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Review

Solid lipid nanoparticles, an effective carrier for classical antifungal drugs

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ABSTRACT

Solid-lipid nanoparticles (SLNs) are an innovative group of nanosystems used to deliver medicine to their respective targets with better efficiency and bioavailability in contrast to classical formulations. SLNs are less noxious, have fewer adverse effects, have more biocompatibility, and have easy biodegradability. Lipophilic, hydrophilic and hydrophobic drugs can be loaded into SLNs, to enhance their physical and chemical stability in critical environments. Certain antifungal agents used in different treatments are poorly soluble medications, biologicals, proteins etc. incorporated in SLNs to enhance their therapeutic outcome, increase their bioavailability and target specificity. SLNs-based antifungal agents are currently helpful against vicious drug-resistant fungal infections. This review covers the importance of SLNs in drug delivery of classical antifungal drugs, historical background, preparation, physicochemical characteristic, structure and sizes of SLNs, composition, drug entrapment efficacy, clinical evaluations and uses, challenges, antifungal drug resistance, strategies to overcome limitations, novel antifungal agents currently in clinical trials with special emphasis on fungal infections.

Contents

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1. Introduction

Nanotechnology is a multi-disciplinary model that evolved in the initial '20s that has many uses and should be clear like the expenditure of material with the typical size on nanoscale ranging from 1 nm up to 1000 nm used for well-being products (Araujo et al., 2021). Nanoparticles (NPs) have arisen as an encouraging means to decrease drug adverse effects by maintaining or improving their beneficial effectiveness (Endo et al., 2020). Emerging NPs as practical drug delivery methods have received a lot of attention in recent years (Matta, 2021a). They have been widely used in cancers researches, and the formulation of medications which are utilized in the treatment of bacterial, viral, and fungal infections as well as other physiological disorders (Matta, 2021b, Raza et al., 2021, Shehabeldine et al., 2021, Hasanin et al., 2022, Hashem et al., 2022, Shehabeldine et al., 2022, Song et al., 2022, Tang et al., 2022). However, many nanocarrier systems are currently in research (Fig. 1), to increase the infusion of some medicines over the stratum corneum coating of the dermis, to attain measured and sustained release of these medicines, and to progress the effectiveness of the dermal therapy. Moreover, many investigators have studied lipid-based nanocarriers, in the form of lipid nanocrystals, solid-lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), to improve the penetrability and attain the prolonged release of the medication on the skin (Waghule et al., 2019). Amongst them, SLNs have been decoding optimistic results for the topical application of various kinds of anti-fungal medicines (Carbone et al., 2018). SLNs are non-toxic transporter schemes that become stable by surfactants and are prepared from solid lipid(s) for well-ordered and besieged conveyance (Akbaba and Ozder, 2021).

SLNs are significant colloidal transporters, comprised of solid lipids in which the medication is entrapped in the lipid core (Palareti et al., 2016, Gambhire et al., 2019, Ehsanfar et al., 2020). Sizes ranging from 50 nm to 1000 nm can enter the lymphatic blood when given in buccal through Peyer's patch the features, for instance, element mass, and zeta potential on elements are famous to distress the uptake (Abdellatif et al., 2019, Banerjee and Pillai, 2019, Raskar and Bhalekar, 2019, Carbone et al., 2020). SLNs are an operative transporter scheme for several water-loving and water-hating actives conveying chemical stability and refining their effectiveness with an impending decrease in adverse drug reactions (Deshkar et al., 2018). These lipid-based nanocarriers can be further divided into three diverse groups mentioned 1)

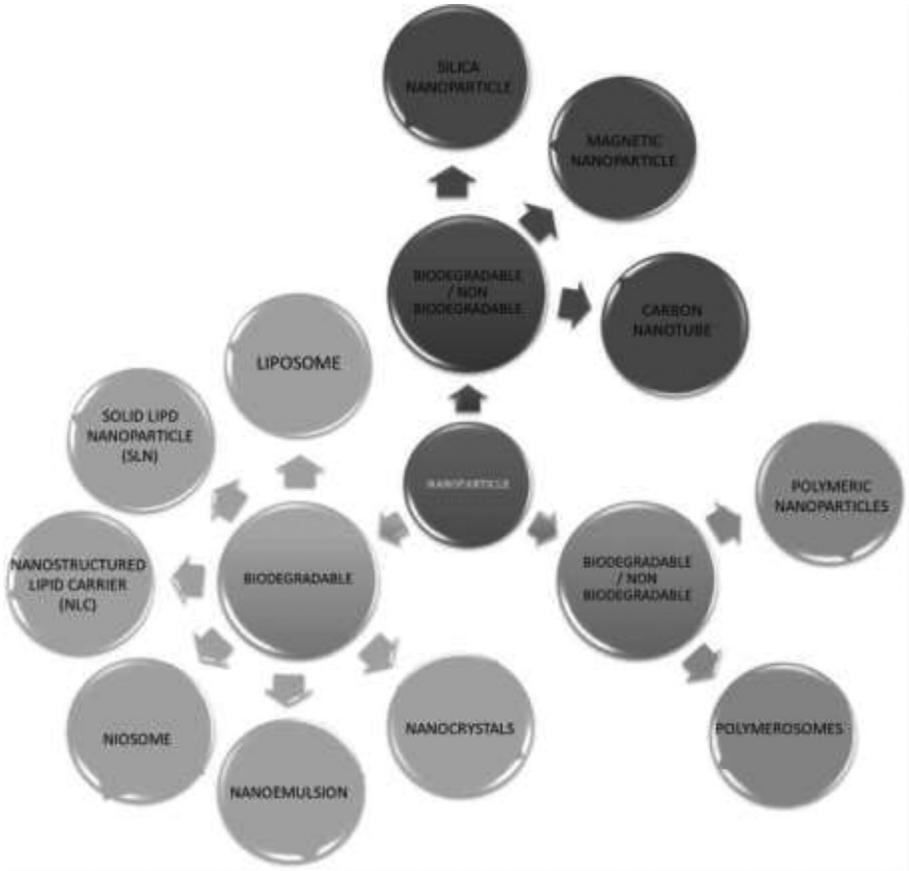

Fig. 1. Types of nanoparticles (by *Duan et al* (Duan et al., 2020); the copyright© 2020 Royal Society of Chemistry).

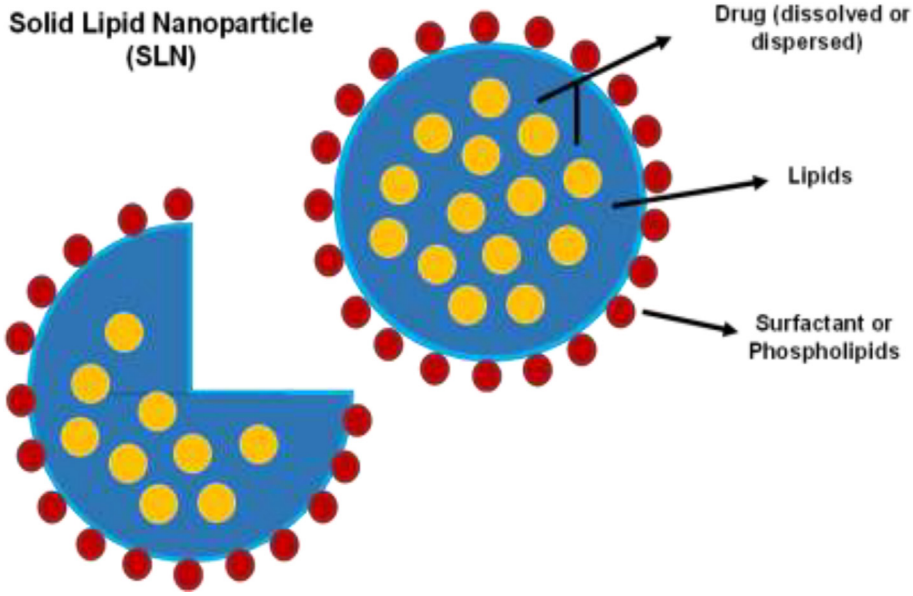

Fig. 2. The SLNs structure (Joseph and Bunjes 2013).

vesicular carriers, 2) nanoparticulate carriers, and 3) emulsion-based carrier(s) (Nene et al., 2021). However, collectively they hydrate the outer dermis because of its occlusive possessions causing decreased aquatic loss and similarly helping the medicine infusion into the dermis (Dudhipala and Ay, 2020).

In this review, the authors aimed to appear the prospective history of SLNs as an alternative transporter system for old colloidal systems for instance liposome, emulsion, and polymeric NPs, to progress the solubility and therapeutic effectiveness of numerous latent anti-fungal medicines (Ramzan et al., 2021).

1.1. Identification of the SLNs

SLNs are colloidal transporters composed of fatty acids they remain in a solid state at a temperature ranging from 25 °C to a normal body temperature of 37 °C (Kumar et al., 2019). SLNs show distinctive properties and numerous benefits over classical formulations. The structure and composition of SLNs have been shown in Fig. 1 and Fig. 2, respectively.

The solid lipids used for SLNs preparation include waxes, triglycerides, and steroid fatty acids. For the oral drug delivery of various active composites, SLNs between 50 and 1000 nm have been well-considered to be advantageous. (Raza et al., 2019, Kraisit et al., 2021).

Furthermore, SLNs manufactured by general regard as safe (GRAS) constituent(s) are biologically more compatible and easily decomposable and indicate little cell toxicity of animal cells, entirely cooperative if used for drug administration purposes. SLNs are the initial age of a band of lipid nanoparticles comprised of solid lipids for making a fat medium in which medicines or active constituents could be condensed. Recently, to enhance the uptake degree and increase the SLNs delivery effectiveness, surface alteration and biopolymer coating have newly been applied (Ahmadifard et al., 2020). SLNs preparations have controlled medication release properties and offer improved chemical stability of medication molecules (Banala et al., 2020, Yaghmur and Mu 2021). Due to their smallest size, SLNs have unique characteristics like better loading efficacy, enhances product targeting and larger surface area, Table 1 and Table 2 (Kang et al., 2019, Shi et al., 2019, Sharma et al., 2020).

SLNs were primarily made by *Schwarz et al.* all through the initial 19th century and were defined as a core of solid lipids enclosed by a solo sheet of lipids making an external shell (Fig. 3).

Table 1
Physico-chemical characteristics of various SLN preparations (Lima et al., 2020).

Nanoparticle Name	PR[a]	pH	Size (nm)	EE (%)[b]
SLN-B	–	6.690	296	–
10-SLN-PHY	1:11	6.485	306	67
5-SLN-PHY	1:5	6.587	301	68
3-SLN-PHY	1:4	6.598	298	68

[a] PR. Pytol ratio.
[b] EE %. (Entrapment efficiency).

Table 2
Drug entrapment efficacy and size of various SLNs and nano-structured Lipid-nano Carrier(s) preparations employed in antifungal drug delivery.

Medicine	Lipid preparation	Size (nm)	Drug EE (%)[a]	References
Itraconazole	SLN(s)	250–545	81–88	(Mirza et al., 2016)
Itraconazole	SLN(s)	126–199	68–94	(Mohanty et al., 2015)
Fluconazole	SLN(s)	85	89.60	(Moazeni et al., 2016)
Miconazole	SLN(s)	23	90.20	(Aljaeid and Hosny 2016)
Clotrimazole	SLN(s)	202–460	41–43	(Cassano et al., 2016)
Ketoconazole	SLN(s)	202–460	33–36	(Cassano et al., 2016)
Voriconazole	SLN(s)	234–343	62–84	(Khare et al., 2016)
Voriconazole	SLN(s)	139–334	40–64	(Kumar and Sinha 2016)
Voriconazole	NLC(s)	75–250	50–68	(Andrade et al., 2016)

[a] EE. entrapping efficiency.

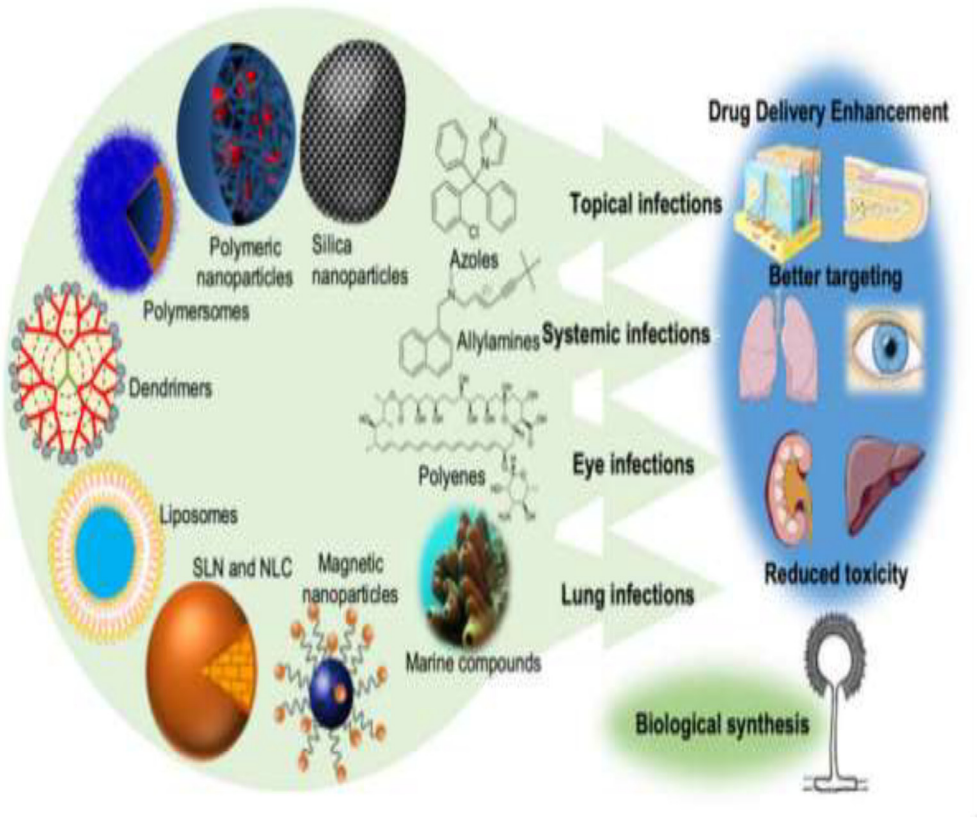

Fig. 3. The innovative drug delivery methods based on nanotechnology (by *Sousa et al* (Sousa et al., 2020); the copyright© 2020 Pharmaceuticals MDPI).

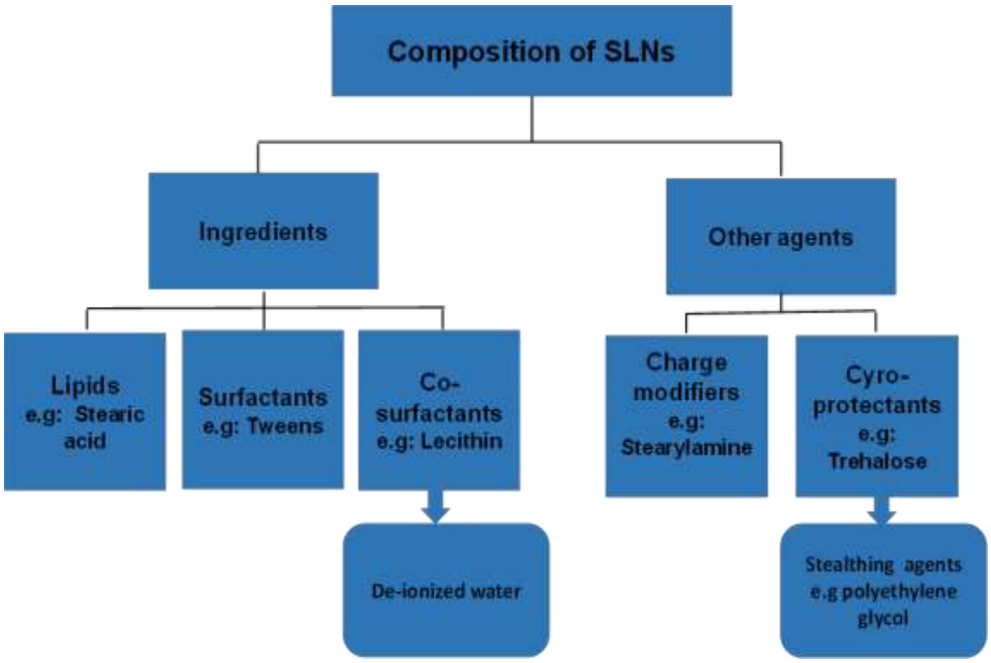

Fig. 4. The Composition of SLNs (Joseph and Bunjes 2013).

Being composed of solid lipids, SLNs have a stiff shape, high physical stability, strong defence in contradiction of the degradation of the consignment and enhanced *in vivo* acceptability compared to other lipid-based colloidal transporters, Fig. 2 (Nafee et al., 2018). The subdivisions designed from solid lipids have been formulated to acquire schemes, which control the movement of the actives ingredients within the vectors, Fig. 4. (Dieng et al., 2021).

SLNs should be classified based on the means of application as oral, other than oral, ophthalmic, over the dermis applied SLNs and SLNs applied in molecular drug and inheritable factor

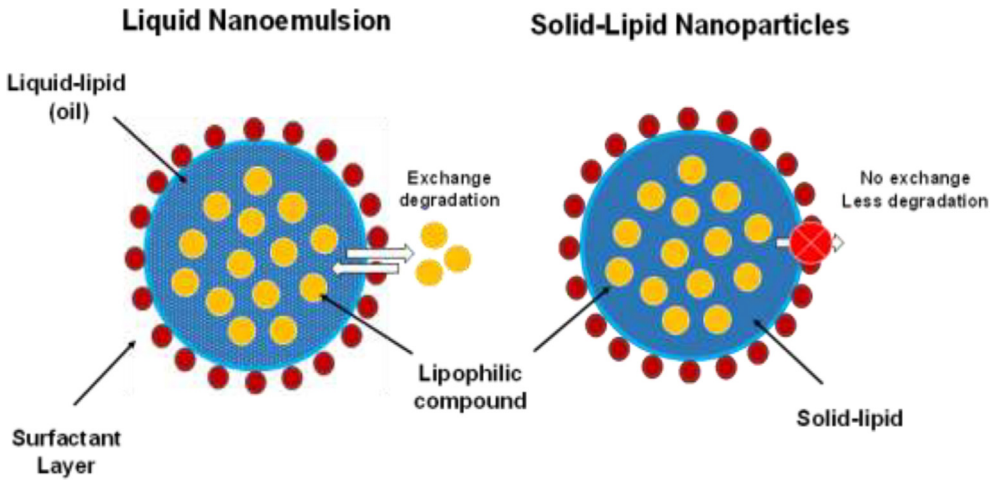

Fig. 5. Enhancement of product stability of liquid nanoemulsions (LNEs) having lipophilic compound and SLN by coating surfactant (by *Matta, V.D.R.* (Matta 2021a, 2021b); the copyright© 2018 Elsevier).

treatment (Sharma et al., 2021). The packing size of SLNs is exaggerated by the solubility of medicines within fatty acid melt, and physicochemical characteristics of solid lipids for instance polymorphic state and melting point (Fig. 5).

However, solid lipid in nanoparticles tends to convert to another well-organized chemical assembly in little time (Özdemir et al., 2019). Because of their essential possessions, fatty acids can liquefy hydrophilic ingredients, pass through the cell membrane and undergo a breakdown by enzymes (proteins). Within the medicinal manufacturing industry, the lipid is generally used as a means of transportation in diverse formulation(s) proposed for all route(s) of drug administration. Emulsion (type oil-in-water) is one of the utmost vital systems because it assists the administration of lipophilic actives (ingredients) all over the different routes (s) (Joseph and Bunjes, 2013). SLNs including medication captured by way of biocompatible sterol, assistances as a possibly effective substitute to overwhelm the drawbacks of oral medication conveyance (Afra et al., 2020, Ameeduzzafar et al., 2021, Devi et al., 2021).

1.2. The benefits of SLNs

SLNs or NLCs were effectively established in the initial 19th century and have revealed wanted features as a class of promising delivery systems (Sharma et al., 2020). However, the SLNs have definite structures of assembly and arrangement, showing aids compared to classical drug preparations (Campos et al., 2020). Therefore, the SLNs are less noxious and more biocompatible than the classic NPs that don't contain fatty acids (Arana et al., 2021). Furthermore, they show a multipurpose and firm alternative to liposomes, as they show the best loading volume for both water-heating and water-loving medications (Fazly Bazzaz et al., 2018).

SLNs also offer site-specific drug delivery and improved drug stability meanwhile the drug is stored inside the body fats, which can avoid medicine dreadful conditions and extend release (Ahmed et al., 2018). Accordingly, the SLNs increase the bioavailability of lipophilic drugs (Santos et al., 2019). Additionally, the SLNs shield the drugs from challenging environmental conditions like easy high-volume production utilizing a high-pressure homogenization method, biocompatibility, and biodegradability. In spite of minor drawbacks (as demonstrated next), the supreme significant characteristics of SLNs are protecting the drug from breakdown by enzymatic and chemical activity, enhances physical stability, water-loving and water-hating medication filling capability, stress-free manufacturing, no requirement for carbon-based solvents in production, capability to concurrent convey dual active mediators, rise medicine effectiveness, easiness of disinfection, minor thickness, application by numerous ways for administrations, easily biodegradable and physically stable, enhances drug efficacy, easily penetrates biological membranes, decrease amount and rate of recurrence of medicine application, frequent detection by phagocytic method, controlled release of medication, precise pointing, can be formulated into sustained release, shield medications in contradiction of therapeutic and noxious possessions, inhibit premature degradation of medication particles, inhibit immune reaction, escalation of medication retaining in tissue, lessen confrontation to medication, increase therapeutic index of medication, lessen medication noxiousness, and advance therapeutic effectiveness (Hosseini et al., 2019).

Lipid nanoparticles have the extra benefit of intermingling with the corneum layer of the skin, and this endorses medicine conveyance to the membrane. Lipid nanoparticles made an occlusive coating on the superficiality of the dermis which upsurges tissue hydration and medication membrane penetration (Mahmood et al., 2022).

1.3. Mechanism of drug release from SLNs

Generally, these small-size SLNs (and liquid nanoemulsions, LNEs) exemplify a principally useful group of medication transporter schemes for the buccal conveyance of all medications that agonize from less-slung solubility, reduced gastro-intestinal penetrability and partial bioavailability concerns (Fig. 6).

However, the SLNs are influential mediators of the whole procedure through which the medication becomes absorbed, conveyed transversely through the epithelial cell obstacles of the gastrointestinal tract and lastly extents the central blood through the capillary lymphatic way (Fig. 7) (Banerjee and Pillai, 2019, Du et al., 2019).

2. Lipid-based preparations for antimycotic agents applied topically

Various mycological infections are every so often well-defined as problematic to treat, with the noxiousness of anti-fungal agents and their interface with former medicine (Kischkel et al., 2020). Utmost predominant dermal mycological infections consist of cutaneous candidiasis, pityriasis versicolor and dermatophytosis,

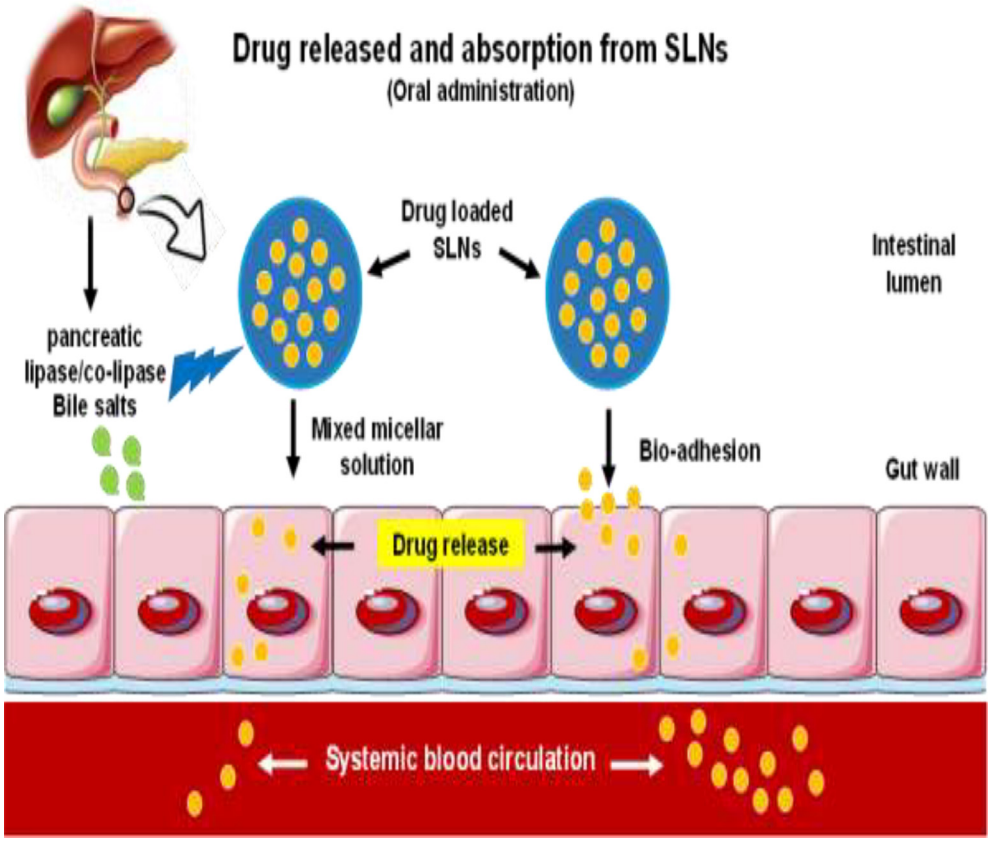

Fig. 6. SLNs preparation for oral administration.

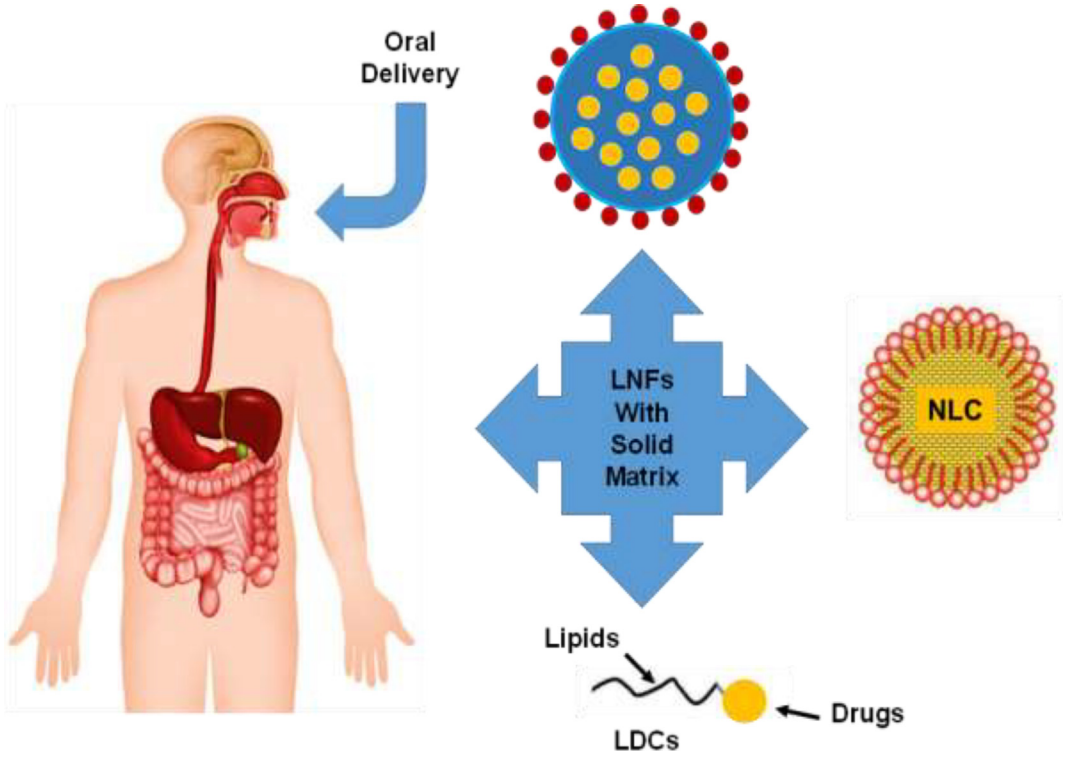

Fig. 7. Mechanisms to enhance the bioavailability of lipid nanoparticle preparation for oral application (*Banerjee and Pillai* (Banerjee and Pillai 2019); the copyright© 2019 Taylor & Francis).

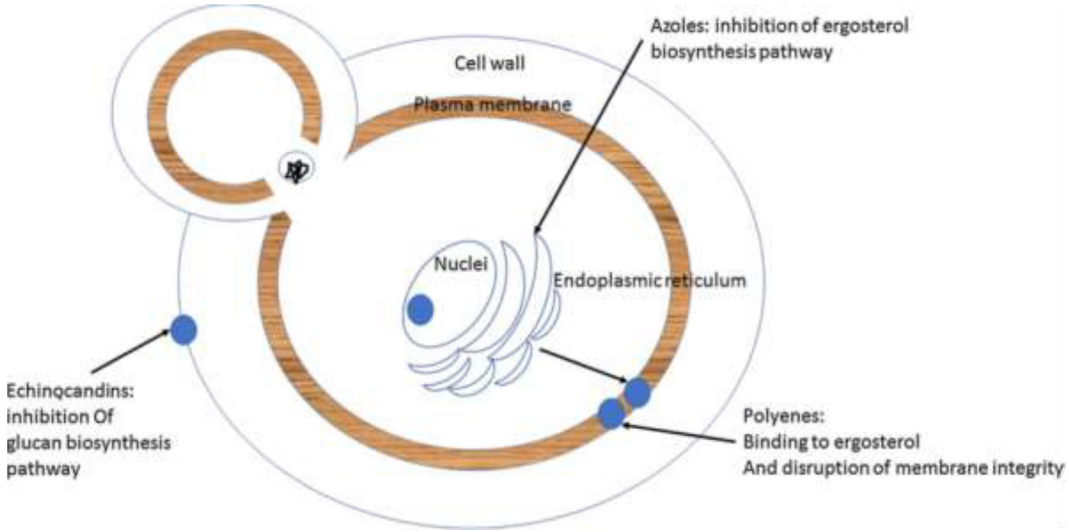

Fig. 8. The mechanism of action of antifungal drugs (by (Chatelon et al., 2019) Chatelon et al., the copyright© 2019 Springer Link). Presently, these four antifungal drug classes (Echinocandins, azoles, polyenes, and echinocandins) are in healthcare setups for fungal infections, as they could be used in oral, topical and I.V. dosage forms (Palareti et al., 2016).

which have been debated in an explanatory way to mark almost new targets, which may be used for medicine scheme and progress through the whole mycological cycle. Oral candidiasis is one of the utmost communal opportunistic mouth infections caused by *Candida albicans* (*C. albicans*) and other species including the genus Candida (Lombardi and Ouanounou, 2020). Kids with hematological cancers and individuals experiencing hematopoietic stem cell transplantation (HSCT) are in danger of developing aggressive mycological infections.

Anti-fungal treatments grew gradually throughout the preliminary ages of the previous period. Initially, potassium iodide was the typical choice of treatment for cutaneous mycological infections including actinomycosis, blastomycosis, sporotrichosis, and tinea from the start of the 20th period until later the Second World War (Shafiei et al., 2020).

Next, the Echinocandins class such as amphotericin B (AmB) agent is the drug of choice for treating various mycotic diseases. AmB has a promising fungicidal activity for the treatment(s) of infections caused by *Candida sp*, *Aspergillus* sp. and *Aspergillus flavus* (Sanguinetti and Posteraro, 2018, Houšť et al., 2020). Unfortunately, its' medical use is pointedly narrow by its noxious and mortal toxicities, for example, high-grade temperature, chills, low blood pressure, eating problems, nausea, vomiting, and noteworthy renal toxicity. Therefore, various formulations of AmB have been designed to enhance its cellular and tissue distribution.

Furthermore, three groups of medicines are primarily used for controlling aggressive mycoses in kids and youngsters. The well-worn and novel azoles, polyenes, and echinocandins (Palareti et al., 2016). However, each has a different mode of action, activity, and predisposition (Tragiannidis et al., 2021), as in Fig. 8. All these drugs target various portions of the mycological cell, specifically, the polyene group comprises the heptaene AmB, which interrelates with ergo sterol, the chief portion of the fungal cell membrane.

Econazole (ECO), a broad-spectrum anti-mycotic drug is applied for the treatment of dermal infections by dermatophytes (Na et al., 2020). Econazole nitrate (ECN) is an imidazole-derived complex, applied principally in the management of superficial fungal infections (Gujjar et al., 2019). Luliconazole is an innovative additional imidazole anti-fungal drug mostly used opposing to diseases caused by Candida and *Trichophyton sp*. Luliconazole utilizes an antimycotic mechanism by hindering enzymes in the mycological cell wall. In addition, 14-alpha-lanosterol demethylase is a sheath enzyme of the CYP51 group in the CYP450 major family of proteins that participated in ergosterol biosynthesis (Baghel et al., 2020).

In recent times, the grouping of two or more medicines in correctly advanced drug-delivery system(s) (DDS) has attracted growing attention from scientists as a latent approach to advance efficiency too by dropping medicine noxiousness. Currently, lipid-based preparations of AmB in clinical trials are Abelcet, AmBisome and Amphotec, manufactured by Sigma-Tau Pharmaceuticals, Gilead Sciences Inc and Sequus Pharmaceuticals, respectively. All of the mentioned agents are under consideration, certain parameters like liberation, absorption, distribution, metabolism, elimination and safety studies are done in contrast to AmB (Joseph and Bunjes, 2013).

Meanwhile, NPs "4S" (size, surface, shape, stability) characteristics give a chance to overcome drug drawbacks for instance unsteadiness, limited efficiency, reduced distribution, and side effects. They give the option to control medicine shortcomings such as volatility, limited effectiveness, reduced delivery, and adverse drug reactions.

Especially, various publications have been described in the literature regarding the opportunity to improve anti-fungal medicines bioavailability using liposomes and LNs. Amongst all, SLNs characterize a multipurpose scheme and they are capable of effectively improving bioavailability (Van Daele et al., 2019, Carbone et al., 2020).

In topical uses, occlusive characteristic(s) of SLNs are also measured which chiefs to a decrease in aquatic loss through the transdermal epithelium layer of skin (Afra et al., 2020). The nanoparticulate carrier schemes of SLNs have been grown attention for the limited treatment of dermal mycotic disease as they help in the penetration of loaded active constituents over the stratum corneal coating (El-Housiny et al., 2018). SLNs and NLCs are designed by lipids, which also seem in the conformation of sebum in the hair follicle(s) (Souto et al., 2020).

Lipid-centred nano-carriers have the prospective to be extremely effective in handling mycological infections. The nanometric bulk array reduces some merits of these conveyance schemes creating them an appropriate conveyance scheme to treat dermal mycological diseases. Constituent part magnitude, superficial charge, and lipid-loving characteristics show a major character

in defining diffusion deepness into various dermal coatings. It is supposed that negatively charged nanostructured lipid carriers fluctuating in dimensions amid 200 to 300 nm indicate larger permeation into bottomless dermal layers for the treatment of cutaneous dermatophytosis (Garg and Jain, 2022).

The use of a dermal anti-mycotic drug is generally enough to eradicate the dermatophyte and treats maximum patients of anthropophilic diseases, zoophilic dermatophytoses in people pose significant problems, specifically tinea capitis and tinea unguium, which mostly need a systemic cure. Furthermore, a significant characteristic of the constituents applied in the management of superficial mycoses is their stress-free permeation into the stratum corneum and perseverance at a persistent concentration all over the treatment. Regardless of the accessibility at the smallest amount some classes of antimycotic agents for medical application, work on a minute quantity of cellular receptors, that is, the cell membrane, cell wall, and nucleic acids and the cell division progression.

The improvement of several antimycotic drugs has previously meaningfully improved the capability to fight dermal mycosis (Lengert et al., 2020). SLNs can make a glue film on the surface of the dermis. They also have occlusive characteristics, which can lessen trans-epidermal water loss and progress the hydration of the skin layer that is beneficial in the cure of more or less dermal infections, for example, long-lasting atopic eczema. The minor mass of these nano-carriers permits them to accord to the corneum layer of the dermis; that's why, their presentation is meaningfully affected by constituent part size. This can improve medication permeation by enlargement of the inter-corneocyte breaches and dropping corneocyte filling (Daneshmand et al., 2018). Litraconazole-loaded NLC gel preparation for dermal use and describe various physical, medicinal and organic factors (Singh et al., 2021). SLNs have the ability to aim or target the epidermal stratum of the dermis and delay the remains of medicine in the dermal coating.

Cutaneous application of triglyceride nanoparticles (Fig. 9) (Garcês et al., 2018). There is scarce information allied to the transdermal penetration of lipid nano-particles, attainment of the circulation by passage dermal barrier or passing over hair follicles. For that reason, there is a necessity for a confined and site-specific conveyance scheme for the well-organized supervision of superficial fungoid infections (Khalid et al., 2021). Manifestation of lipids in SLNs clues to medicine exclusion or spurt discharge rather than measured discharge. This drawback confines the application of SLNs in transdermal medication conveyance schemes (Sudhakar et al., 2021). SLNs were the recorded operative in controlling mycological infections causing agents for instance *Rhizopus stolonifer* and *Alternaria sp*. in vitro circumstances (Trinetta et al., 2020). Therefore, topical use of SLNs-based gel with improved diffusion and retention in the skin on account of lipid nano-preparation will be abundant and auspicious for the dermal cure of mycological diseases and indicative aid (Ehsanfar et al., 2020).

As mentioned previously, AmpB medical use is pointedly narrowed by its noxious and mortal toxicities, for example, high-grade temperature, chills, low blood pressure, eating problems, nausea, vomiting, and noteworthy renal toxicity. Therefore, various formulations of AmB have been designed to enhance its cellular and tissue distribution. A nanoparticle laden with AmpB displays worthy effectiveness once used to treat Leishmania (Du et al., 2019).

A favourable approach to progress particle permeation through the subcutaneous layer of the dermis is the application of nanosystems, subsequently their lipid-loving property affluence the integral lipid layer passage. However, these transporters might enable particles conveyance with the help of hair follicles or arrange for controlled release by making marks on the dermis. In this background, lipid nanoparticles have been displaying auspicious outcomes to improve particles permeation up to the skin, decreasing blood absorption, and offering chemical stability to photoactive and light-sensitive compounds.

Fluconazole-loaded solid lipid nanoparticles (FLZ-SLNs) are a well-known SLNs-based treatment for *pityriasis versicolor* (PV). FLZ-SLNs were studied. Furthermore, the improved FLZ-SLN compound was integrated into the gel using Carpobol 934. A randomized controlled clinical study (RCT) of possible batches was performed on 30 well-diagnosed PV patients in comparison to the market product Candistan® 1% cream. Clinical and skin lesion KOH exams were performed every 4 weeks for 4 weeks. The results indicated that FlZ-SLNs were virtually spherical in form, with colloidal sizes and no aggregation. The drug entrapment efficiency

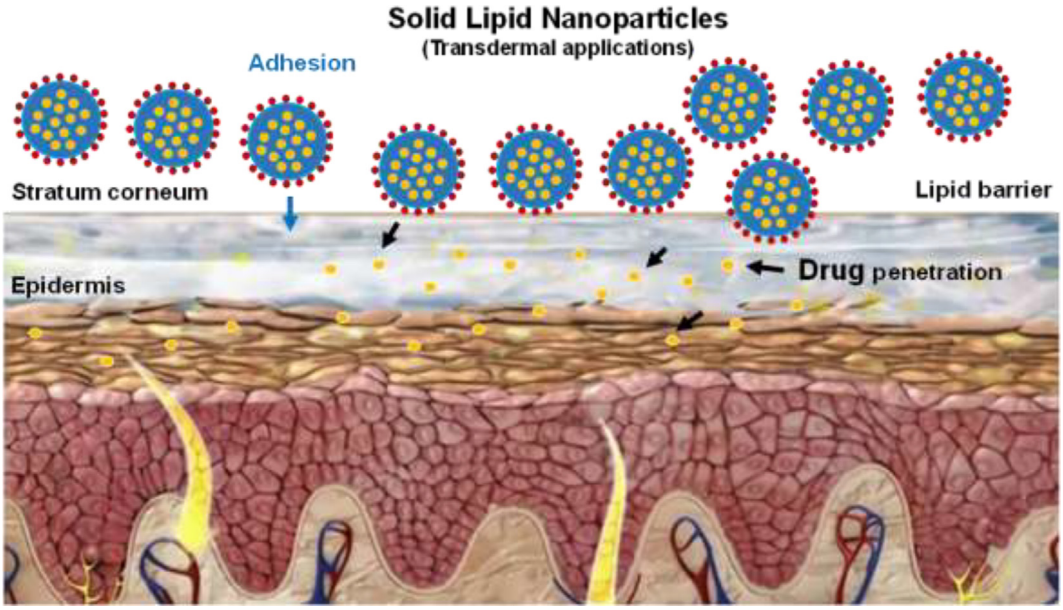

Fig. 9. The chemical protection of the merged constituents, permitting the dermal use of labile particles that are problematic to conveyance in classical semi-solid preparations; enhanced medication bioavailability, linked to the opportunity of modifying particle release, endorsing their dermal permeation and retaining.

ranged from 55.49% to 83.04%. The zeta potential values range from 21 and 33 mV, indicating excellent stability. FLZ demonstrated extended in vitro release from SLNs dispersion and its Carbapol gel using the Higuchi order equation. Clinical trials found a considerable increase (at the P = 05) in treatment response (1.4-fold; healing%, 4-fold; full eradication) in terms of clinical cure and mycological cure rate from PV compared to commercialized cream. The study's findings imply that the proposed FLZ-loaded SLNs topical gels outperform commercially available Candistan® cream in terms of the considerable quick therapeutic index in the treatment of PV.

2.1. Lipid-based preparations for the treatment of vulvovaginal candidiasis (VVC)

The most recommended treatment for vulvovaginal candidiasis is confined to the vaginal administration of imidazole antifungals. Miconazole nitrate is extensively and efficiently applied for the treatment of VVC (Kenechukwu et al., 2018). Vaginal conveyance of anti-mycotic drugs by unadventurous approaches, *viz*, lotions, ointments, gels and emulsions confines the efficacy of medication remedy as the active constituents are provided in comparatively higher concentrations but to a little extent. This could let propagation of the microbes, initiating worsening of the vaginal sides. Moreover, it might similarly lead to an increase in resistance because sequences of short-term over-medication are shadowed by long-standing under-medication dependent upon the rate of recurrence of use of the drug. This mark the necessity to make vaginal medicine conveyance schemes that will offer extraordinary mucosal tissue levels with minor systemic experience for sustained ages of the period in handling vaginal candidiasis. Nano-particulate carriers, due to their minor mass, can excellently cross and confine in many organic barricades and can similarly source modification in the micro-structure of mucus, thus increasing medication conveyance to the mucosal exteriors (Gardouh et al., Gintjee et al., 2020).

The smallest size of these systems significantly impacts the discharge summaries of captured medicines at the spot of action that could be organized, in this manner decreasing the rate of practice for improving patient acceptance. The existence of liquescent lipids convenes longstanding colloidal constancy and larger medication encapsulation and filling due to defective cry Writings hearsays the harmless sequence as selected or chosen remedy for vaginal infection for the duration of gestation is the application of dermal conveyance and no noxious effects on the unborn baby have been accredited. Therefore, the lipid nanocarrier-based gel of fluconazole (0.5% w/w) can be suggested to express improved beneficial properties in contending vulvovaginal candidiasis. The optimized formula for Fluconazole nanolipid vaginal gel is given in the following Table 3 (Takalkar and Desai, 2018). SLNs-based gel deals with high vaginal mucosal binding, consequently, increasing gel bond, medication permeation and preservation. Fizzy vaginal pills are also a modern progress that permits the rapid absorption of active pharmaceutical ingredients at the use site.

Table 3
Optimized formula for fluconazole nanolipid vaginal gel (Takalkar and Desai 2018).

Ingredients	Quantity (% w/w)
Fluconazole	0.5
Precirol ATO 5	3.5
Oleic acid	1.5
Kolliphor RH 40	2.0
Carbopol 974 P	1.0
Methylparaben	0.02
Disodium EDTA	0.1
Purified water	Qs[a] 100 g
Triethanolamine	Qs

[a] QS. Quantity sufficient.

They reveal superior effectiveness in antimycotic conveyance when related to old solid preparations. An additional different but similarly stimulating ground of NDDS discovered for intravaginal medication conveyance is CCS. All these methods comprise the loves of polymeric, micellar, liposomal and SLNs. They emphasise the enhancement of API conveyance and absorption at the use place by a lessening in constituent part mass and site medication conveyance (Firdaus et al., 2021).

2.2. Lipid-based preparations for ophthalmic agents applied topically

The cornea, conjunctiva, and sclera obstructions prevent sufficient drug diffusion to the latter superficiality of the eye. Present research on nanomedicine, as a healing method supported in marking the key cause of vision loss related to cataracts and diabetic retinopathy by dropping intra-ocular stress as the nanomedicine heightened and amended the medication-release summary and treatment summary by dipping the noxious effects of medicines. Numerous methodologies like the application of liposomes, Nanostructured lipid nanocarrier, hydrogel, nanoemulsion, polymeric micelles, SLNs, noisome, and inorganic nanoparticles, highlighted the necessity of nanomedicines for aiming the treatment of ophthalmic diseases (Qamar et al., 2019). Antifungal agents, Polyene and Azoles are used in topical Ophthalmic treatment and have physiochemical characteristics which affect their capability to enter the ophthalmic hurdles and spread to the spot of action in the optical milieu. Transporting these anti-fungal medicines to the various disease-ridden ophthalmic tissues, is now one of the tough tasks of antifungal drug therapy, mainly due to the complex makeup of the eye and the physicochemical characteristics of the several groups of anti-fungal medications (Lakhani et al., 2019).

3. SLNs challenges in case of the antifungal drug resistance

Anti-fungal drug resistance states stable genetic modifications of fungal infection-causing agents for a definite class of antifungal medicines that outcomes in an enlarged chance for therapy failure, Fig. 10 (Arastehfar et al., 2020). Anti-fungal resistance has arisen as a severe issue in the clinic for healing (Xu et al., 2020). *Candida auris* is a different ascomycetous yeast species initially insulated from the exterior earlobe tube of a patient in a Japanese clinic recently. The entity has then come to be the initial universally developing fungal infection-causing agent that displays multi-drug resistance along with a strong perspective for nosocomial spread (McCarthy et al., 2018).

In broad, medical antimycotic resistance is well-defined as the insistence on disease or indications instead of the application of suitable antimicrobial drugs that results in disappointment to eradicate the mycotic disease. Cellular pressure produced by the reaction to an antimycotic medicine activates mechanisms enabling dermatophyte existence. By advancement, these mycoses have settled composite cellular reaction methods as well as components of the environment cell signalling system, reactions to stressors and resistance to antimycotic substances.

The only procedure was accountable for the resistance of dermatophytes is the set-up of the overflow pumps, which actively propel numerous materials from the fungoid cell, together with antimycotic medicines, active constituents, disinfectants, etc. Multi-drug resistance consequences principally from the enlarged appearance of genetic factors have their place in the superfamily of ATP-binding cassettes, and mainly ABC carriers, which happen in mutually prokaryotes and eukaryotes. The ABC carriers

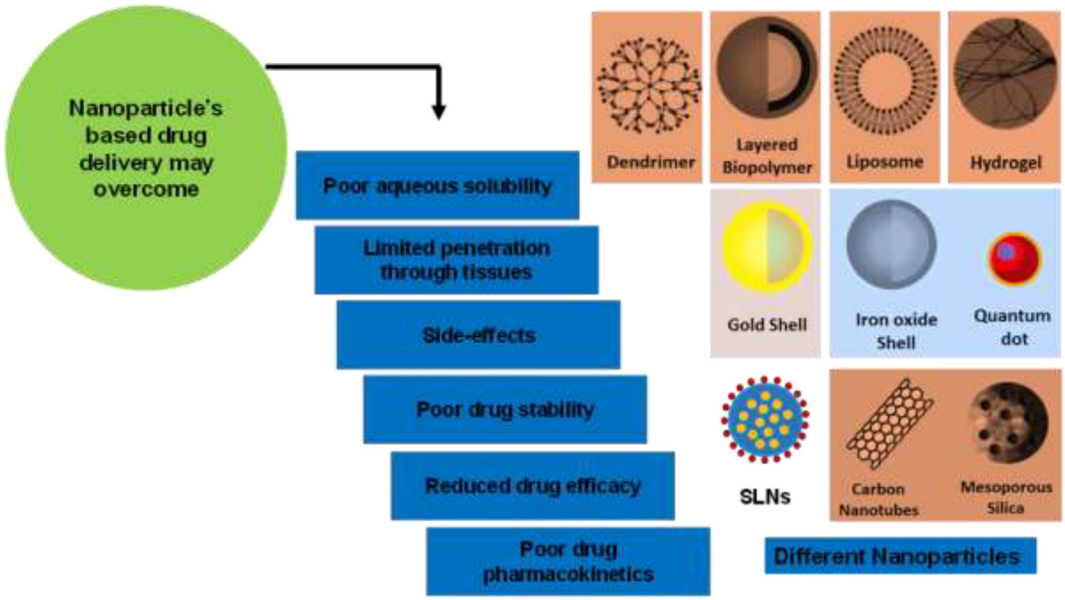

Fig. 10. Limitations that can be improved by nanoparticle applications.

vigorously hand over numerous physically and chemically varied complexes across cell membranes by ATP binding and hydrolysis, thus decreasing their assembly in the cell (Gnat et al., 2020)**.** Therapeutic drug monitoring (TDM) of azoles is broadly documented as a vital tool to offer ideal antimycotic treatment and is suggested for patient management (Furfaro et al., 2019).

The failure of antifungal remedies is difficult and hinges on aspects related to microbes and hosts (i.e. clinical resistance). The four most important mechanisms of resistance to antimycotic agents have been mentioned in the following:

3.1. Drug efflux pump

The stimulation of membrane-associated efflux pumps ejects the medicine outside of the cell, reducing its dose inside the cell, causing the minute quantity of medicine at the location of the mechanism.

3.2. Target mutation

The ERG11 gene encrypts the protein lanosterol 14a- demethylase in moulds, which is the mark protein for azoles. As a result, point alterations in this genetic factor modify the azole-binding site, ensuing in cheap attraction or failure to bind drug protein.

3.3. Target expression deregulation

In the existence of an azole representative, *Candida sp*. can progress a response mechanism in reply to ergosterol reduction with over-expression of the ERG11 genetic factor, causing increased production of lanos- terol 14a-demethylase. A rise in target profusion needs extra antifungal medicine for blockade-causing resistance.

3.4. Ergosterol biosynthesis pathway alteration

Furthermore, the alteration in the inheritable factor encrypting the lanosterol 14a-demethylase protein, the pathway of resistance also modifies other proteins from a similar pathway. The contact with azoles consequences in declined mycological sheath ergosterol and gathering of the mycological growth inhibitor 14a-methyl-3,6-diol. Alteration in the ERG3 gene inhibits 14a-methyl-3,6-diol from the 14a-methyl-fecosterol development and gathers forerunners that can substitute the cellular ergosterol. These two influences may lead to purposeful membranes and subsidize the progress of resistance in *Candida* sp. (Fuentefria et al., 2018).

Logically intended drug delivery systems can improve medication performance and overwhelm lots of these drawbacks (Dudhipala et al., 2020, Shah et al., 2021, Kamal et al., 2022), Certainly, lipid-based preparations of AmB, such as lipid complex (LC), colloidal dispersion (CD) and liposomal AmB, presented a prodigious lessening in AmB renal toxicity without affecting its broad-spectrum antifungal activity. These outstanding outcomes encouraged the use of several novel drug delivery schemes to expand the care of antifungal drugs even as maintaining or improving their efficiency. Amongst numerous novel medicine conveyance schemes presently in active examination in production and academic circles, NPs have arisen as an advanced and hopeful stage capable to lessen unwanted drug noxious effects while keeping or improving its healing efficiency (Kraisit et al., 2021).

4. New simplified sampangine byproducts with effective antifungal activities against *Cryptococcal meningitis*

Based on the antimycotic natural product sampangine, these new basic isoxazole derivatives were recognized to have outstanding inhibitory action against *Cryptococcus neoformans* (*C. neoformans*). Principally, 9a (novel synthetic histone deacetylase compound) was extremely active (the minimum inhibitory concentration of 80% inhibition, MIC_{80} = 0.031 g/mL) and pointedly repressed biofilm development, melanin, and urease markers of *C. neoformans*. The 9a deacetylase compound had good blood–brain barrier penetrability and efficiently compacted the brain fungous load in a murine model of *cryptococcosis*. The antimycotic mechanism of action of compound 9a was preliminarily explored by transmission electron microscopy (TEM) and flow cytometry. It could cause necrocytosis of *C. neoformans* cells and capture the cell cycle in the G1/S phase. Isoxazole compound 9a denotes a hopeful lead compound for the progress of new Cryptococcal meningitis healing agents (Li et al., 2019).

4.1. New antifungal agents to combat resistance

Novel antifungal agents are designed, in response to increasing issues of fungal resistance toward medications, which efficiency of classical antifungal agents used against invasive and resistant fungal illnesses. Three novel antimycotic drugs, namely ibrexafungerp, olorofim, and fosmanogepix, specifically Ibrexafungerp, have similar structures and mechanisms of action as echinocandins, they accomplish their action by preventing fungal beta-1,3-glucan synthase enzyme and also are useful against *tri*-azole-resistant *Aspergillus* sp. Unlikely, the two other agents, fosmanogepix and Olorofim have a new mechanism of action; which inhibit a vital fungal protein named dihydroorotate dehydrogenase, which is important for mycotic DNA synthesis, they also accomplish their antifungal activity by inhibiting the alteration of mannoproteins by Gwt1 enzyme, mannoproteins are important for cell wall consistency. All these drugs are useful in treating fungal infections caused by *Aspergillus* sp., as well as A. fumigatus (Mohamed et al., 2020).

Many antifungal agents with novel mechanisms of action have been patented in this decade, for example, Corifungin by ACEA Biotech Inc. (USA), comprises a hydrophilic sodium salt of AmB, produced through fermentation by *Streptomyces nodosus* strain (NRRLB- 2371), having a well in vitro and in vivo extended spectrum against fungi. Additionally, C3 Jian (USA) and Wisconsin Alumni Research Foundation (USA) patented various beta-peptides, containing cyclically controlled beta-amino acid deposits with helical conformations, with a virtuous in vitro activity against both planktonic- and biofilm-forming *C. albicans* cells. The lab-made compound byproducts from 8-hydroxyquinoline-7-carboxamide were patented by Polichem SA, Luxembourg (Switzerland), which showed the best results against yeasts and filamentous fungi from side-to-side iron chelation. Further synthetic compounds, with an advanced mode of action, are the quinazolinone derivatives patented by F2G Limited (Great Britain) that inhibit the fungal enzyme dihydroorotate dehydrogenase (DHODH), showing good activity against *Aspergillus* sp. (Silva et al., 2019).

4.2. Photodynamic inactivation of fungi

In the past three decades, photodynamic inactivation (PDI) of fungi has become a promising approach for fungi treatment owing to several features, including non-drug resistance, spatiotemporal selectivity, minimum invasion, and allowance of repetitive treatments. In PDI, photosensitizers upon light illumination generate reactive oxygen species (ROS), which would cause damage to surrounding cells or tissues. Among the various photosensitizers used for photodynamic antifungal therapy, phthalocyanines (Pcs), as the second-generation photosensitizers, have drawn great interest because of their long absorption wavelength (λ_{max} > 660 nm), high extinction coefficient (ε_{max} > 105 $L{\cdot}mol^{-1}{\cdot}cm^{-1}$), and tunable photophysical and photochemical properties via facile chemical modification (Tang et al., 2020).

4.3. Lipid-based preparations for the treatment of Candida sp. Infection in diabetic patients

Rodrigues et al. stated in their assessment that how high blood glucose levels in diabetic mice condensed the proneness of *Candida* sp. to voriconazole and AmpB (Rodrigues et al., 2019). Lesser proneness to antimycotics in diabetic patients has also been confirmed in the medical situation (Bhuyan et al., 2018) received an important variance in the figure of *C. albicans* and *Candida parapsilosis* that is resistance to fluconazole in diabetes patients linked to hale and hearty controls. Similarly, 47% of patients with diabetes Mellitus which is a high proportion, testified to having *Candida* sp. quarantines that are resistant to ketoconazole in additional research.

As emphasized by *Rodrigues et al.* (Rodrigues et al., 2019), biofilm construction by *Candida sp.* is an important feature that hinders the actual cure of mycological disease. A maximum of the diseases produced by *Candida sp.* are the effect of biofilm development. Biofilms give *Candida* sp. safety to endure the higher amount of antimycotics (Mohd Sazlly Lim et al., 2020).

5. SLNs limitations and drawbacks

SLNs evade limitations like poor stability, easy degradability, drug leakage and sterilization problems associated with former colloidal systems for instance liposomes, microemulsion, and polymeric nanoparticles (Mahmoud et al., 2020). Although it has certain drawbacks, such as lower loading capability and possible exclusion of biologically active substances (Ghanbarzadeh et al., 2019). Even though these SLNs have numerous merits but also have some demerits for instance unrestrained medication ejection and poor medication loading capability in contrast to NLC (Yaghoubi et al., 2015). NLCs have been presented as a novel group of SLNs to solve numerous drawbacks related to the SLNs (Gomaa et al., 2022).

6. Conclusion and prospects

SLNs are a new and emerging drug delivery strategy used to deliver drugs to their respective targeted sites, that benefits us in the form of increased efficiency and solubility of many classical and latent antifungal agents. In comparison to bases and vehicles used for older antifungal preparations, SLNs are generally regarded as biocompatible and easily decomposable and have little cell toxicity to mammalian cells. Additionally, they also showed the best loading volume for hydrophilic as well as hydrophobic drugs. SLNs also increase the bioavailability of lipophilic drugs, have targeted delivery and protect drugs against harsh environmental conditions and have greater physical stability.

SLNs have shown promising responses in antifungal drug delivery. Although they have certain limitations; for example, in developing SLNs which are intended for parenteral administration must be sterilized, and upon sterilization, they can lose physical and chemical stability. However, it should be kept in mind that the physical and chemical stability of any drug formulation must not be compromised, so in the case of SLNs, sterilization affects the stability. In addition, sterilization through gamma radiation fosters the generation of free radicals that could make chemical modifications in the SLNs, while sterilization through heat can increase the particle size and render the physical stability of the formulation. Crystal growth is another problem associated with SLNs, to avoid crystal growth by "Ostwald ripening", the SLNs must have enough chemical stability and particles must also have a very narrow size distribution. Additionally, bulk surface properties and molecular characterization of the lipid greatly affect the physical, chemical strength and appropriateness of SLN preparations. Lipid molecules sometimes undergo structural alterations which result in decreasing lipid layer organization during drug loading, as the drug gets integrated between lipid layers. Surfactants are also important for the stability and formation of SLNs, hence the selection of specific and most appropriate surfactants must be sought out. Lastly, if SLNs are cooled below their crystallization point, it will result in irreversible phenomena like gelling or expulsion of the incorporated drug.

Future research should focus on combating the limitations to improve the physicochemical stability of SLNs, focus on alternative methods for sterilization of SLNs intended for parenteral use and

select the most appropriate surfactant for their stability. Lastly, further studies should focus on the feasibility of formulating drugs with SLNs to enhance their action and reduce antimicrobial resistance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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