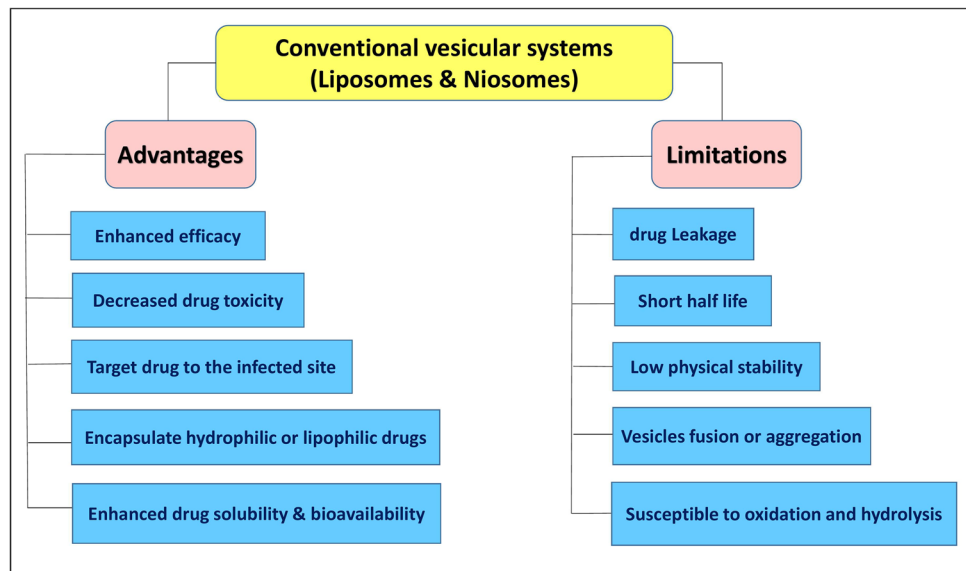
Despite conventional vesicular systems such as liposomes and niosomes being first reported, their low physical stability issues like leakage, aggregation, and fusion of drugs limit their usefulness and effectiveness, as shown in Fig. 2 [17]. To overcome this issue, several recent vesicular systems have been used for delivering antifungal drugs successfully, as demonstrated in Table 1. The structure of different advanced vesicular systems is presented in Fig. 3.

Proniosomes

Proniosomes are dry surfactant-coated free-flowing vesicular carriers [18]. They are more stable than conventional niosomes, more uniform in size, stable and easy in handling and storage [12]. Proniosomes overcome physical problems such as hydrolysis and leaking of entrapped drug, aggregation, sedimentation, and fusion upon storage. Moreover, they can accommodate drug molecules with different solubilities [19].

The study of Samy et al. involved the preparation of proniosomes for transdermal application of itraconazole [20]. Proniosomes were prepared applying the slurry method by dissolving the drug, Span 60, and cholesterol in chloroform:methanol (1:1). The study results revealed that itraconazole proniosomal gel had high spreadability, high drug content,

Fig. 2 Advantages and limitations of conventional vesicular systems



and high drug permeation from proniosomal gel through the skin. The proniosomal gel also showed higher bioavailability in rats compared with the marketed Sporanox[®] capsule and Sporanox[®] solution.

El-Emam et al. prepared ocular inserts of voriconazole-loaded proniosomal gel for the treatment of ocular fungal infections [21]. The formulations were prepared using the coacervation technique. They had a spherical shape, high entrapment efficiency, biphasic in vitro release profile, and high stability. Ocular inserts of the optimum formulation were developed by the addition of 1% w/w hydroxypropyl methyl cellulose and 0.1% w/w carbopol 940. The ocular inserts had a significant antifungal activity compared with the drug suspension and natamycin 5% market eye drops. The study considered the formulated vesicles as promising stable sustained release carriers for the treatment of ocular fungal infections.

In another study done by Mahajan et al. proniosomal gel of ciclopirox was formulated and evaluated for topical antifungal therapy [22]. Ciclopirox is a hydroxypyridone derivative broad-spectrum antifungal drug that inhibits almost all yeasts, dermatophytes, and molds, including *Candida* azole-resistant species, *Candida krusei*, *Candida glabrata*, and *Candida guilliermondii* [23]. The coacervation method was used to prepare ciclopirox loaded proniosomes by combining different grades of Span, cholesterol, and lecithin. Results of this study showed that prepared vesicles improved skin penetration and residence of the drug compared to the marketed product. Also, they had a controlled release which prolonged the drug release for extra hours.

Also, Kondawar et al. prepared a proniosomal gel for transdermal delivery of clotrimazole. Proniosomes were prepared by coacervation phase separation method combining the drug with cholesterol, lecithin, and different types

and amounts of surfactants. Formulations were transformed into proniosomal gel and evaluated. Results showed that prepared vesicles had high entrapment efficiency and sustained release profile [24]. In conclusion, proniosomes may be considered a promising carrier for antifungal drugs, especially for their stability and simple production.

Transferosomes

Transferosomes are biocompatible and biodegradable vesicular carriers that were presented by Cevc et al. in the 1990s [25]. They are composed of phospholipids and edge activator. The presence of an edge activator in the structure of transferosomes gives the vesicles ultra-deformable characteristics called self-optimizing deformability. This additional feature allows the transferosomes to change their flexibility and pass through the skin pores naturally, as well as, the very narrow pores [26]. Therefore, transferosomes are preferred to be used for topical and transdermal administration. However, transferosomes have some limitations such as low purity of natural phospholipids, and high production cost; also, they are slightly unstable chemically [12].

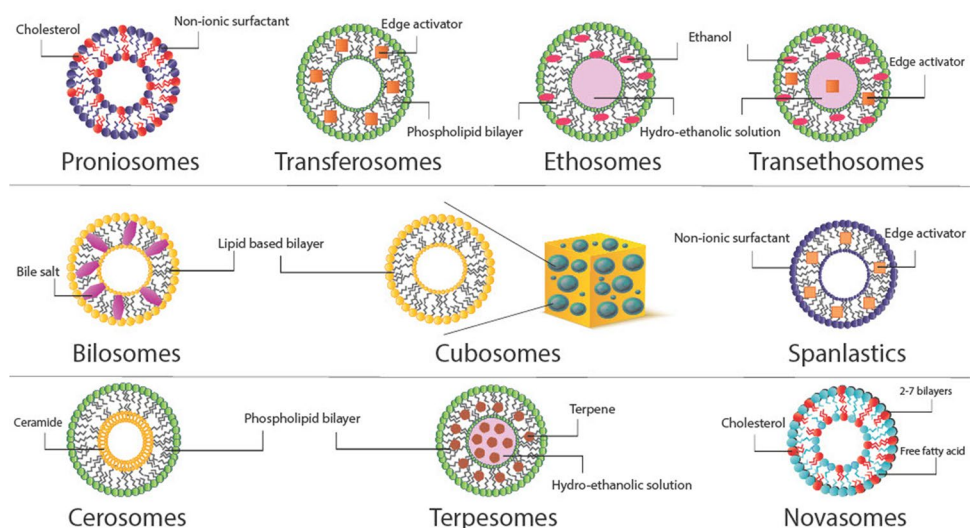
Qushawy et al. prepared a transferosomal gel using miconazole nitrate for the treatment of *Candida* skin infections [27]. Miconazole nitrate-loaded transferosomes were prepared using a thin lipid film hydration technique applying 2³ factorial design, using three independent factors: type of surfactant, total lipids, and the phospholipid: surfactant ratio. They had high drug encapsulation and small particle sizes. Also, the drug transferosomal gel showed superior antifungal activity than Daktarin[®] cream 2%. Miconazole nitrate transferosomes also showed a high ability to penetrate the skin.

Table 1 Advanced vesicular systems for effective treatment of fungal infections

Vesicular system	Antifungal drug	Composition	Route of administration	Method of preparation	Special features	Ref
Proniosomes	Itraconazole	Cholesterol and Span 60	Transdermal	slurry method	High drug permeation and bioavailability	[20]
	Voriconazole	Cholesterol and different surfactants	Ocular	coacervation phase separation method	Stability, sustained release, and superior antifungal activity	[21]
	Ciclopirox	Cholesterol, different surfactants, and lecithin	Topical	coacervation phase separation method	High skin penetration, residence time, and sustained release profile	[22]
	Clotrimazole	Cholesterol, different surfactants, and lecithin	Transdermal	coacervation phase separation method	High drug loading and sustained release profile	[24]
Transferosomes	Miconazole nitrate	Phospholipid and different surfactants	Topical	Thin film hydration method	High ability for skin penetration and superior antifungal activity	[27]
	Amphotericin B	Soybean phosphatidylcholine and edge activator	Topical	Thin film hydration method	High skin accumulation and superior antifungal activity compared to market product (Ambisome®)	[28]
Ethosomes	Ciclopirox olamine	Lipoid S PC-3, ethanol, and water	Transdermal	Ethanol injection method	High flexibility and deep skin permeability	[31]
	Amphotericin B	Phospholipid, ethanol, and water	Transdermal	Cold method using a probe sonicator	High skin permeation and antifungal efficacy	[32]
Transethosomes	Voriconazole	Lipoid S100, different edge activators, ethanol, and water	Topical	Thin film hydration method	High elasticity and skin deposition	[35]
	Ketoconazole	L- α -phosphatidylcholine, Tween 80, stearyl amine, ethanol, and propylene glycol	Ocular	Thin film hydration method	Superior penetration and antifungal activity	[36]
Bilosomes	Terconazole	Span 60, cholesterol, different bile salts, and different edge activators	Topical	Ethanol injection method	High deformability, skin deposition, and antifungal activity	[39]
	Natamycin	Cholesterol, sodium taurocholate and Span 60	Ocular	Thin film hydration method	Viscoelastic and adhesive characteristics and high corneal permeability	[42]
	Terconazole	Cholesterol, sodium taurocholate, Span 60, and different types of Cremophor	Ocular	Ethanol injection method	High elasticity and corneal permeability	[43]
Cubosomes	Nystatin	Glycerol monooleate and different types of surfactant	Inhalable	Modified course method	Superior antifungal activity	[46]
	Voriconazole	Monoolein and Pluronic F127	Ocular	Melt dispersion emulsification method	High mucoadhesive properties and enhanced precorneal residence time	[47]

Table 1 (continued)

Vesicular system	Antifungal drug	Composition	Route of administration	Method of preparation	Special features	Ref
Spanlastics	Clotrimazole	Span 60 and different edge activators	Ocular	Ethanol injection method	High flexibility, corneal permeability, and superior antifungal activity	[51]
	Luliconazole	Span 20 and Tween 20	Topical	Ethanol injection method	High skin penetration and antifungal efficacy	[52]
	Miconazole nitrate	Span 60 and different types of edge activators	Ocular	Ethanol injection method	High ocular permeability	[53]
Cerosomes	Fenticonazole nitrate	Ceramide, phospholipid, and different types of Brij®	Topical	Thin film hydration method	High stability, permeability, and drug bioavailability	[57]
Terpesomes	Fenticonazole nitrate	Sodium deoxycholate, terpenes, and phospholipids	Vaginal	Thin film hydration method	High flexibility, penetration, and superior antifungal effect	[60]
	Fenticonazole nitrate	Terpenes and phospholipids	Ocular	Thin film hydration method	High ocular retention	[61]
Novasomes	Terconazole	Cholesterol, different surfactants and free fatty acid	Topical	Ethanol injection method	High elasticity, skin deposition, and antifungal activity	[64]
	Fenticonazole nitrate	Cholesterol, Span 60, oleic acid, and Brij®	Topical	Ethanol injection method	Superior antifungal activity compared to Miconaz® cream	[65]

Fig. 3 Schematic diagram represents the structure of different advanced vesicular systems

Perez et al. prepared amphotericin-B loaded transferosomes for the topical treatment of leishmaniasis and cutaneous fungal infections [28]. Transferosomes formulations were prepared using Soybean phosphatidylcholine as lipid components and Na Cholate or Tween 80 as an edge activator using thin film hydration technique. The *in vitro* antifungal activity of amphotericin-B loaded transferosomes was assessed and revealed that fungal strains were highly

sensitive to transferosomes formulations than mammal cells. Moreover, the drug-loaded transferosomes accumulated in the human skin were forty times higher than liposomes market product of the drug (Ambisome®). Transferosomes had deep epithelial layers penetration of the drug. In conclusion, topical treatments of leishmaniasis and cutaneous fungal infections with transferosomes have a promising clinical significance.

Ethosomes

Ethosomes are high alcohol-containing vesicular carriers consisting of hydroalcoholic phospholipid. Ethosomes may contain different phospholipids like phosphatidylglycerol, phosphatidylcholine, hydrogenated phosphatidylcholine, phosphatidylinositol, phosphatidic acid, phosphatidylserine, and phosphatidylethanolamine in addition to alcohol, water, and propylene glycol [29]. Studies showed that ethosomes have a great ability to permeate through human skin due to their high flexibility. They can transport different types of drugs more efficiently across the skin barrier; therefore, ethosomes are mainly used topically [30]. Ethosomes are composed of natural phospholipids, so purity may be an issue [12]. They may clump together causing precipitation; also, a high concentration of alcohol may cause irritation to the skin [14].

Girhepunje et al. prepared ethosomes for the treatment of cutaneous *Candida* infections by enhancing dermal delivery of ciclopirox olamine [31]. Ethosomes were prepared using different concentrations of Lipoid S PC-3 and ethanol. The optimum ethosomal formulation of ciclopirox olamine showed a higher encapsulation efficiency and a stable profile. Transmission electron microscopy showed unilamellar spherical shape vesicles. The ciclopirox olamine loaded ethosomes highly accumulated inside the skin which targeted the drug to the epidermal and dermal sites. These outcomes showed that ethosomes are a great carrier for transdermal delivery and more topical applications of ciclopirox olamine in the treatment of fungal infections.

Also, amphotericin-B ethosomal gel was formulated by Kaur and Maurya, and antifungal activity was evaluated [32]. The formulation was prepared using the cold method. The study included in vitro antifungal assessment which showed that the ethosomal gel had a higher zone of inhibition against *Candida albicans* than marketed liposomal gel. Also, ethosomal gel formulation had significant efficacy in treating *Candida* infections induced rat mycosis model compared to drug solution and marketed liposomal gel of the drug. These results ensured the therapeutic potential effectiveness in the treatment of dermal mycosis caused by *Candida albicans*. Results recommended that ethosomal gel can be the most capable carrier system for dermal and transdermal delivery of amphotericin-B to treat dermatomycoses.

Transethosomes

Transethosomes are innovative vesicular systems that are similar in composition to ethosomes with an extra edge activator or penetration enhancer. They have the advantages of transferosomes and ethosomes [33]. Transethosomes are highly flexible vesicles with a high flux rate and high skin permeability compared to other vesicular systems. They are

highly stable, biocompatible, and bio-degradable with high patient compliance [34]. However, the drugs' molecular size must be reasonable to be absorbed percutaneously. Also, since transethosomes contain high alcohol concentration they may cause skin dermatitis as ethosomes [33].

Song et al. formulated voriconazole-loaded transethosomes to treat skin fungal infections [35]. Transethosomes were formulated applying thin film hydration method containing Lipoid S100 and different types of edge activators. Voriconazole-loaded transethosomes had spherical morphology. They had high skin deposition of the drug in the dermis and epidermis area compared to liposomes, ethosomes, and polyethylene glycol drug solution.

Ahmed et al. prepared ketoconazole loaded transethosomes for the ophthalmic treatment of fungal infections [36]. Vesicles were prepared using thin film hydration method, containing different ratios of L- α -phosphatidylcholine, Tween 80, and stearyl amine with ethanol and propylene glycol. The formulated transethosomes were spherical, highly flexible, and with high entrapment efficiency. Draper-Lin small composite design was used to evaluate the studied factors and select the optimum formulation. Ketoconazole antifungal activity of the optimum formulation was significantly enhanced, and formulations were safe for the cornea. Transethosomes vesicles penetrated the posterior eye segment. In a conclusion, ketoconazole transethosomes are considered a promising system for the ocular treatment of deep fungal eye infections.

Bilosomes

Bilosomes are vesicles formed of non-ionic amphiphiles and bile salts [37]. The structure of bilosomes provides more flexibility to the vesicles allowing them to squeeze themselves carrying the drug to the site of action [38]. Bilosomes have high chemical gastrointestinal tract stability; they do not require special conditions in storage and handling; also, they have high patient compliance [39]. Yet interactions between oral bilosomes and ingested food have not been studied sufficiently until now; also, a complete simulation of in vivo digestion of bilosomes is still not available [40]. One of the most important applications of bilosomes was vaccines [37]. However, bilosomes long-term stability is still an issue and requires further assessment. Also, some bile salts when used in the preparation of bilosomes reported toxicity to the cornea [40]. Another weakness of bilosomes is that they encapsulate cationic drugs more efficiently than anionic drugs; this might be explained by the presence of bile salts which hold a negative charge and hydrophilicity [41].

Mosallam et al. prepared terconazole-loaded bilosomes for topical delivery of the drug [39]. Vesicles were prepared using the ethanol injection method by altering the type of bile salt and edge activator, bile salt amount, and time of

sonication. Statistical analysis was done using the Design-Expert[®] software applying 2⁴ full factorial design. Highly deformable bilosomes were also prepared by modifying the bilosomes composition using different types of edge activators. Both the bile salt and edge activator can decrease the lipid bilayer surface tension and increase the deformability of the vesicles to overcome subcutaneous tissues and penetrate deeply into the skin. The study confirmed the marked efficacy of bilosomes for topical delivery of terconazole.

Janga et al. prepared natamycin-loaded bilosomes to prolong and enhance ocular delivery of the drug [42]. Natamycin-loaded bilosomes were composed of different amounts of Span 60, cholesterol, and sodium taurocholate, and they were prepared using thin film hydration technique. The formulated bilosomes were subjected to statistical analysis applying Tukey's post hoc HSD. Corneal histology and cytotoxicity confirmed the ocular safety of natamycin-loaded bilosomes; also, an efficient ocular penetration was displayed. The study ensured the bilosomes pronounced efficacy for ocular delivery of natamycin.

In another study, terconazole-loaded bilosomes were prepared by Abdelbary et al. for the treatment of ocular fungal infections [43]. Bilosomes contained the bile salt, Span 60, and cholesterol along with an edge activator for extra flexibility. The ethanol injection method was utilized for the preparation of bilosomes applying 2³ full factorial design. The Design-Expert[®] software was used for the investigation of different formulation variables and the selection of the optimum formulation. Corneal permeation, in vivo ocular tolerance, and histopathological studies showed the superiority of the bilosomes over niosomes and drug suspension for promising ocular drug delivery.

Cubosomes

Cubosomes are liquid crystalline optically isotropic cubic nanoparticles; composed of lipid layers, separating non-intersecting water channels [44]. Cubosomes are biocompatible, non-toxic, bioadhesive, and non-immunogenic drug delivery systems. They have a unique geometric structure that can incorporate a wide variety of drugs with a high amount due to their high internal surface area [45]. Limitations of cubosomes are low stability which may cause drug leakage, and difficulty in large scale production [45].

Kazi and Dehghan prepared inhalable nystatin cubosomes for the effective treatment of invasive pulmonary *Aspergillus* [46]. Nystatin-loaded cubosomes were prepared using a modified coarse method using different surfactants. The efficacy of nystatin-loaded cubosomes against *Aspergillus fumigatus* was estimated; they displayed a significantly higher zone of inhibition compared to nystatin suspension.

Another application of cubosomes for the delivery of antifungal drugs was done by Said et al. that prepared ocular

mucoadhesive cubosomes for the delivery of voriconazole [47]. Cubosomes were formulated using the melt dispersion emulsification technique and designed using a central composite face-centered design to investigate the effect of changing DL- α -Monoolein and Pluronic F127 concentrations on cubosomes characteristics. Formulated cubosomes increased ocular residence and transcorneal permeation of the drug compared to the drug suspension, providing high biocompatibility and safety. Also, the chitosan-coated cubosomes prepared in the study were considered a promising drug delivery system for voriconazole.

Spanlastics

Spanlastics are highly elastic nanovesicles that consist of an edge activator and a non-ionic surfactant [48]. They have several advantages such as convenience, target specificity, chemical stability, and high patient compliance [49]. However, they have a low release profile in ocular delivery [50]. Spanlastics could be promising vesicles for the delivery of antifungal drugs due to the presence of an edge activator which provides great flexibility improving the permeability of the drug.

As introduced by Abdelbari et al., spanlastics were used as nanovesicles to treat ocular fungal infections using clotrimazole [51]. Span 60 with different types of edge activators were used in the formulation of clotrimazole-loaded spanlastics using the ethanol injection technique, applying 3² full factorial design, and analyzed using the Design-Expert[®] software. The optimum formulation had spherical morphology, showed a sustained in vitro release profile, and a significantly higher corneal permeation than clotrimazole suspension. The higher corneal permeability of clotrimazole-loaded spanlastics was caused by their high elasticity. The optimum formulation also had a superior activity against *Candida albicans* relative to clotrimazole suspension. The study showed that spanlastics vesicles offer a promising and convenient system for the delivery of clotrimazole to cure ocular fungal infections.

Alhakamy et al. developed luliconazole loaded spanlastics to enhance the antifungal activity of the drug against *Candida albicans* [52]. Luliconazole is a new imidazole antifungal drug that treats skin infections. However, it has some limitations that decrease its applications, as it has low solubility and poor skin penetration. The study aimed to improve the drug's therapeutic effectiveness by formulating spanlastics containing the drug. Spanlastics were prepared using the ethanol injection method and were optimized using a combined mixture-process variable design. The optimized formulation was put into a hydrogel to increase skin penetration and increase the efficacy against *Candida Albicans* present in the wounds of experimental mice. It had significant antifungal efficacy against *Candida* with no irritation

compared to the drug suspension. Thus, luliconazole spanlastics enhanced topical antifungal activity against *Candida albicans*.

Another study by Mohanta et al. included the preparation of spanlastics for the ocular delivery of miconazole nitrate [53]. Formulations were prepared by ethanol injection method using different surfactants. The permeability of spanlastics was higher compared with conventional niosomes formulation of the drug. Results concluded that spanlastics act as a promising delivery for the treatment of ocular fungal infections over traditional niosomes.

Cerosomes

Cerosomes are ceramide-containing vesicles prepared using phospholipids and different surfactants. They have high permeability, stability, and high drug bioavailability when applied topically [54]. Vesicles are formulated of lipidic phosphatidylcholine-ceramide mixture with the addition of surfactant in order to increase vesicle stability [55]. As cerosomes preparation includes the addition of phospholipids, purity may be a problem [12]. Another limitation of cerosomes is that they consist of two long chains and a small head group providing a critical packing parameter of 1.2 which is considered a high value; this problem can be solved using mixed systems [56].

As an application of cerosomes for the delivery of the antifungal drug is the study done by Albash et al. which involved the preparation of cerosomes for topical delivery of fenticonazole nitrate to treat skin fungal infections [57]. The study involved the addition of PEGylated surfactant to formulate fenticonazole nitrate-loaded PEGylated cerosomes. Cerosomes were prepared by thin film hydration method applying 2^3 full factorial design. They had small particle size, high encapsulation efficiency, and suitable zeta potential value. Safety and dermatokinetic studies were done for the formulated cerosomes which ensured topical safety and displayed higher localization and concentration of fenticonazole nitrate in the skin in relation to the drug suspension. Overall, the study confirmed the success of using PEGylated cerosomes in enhancing the activity of fenticonazole nitrate as a topical antifungal agent.

Terpesomes

Terpesomes are vesicles containing terpenes, which are natural constituents that consist of several isoprene units and are derived from essential oils. Terpenes have antimicrobial and antifungal activities as their lipophilic nature allows essential oil constituents to be delivered inside the cell, causing cytoplasmic infiltration and cell death [58]. Despite the great advantages of terpesomes, they may cause skin toxicity

and irritation due to the presence of terpenes in their structure, as well as the high production cost [59].

Albash et al. prepared fenticonazole nitrate-loaded terpesomes to treat vaginal candidiasis [60]. Terpesomes were prepared by thin film hydration method and then statistically optimized using Box-Behnken design using three different independent variables. Vesicles formed had high entrapment efficiency, small particle size, and high elasticity. The in vivo study presented a significant inhibition effect in rats from fenticonazole nitrate-loaded terpesomes gel compared to the drug gel. These findings ensured the potency of fenticonazole nitrate terpesomes gel for the treatment of vaginal candidiasis.

Albash et al. also prepared terpesomes for effective ocular delivery of fenticonazole nitrate [61]. Terpesomes were prepared using different types and amounts of terpenes, then analyzed statistically using the Design-Expert[®] software. The in vivo ocular retention study showed superiority of the optimized fenticonazole nitrate-loaded terpesomes compared to the drug suspension. Also, the biocompatibility and safety of the prepared terpesomes were ensured. Overall, the study results confirmed the safety and efficacy of terpesomes for the ocular delivery of fenticonazole nitrate.

Novasomes

Novasomes are vesicular carriers composed of cholesterol, free fatty acid, and monoester of poly-oxyethylene fatty acid. Novasomes are multi-bilayered nanosized vesicles with a central core high capacity and site specificity, and can deliver a large amount of drug. They have wide applications in the development of vaccines, cosmetics, foods, personal care, and chemicals [62]. However, the presence of free fatty acid in the structure of novasomes may cause some stability issues [63].

Mosallam et al. encapsulated terconazole into novasomes to improve its skin penetration and modify its therapeutic efficacy [64]. Novasomes in the study were prepared using the ethanol injection method applying 2^4 full factorial design using the Design-Expert[®] software. They possessed a small particle size, high encapsulation efficiency, and rounded morphology. Microbiological evaluation of the optimized novasomes formulation showed high activity against *Candida albicans* compared to niosomal formulation and drug suspension. Also, terconazole-loaded novasomes displayed higher skin deposition compared to traditional niosomes and drug suspension due to their high elasticity. Dermatological safety of the formulated novasomes was ensured by clinical trials. A clinical study was performed on twenty infants having napkin candidiasis that appeared as redness, pustules, and erosions. Infants which received the optimum novosomal formulation showed 100% improvement. Also, skin scrapings became negative for *Candida albicans* after

10 days of therapy in 100% of infants. These results showed the superiority of novasomes over placebo in providing a complete clinical treatment of *Candida albicans* infections. The study ensured that novasomes are promising vesicular carriers of terconazole for treating skin fungal infections.

Moreover, Albash et al. formulated trans-novasomes containing fenticonazole nitrate for the treatment of tinea corporis [65]. Trans-novasomes were prepared using Span 60, cholesterol, and oleic acid, along with the addition of Brij® as an edge activator, for the enhancement of the topical delivery of the drug. The ethanol injection method was used for the preparation of the vesicles based on D-optimal design. The optimum formulation had high entrapment efficiency and spherical morphology. It also inhibited the growth of *Trichophyton mentagrophytes* growth effectively compared with the drug suspension applying tetrazolium salt reduction assay. Moreover, a clinical assessment was performed on patients with fungal lesions caused by tinea corporis. The clinical study confirmed that the optimum formulation had a superior cure of tinea corporis than Miconaz® cream. Thus, novasomes could be considered promising vesicles for boosting the antifungal efficacy of fenticonazole nitrate for the topical treatment of tinea corporis.

Conclusion

Since fungal infections are increased over time and are considered life-threatening diseases, the necessity to develop innovative drug formulations increases to overcome the limitations of conventional systems. Advanced vesicular carriers are novel drug delivery systems that increase the antifungal activity of antifungal drugs, by targeting them to the site of action and minimizing their side effects, therefore increasing the therapeutic efficacy of these drugs to treat fungal infections. In conclusion, novasomes and terpesomes are recommended as excellent vesicular systems to entrap antifungal drugs. As both vesicles might have an antifungal effect on their own without any assistance of drugs due to the presence of free fatty acid and terpenes in the structure of novasomes and terpesomes, respectively. Subsequently, we speculate that these vesicles might have an additional antifungal effect when used as carriers for antifungal drugs. The advanced vesicular carriers are expected to replace the conventional systems as more preparations become available commercially.

Author Contribution Shaimaa Mosallam: conceptualization, writing, data curation, reviewing, and editing.

Rofida Albash: conceptualization, data curation, reviewing, and editing.

Manar Adel Abdelbari: visualization, data collection, writing, and data curation.

Funding Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB). This review was funded by the authors.

Declarations

Conflict of Interest The authors declare no competing interests.

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