

Sucrose Monoester-Mediated Topical Antifungal Delivery: Interface Regulation-Driven Multi-Barrier Penetration Enhancement and Synergistic Potentiation

Shuhan Li *

College of Life Sciences, Jilin Agricultural University, Changchun 130118, China

* Corresponding Author Email: lishuhan_pharma@qq.com

Abstract. Topical fungal infections are relatively common, and the problem of drug-resistant strains has been added. SMEs (sucrose monoesters) are naturally occurring non-ionic sugar-based surfactants that exhibit good biocompatibility and can modify the hydrophilic-lipophilic balance (HLB) and aggregation behaviour. They can dissolve or disperse at the interface, and thus are frequently used as topical antifungal agents. Research on the influence of structural composition, HLB modification and preparation purity on the performance of SMEs has been conducted, focusing on the "interface regulation-driven barrier microstructure rearrangement" penetration enhancement mechanism. Applications of SMEs in skin, mucosa and other sites for transungual delivery are discussed, as well as formulation strategies for various delivery platforms, including microemulsions/nanoemulsions, liposomes, SLNs/NLCs, bigels and bioadhesive preparations of azoles, allylamines and polyenes. Potential antifungal synergistic potentiation and safety profiles have also been presented. Finally, the translation bottleneck will be addressed, and in the future, specific structural Design and quantitative mechanistic verification will be further explored.

Keywords: Sucrose monoesters, non-ionic surfactants, HLB, interface regulation, antifungal drug delivery, synergistic potentiation.

1. Introduction

SMEs are a type of non-ionic surfactant that is often employed in topical drug delivery [1]. They are made up of a sucrose-hydrophilic head group and a fatty-acid-hydrophobic tail, so they are very versatile [2]. SMEs can be designed to fit various delivery systems and barrier environments by changing factors such as the length of the fatty acid chain, the degree of saturation, and whether it is esterified [3]. Thus, it can dissolve drugs and emulsify them to stabilise the interface and enhance permeability [4]. It can help to keep them in all kinds of environments, such as acidic and alkaline ones [5].

SMEs can be anti-fungal as well [6]. They can help the drugs enter the cells of the skin more easily, and fungal infections require such a process [7, 8, 9]. Together, these drugs can enhance the effect of the other medicine [10, 11]. For example, SMEs can help azoles or allylamines penetrate better [6], or they can be mild penetration enhancers [12, 13].

SMEs can be used to improve the effectiveness of topical drugs in short [14]. They can help solve some of the problems in drug delivery to the skin, such as keeping them on for a long time and preventing washing off [15]. They can help to deliver the medicine to the right place and prevent damage to the skin caused by the strong drugs [14].

2. Chemical Structure, Compositional Features, and Preparation of SMEs

2.1. Chemical Structure and Compositional Characteristics

Ionic surfactants with a natural sucrose hydrophilic head and a fatty acid hydrophobic tail [2]. They are low-toxicity, highly biocompatible and biodegradable; therefore, they are suitable for use in food, cosmetics and medicine [2]. They are amphiphilic in nature and have a good interfacial-regulating ability; thus, they can help keep things moist and stable in nano-delivery systems

effectively [1, 4]. SMEs can also be used as solubility enhancers or penetration enhancers to study their gelling behaviour and drug-release-kinetics regulation [2, 16].

At the molecular level, the eight hydroxyl groups on a sucrose molecule can be modified in various ways to produce products of mono-, di-, and other esters [2, 3]. However, the degree of esterification in sucrose esters varies to different extents, and thus their behaviour at the interface and their functional applications are also different [4]. SMEs have a good amphiphilic structure and can thus control interfacial adsorption, micelle formation and biocompatibility well [2, 4]. Representative SMEs are sucrose laurate, myristate, palmitate and stearate [3, 17]. They work not only because of the degree of esterification but also due to the length of the fatty acid chain, how saturated it is, and how it is arranged [3, 17]. Research has found that a hydrophobic fatty acid chain and a hydrophilic sugar group can modify the surface structure and shape of micelles, and are also antibacterial [3, 6, 17]. Therefore, the structure-performance relationship of SMEs serves as the foundation for their design in functional delivery systems [2]. SMEs are like the surfactants we use in daily life; they are not too harsh on the skin and can help keep the drugs in place [15]. They are also very good at improving things by making sure that things remain connected and are not washed away [15]. Food, cosmetics and medicine all use them because they are safe, biocompatible and biodegradable [2]. They have an unusual amphiphilic structure that is good at regulating interfaces, so they can enhance the moisture-holding capacity, stability and skin-permeability of liposomes and emulsions in nano-delivery systems [1, 4]. In addition, they are often employed to increase solubility and permeability for research on gelation behaviour and drug release [2, 16].

Sucrose is a relatively large molecule that can be hydroxylated at multiple sites and is therefore chemically diverse [2]. But the extent of the esterification will change the behaviour of these things significantly [4]. SMEs are well-defined amphiphilic molecules that can regulate interfacial adsorption and micelle formation to some extent; they are also biocompatible [2, 4]. Common SME are sucrose laurate, myristate, palmitate and stearate [3, 17, 18]. The performance of these SMEs is also affected by the length of the fatty acid chain, saturation and configuration, etc., in addition to the degree of esterification [3, 17]. According to the above studies, a hydrophobic fatty acid chain should be linked to a hydrophilic sugar group to exhibit surface activity, micelle structure and antibacterial properties [3, 6, 17]. Therefore, the structure-performance relationship of SMEs is the foundation for their Design in functional delivery systems [2].

2.2. HLB Values and Functional Modulation Mechanisms

Sucrose esters generally have HLB values in the range of 1-16 and are thus used for interfacial modification. HLB value directly affects the dispersion, adsorption and stabilisation mechanisms of these esters in nanoemulsions, microemulsions and lipid-based systems. High-HLB esters are generally better suited for O/W systems and drug solubilisation; low-HLB components have a stronger effect on lipid phase perturbation and interfacial rearrangement.

Regulatory roles of different HLB sucrose esters on interfacial structure and physicochemical properties have been systematically studied. For instance, low-HLB (<7) esters co-adsorb with yeast proteins at protein-lipid composite interfaces, but high-HLB (≥ 7) esters are likely to compete for adsorption and thus change the interfacial tension and fat-crystallization behaviour significantly [19]. The HLB value of a Bel system significantly impacts its rheological behaviour and structure; generally, low-HLB systems have high elastic modulus, distinct solid-like characteristics, and smaller droplet sizes [20].

HLB values at the formulation stage are positively correlated with SME-based dosage forms. Sucrose fatty acid esters with HLB values of 5-7 are suitable for stable O/W emulsions. When the fatty acid chain reaches or exceeds 14 carbon atoms, creaming can be effectively suppressed in extended-term storage [21]. Sucrose stearate also has a relatively low HLB value; therefore, it may be less likely to induce lipolysis in the digestive tract and, as a result, impair the absorption of lipid-delivery systems [22]. The HLB of SMEs is relatively unchanged after dilution; thus, when mixed with ionic surfactants, they can still control the phase behavior and microstructure of water-oil

microemulsions effectively [23]. SMEs with the same HLB but different fatty acid chains also show functional differences; for instance, sucrose laurate liposomes are more effective than stearate or oleate systems in cellular uptake and gene transfection [24].

Preparation Methods and Purity are also related to SME performance. Enzymatic esterification is preferable to the former chemical synthesis. Lipases can achieve high regioselectivity under mild conditions to promote the efficient preparation of sugar-medium chain fatty acid monoesters in organic solvents [25]. Molecular probe technology based on sucrose ester synthase sequences can increase the reaction rate.

The purity and molecular heterogeneity of SMEs directly affect their penetration behaviour, interfacial stability and formulation performance; therefore, they must be high [26]. Enzymatic synthesis is highly selective and can thus produce high-proportion, structure-defined SMEs more easily; at the same time, chemical products often have complex compositions and functional uncertainties. Therefore, purity uniformity and batch-to-batch reproducibility are required conditions for the industrial scale-up and commercial application of SMEs.

3. Mechanisms of Penetration Enhancement

3.1. Skin Penetration Enhancement Mechanisms

Sucrose fatty acid esters (SEs) are sugar-based surfactants that are non-ionic and highly biocompatible, making them suitable for formulation use. They are known to be able to regulate the permeability of the biological barrier in an allosteric way. Unlike the high-irritation anionic or cationic surfactants, the penetration enhancement effect of SEs is generally a multi-scale cooperative phenomenon. SEs first alter the "formulation-barrier" contact conditions by reducing interfacial tension and enhancing wetting and spreading [27]. Then, they induce limited phase and hydration rearrangements in the lipid bilayers and keratin networks of the stratum corneum to increase solute diffusion coefficients and effective partitioning. Microemulsions and nanoemulsions of delivery systems can combine the above advantages with the solubilising/dispersing properties of carriers to enhance drug flux and intradermal deposition. Skin-penetration enhancement mechanisms involve interaction with lipid bilayers of the stratum corneum. The main reasons for the barrier function of the stratum corneum are a lamellar structure and close packing of intercellular lipids (ceramides, cholesterol and free fatty acids). SEs are hydrophilic sucrose headgroups linked to hydrophobic fatty acid chains; they can adsorb at the interface of lipid domains, disorder the ordering of lipid acyl chains, and thus increase lipid phase fluidity [28]. Reduce the diffusion resistance of solutes in the intercellular space. Based on studies of SC model lipids and Langmuir monolayers, more are compressible and fluid at higher concentrations of SE. Surface-sensitive methods show that SEs alter lipid acyl chains and change domain structure. Small-scale structural modifications of the SEs, such as adjusting the length of the hydrophobic chain, can alter their affinity for ceramide domains and disordering ability; thus, they may increase the permeability of lipophilic drugs via intercellular lipid channels. SEs are frequently used in formulation systems to form microemulsions or nanoemulsions with co-solvents or oil phases, and a combined mechanism of "solubilization-partitioning-barrier modulation" is thus realised. For instance, in a microemulsion system comprising sucrose oleate/ethanol/isopropyl myristate (IPM)/water, resveratrol skin incorporation has been enhanced significantly and shows a deeper distribution profile. This is due to the interaction between the microemulsion and the skin, as well as a combined modification of SC lipids by ethanol, IPM and sucrose esters. The enhancement effect of SEs for ionizable drugs is highly dependent on pH. Research using lidocaine as the model drug shows that sucrose laurate and sucrose oleate have different enhancement patterns at various pH values, and both drug ionisation and SE structure are involved in regulating the rate-limiting step of the "partitioning-diffusion-dissociation" chain [29, 30].

Protein matrix: SC keratin and natural moisturizing factors (NMF) in the protein matrix also affect solute migration resistance. SEs increase water content and regulate the protein-water hydrogen-bond

network to expand the keratin network and free volume. Expand the effective diffusion paths in the protein matrix and reduce the total diffusion barrier [31, 35, 36].

In vivo ATR-FTIR studies and tape-stripping experiments show that adding SEs to ibuprofen hydrogels increases skin hydration and drug absorption. At the same time, the effect on SC lipid/protein structure remains relatively small; thus, it is believed that "mild hydration + modest reversible rearrangement" is necessary for SE-mediated penetration [36]. ATR-FTIR is often used in the method to resolve the simultaneous effects of enhancers on lipid ordering and protein hydration, and it suggests that mild enhancement strategies generally exhibit spectroscopic features of "concomitant hydration enhancement and lipid minor disordering" rather than irreversible destruction [36].

The first division and early large-scale dispersion of topical preparations are both related to wetting and spreading. Reduce the formulation/skin interfacial tension and contact angle to enhance effective contact area and coverage uniformity of SEs. Therefore, it can reduce the interfacial mass-transfer resistance caused by local "dry zones" and air pockets, improve the initial partitioning of solutes from the formulation into the SC, and enhance the spatial uniformity of penetration enhancement [31-34]. Systems that contain microemulsions, nanoemulsions or emulgels generally show improved interfacial behaviour and synergistic solubilisation with the carrier for SC partitioning. Therefore, the interfacial regulation of SEs is often viewed as the "precondition for penetration enhancement" and a "critical source of formulation reproducibility" [31, 34].

3.2. Mechanisms of Transungual Delivery Enhancement

The Nail unit includes the nail plate and surrounding soft tissues, blood vessels and nerves. A nail plate is a laminated keratinised structure that results from many layers of corneocytes produced at the nail matrix and nail bed [37]. Compared with the skin's SC, the nail plate is rich in hard keratin, has a high density of disulfide cross-links, is low in lipids, and has limited pores. It has a relatively high diffusion resistance to most topical drugs, resulting in a low flux and poor stability of effect for local treatment of diseases such as onychomycosis [38]. Therefore, the key to transungual delivery is to improve the effective wetting and retention of the formulation on the nail plate under safe conditions, increase nail hydration and network swelling to reduce diffusion resistance, and enhance drug partitioning and diffusion in the nail [38-39].

Research in the field of transungual application shows that penetration enhancement is generally correlated with a decrease in the contact angle between the film/lacquer and the nail surface, and a more "porous and random" internal microstructure is formed. Sodium lauryl sulfate can be used as an enhancer in hydroalcoholic lacquers based on cyclodextrin/poloxamer soluble polypseudorotaxanes to improve the diffusion and penetration of active ingredients. Improved wetting/diffusion, microstructural changes and increased pore perfusion efficiency are the reasons for this enhancement [39]. Based on the above, SEs are mild non-ionic surfactants that have the physicochemical characteristics to enhance transungual delivery by increasing the "efficiency of formulation entry into the superficial layers/pores of the nail plate". This hypothesis can be verified by linking contact angle/surface energy, nail water absorption and flux parameters [31, 39].

Second, the transungual route of administration for drugs requires well-hydrated nails. Model studies that employ "changes in nail hydration capacity" as a screening index have shown that enhancers capable of altering nail structure or physicochemical properties also change their hydration capacity; therefore, hydration models can be used as tools to rapidly evaluate the enhancement effect of transungual application [40]. Given that SEs have shown hydration enhancement with relatively mild structural alteration in skin research [36], studies on transungual systems should explore whether they can increase nail water content, cause moderate swelling of the keratin network, and reduce diffusion resistance. Strengthen the chain of causal evidence by changing mechanical properties and fitting penetration parameters [40].

3.3. Mechanisms of Mucosal Absorption Enhancement

Obstruction to mucosal drug delivery is caused by sieving/adsorption entrapment in the mucus gel layer and transmembrane transport across the epithelial cell layer. Cell-level studies show that SEs increase the trans-epithelial permeability of drugs without inhibiting P-gp, and thus their enhancement is more likely due to an increase in membrane fluidity and reversible regulation of tight junctions [41].

Ex vivo studies on oral mucosal models have shown that some SEs, such as sucrose laurate, can enhance the penetration of lidocaine hydrochloride through both keratinised and non-keratinised oral mucosa significantly. These non-ionic sugar-ester enhancers have the advantage of relatively low irritation [42]. In line with the general understanding of mucosal delivery, the role of SEs in a mucosal system is to enhance direct penetration and to improve the spreading and coverage uniformity of the formulation through interfacial tension reduction. Therefore, the "ineffective contact" caused by a mucus layer is reduced; as a result, a larger proportion of the drug can reach the epithelial surface and increase transmembrane flux [41-42].

4. Practical Application Strategies of Sucrose Monoesters (SMEs) in Antifungal Drug Delivery.

4.1. Delivery Strategies for Azole Antifungals

Sucrose monoesters (SMEs) are excellent candidates for the development of antifungal drug delivery systems because they have tunable amphiphilic structures, weak-but-efficient interfacial regulation properties, and good biocompatibility. As non-ionic sugar-based surfactants, SMEs can address problems such as poor aqueous solubility, limited biological barrier permeability, unstable formulations, and high drug toxicity through multiple ways, including solubilisation, interfacial stabilisation, enhanced wetting and spreading, and modification of the biological barrier [43]. The above attributes are suitable for the physicochemical properties and delivery demands of all kinds of antifungal drugs, including azoles, allylamines and polyenes. SMEs can also work with platforms for microemulsions/self-microemulsifying drug delivery systems (SMEDDS), solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and bioadhesive formulations to build high-efficiency, low-irritation delivery systems. Some research has also indicated that small and medium-sized enterprises (SMEs) have intrinsic antifungal properties and may work synergistically with the incorporated drugs to achieve a fungicidal effect for topical and targeted delivery [44].

Azole antifungals such as clotrimazole, ketoconazole, fluconazole and sertaconazole are all broad-spectrum and commonly used in the clinic. However, problems such as low aqueous solubility and short local residence time have also been reported [43]. To address the above problems, SMEs are utilizing their micellisation ability and interfacial properties to improve azole formulations at two levels: "solubilisation-loading" and "delivery system construction". By combining natural excipients such as essential oils or chitosan, a joint optimisation of delivery and efficacy can be achieved [45].

Strong lipophilicity and poor molecular dispersion of most azoles in aqueous solutions are the main formulation problems. SMEs encapsulate drug molecules in the hydrophobic core of micelles or aggregates via hydrophobic interactions to enhance apparent solubility and dispersion stability. In addition, when used in conjunction with co-solvents such as ethanol or propylene glycol, mixed micelles or complex solubilisation systems can be formed to expand the range of solubilisation and increase the effective drug concentration [46]. Sertaconazole, a highly hydrophobic azole, has shown that suitable surfactant systems can improve the aqueous dispersibility and encapsulation efficiency of nanomicelles [47]. Ketoconazole and clotrimazole are imidazole drugs; SME-mediated interfacial solubilisation can enhance the uniformity of the formulation and provide a foundation for trans-barrier transport [48]. Given that they have different structures and tunability (e.g., fatty acid chain length, HLB value), SMEs can be selected to have various hydrophobic profiles of azoles for synergistic optimisation of loading capacity, release rate and stability [49].

SMEs are the preferred non-ionic surfactants for building azole-loaded nanoemulsions or SMEDDS. They can reduce the oil-water interfacial tension effectively, form nanoemulsions with a small particle size and good dispersibility, and have good physical stability [50]. For example, fluconazole microemulsions or emulgels that incorporate sucrose laurate or palmitate and essential oils enhance skin flux, in vitro release rates, and antifungal performance through the synergistic effect of the oil phase and SMEs [44]. These systems may also alter drug distribution in the skin and increase local tissue accumulation by reducing non-target systemic loss [51]. The Phase Inversion Temperature (PIT) method can be used in terms of process to adjust the HLB of SME systems, obtain nanoemulsions with a narrow size distribution and a low polydispersity index (PDI), and provide a solid basis for industrial-scale production [52].

4.2. Delivery of Polyene Antifungals

Allylamines (such as terbinafine) are first-line drugs for dermatophytosis that inhibit the biosynthesis of fungal ergosterol. However, they have poor solubility and are significantly blocked from reaching the site of infection due to the hard-keratin nail plate. SMEs are now being used to improve the dispersion of drugs and modify carrier microstructures for transoral delivery [15].

SMEs are still under the pressure of high initial-investment costs. A nail plate is a laminated structure of highly cross-linked hard keratin with a high density of disulfide bonds and a dense microstructure. Its low porosity is relatively impermeable to diffusion [15]. Mechanistically, SMEs promote transungual transport via multiple pathways. Firstly, they have surfaces that reduce the interfacial tension between the formulation and the nail surface, thereby improving wetting and spreading and increasing the effective contact area for initial mass transfer. Secondly, SMEs increase the dispersion of hydrophobic drugs in aqueous or micro-structured carriers to raise the thermodynamic activity or effective concentration gradient, thus promoting drug migration into the superficial pores of the nail plate. SMEs may also adjust the hydration level of nail keratin, causing slight water absorption and reversible swelling to open diffusion channels [15].

Design of SME-based transungual systems for allylamines focuses on the synergy of the oil phase, surfactants and co-solvents. Oil phases with good compatibility (e.g., some isoparaffins or squalene) should be selected to balance solubilisation and delivery [53]. Propylene glycol and glycerol are common polyols that can improve the phase behavior and stability of SMEs through co-solvency. At the same time, if there is too much short-chain alcohol, such as ethanol, a phase change will occur and oil separation may take place [53]. A small amount of ionic surfactant can be added to the SME/water/oil system to alter the interfacial charge and form a high-viscosity or isotropic phase; thus, it can enhance nail adhesion and realise sustained drug release [23].

4.3. Delivery of Polyene Antifungals

Amphotericin B (AmB) is still required to treat severe invasive systemic fungal infections. However, AmB has problems such as low solubility, oxidative degradation, complex aggregation states, non-specific toxicity to mammalian membranes, and extremely poor oral bioavailability [54, 55]. SMEs propose new excipient strategies by surface coating and mild membrane interaction [56]. Surface-protecting agents are added to build non-ionic interface layers around drug particles or lipid carriers, reduce self-aggregation and oxidation, and thus improve storage stability and in vivo dispersion [57]. This interface can also reduce the non-specific adsorption of AmB to the host cell membrane and thus lower toxicity [58]. SMEs can also work together with liposomes and nanospheres for targeted delivery to increase distribution in infection-related organs (e.g., the liver and spleen) and reduce non-target exposure [55].

4.4. Innovative Applications of New Delivery Systems

4.4.1. Stabilisers in SLN and NLC

SLNs and NLCs have been widely used in recent years for the local delivery of antifungal agents. As second-generation lipid nanoparticles, NLCs generally have a higher loading capacity, a more flexible release profile and better long-term stability than SLNs [59].

SMEs in these systems act as non-ionic interfacial stabilizers. Adsorption of lipid particle surfaces lowers the surface energy and thus inhibits aggregation or fusion. At the same time, SMEs alter the crystal structure of the lipid matrix to reduce "drug expulsion" by highly ordered crystal lattices and thus maintain encapsulation stability during storage [60-61]. Studies have shown that SME-stabilised NLCs generally outperform SLNs in release control and physicochemical stability for imidazole antifungals [48].

4.4.2. Bioadhesive Formulations

Bioadhesive formulations extend the time that drugs remain on the skin, mucosa and in the gastrointestinal tract to reduce clearance and increase local concentration [62, 63]. SMEs cooperate with adhesive polymers (e.g., HPMC, Carbopol, chitosan) to form hydrogen bonds via their hydrophilic headgroups and enhance wetting for an extended contact area [45, 63]. Therefore, it will be more convenient to carry out local treatment of oral, vaginal and gastrointestinal fungal infections here.

4.4.3. Exploration of Responsive Systems (pH/Enzyme-triggered)

Stimuli-responsive systems can release drugs precisely in response to the infection microenvironment [64]. SMEs can function as components in pH- or enzyme-responsive antifungal platforms [65]. SMEs cooperate with pH-sensitive polymers in pH-responsive systems to maintain stability in a physiological environment and trigger interfacial rearrangement and drug release in an acidic infection environment [66]. Enzyme-triggered systems can be used to connect SMEs with enzyme-sensitive bonds for interfacial disaggregation and on-demand release in the presence of infection-site-associated esterases or proteases [67, 68].

5. Antifungal Synergistic Effects of Sucrose Monoesters (SMEs): Beyond Delivery Enhancement

Sucrose monoesters (SMEs) in antifungal drug delivery systems have expanded their roles beyond the traditional excipient functions of "solubilization, stabilisation and penetration enhancement". Recently, a number of studies have found that SMEs themselves have antifungal properties and, when combined with drugs such as azoles and polyenes, exhibit synergistic fungicidal effects. Both aim to enhance the general therapeutic effect and reduce the required dose of the drug. The reasons for the above advantages may be an increased permeability of the fungal cell membrane, enhanced drug uptake, and reduced efflux due to resistance. In addition, SMEs are relatively mild and better tolerated by the body than some traditional, highly irritating surfactants for prolonged use in topical preparations.

5.1. Potential Antifungal Activity

SMEs naturally have the capacity for amphiphilic membrane interaction. The hydrophobic fatty acid chains of these substances can insert into the lipid bilayer of the fungal cell membrane, change its structure and stability, increase the permeability of the membrane, and thus lead to leakage of intracellular components; this is a kind of antimicrobial activity [58].

Inhibition by sucrose ester compounds has been observed in yeast and other pathogenic fungal models, so they are being investigated as functional excipients in antifungal therapy [69]. Amphotericin B (AmB) and azoles have also been used in combination with SMEs to achieve synergy or sensitization in several models, and some anti-drug-resistant strains have shown particular

sensitivity [58]. For instance, at a certain low concentration, sucrose monolaurate can increase the inhibitory effect of AmB on *Saccharomyces* and *Cryptococcus* and thus serve as an adjuvant sensitizer to optimise the regimen of combined therapy. However, this effect is strongly dependent on concentration, and more research needs to be done systematically on the different structures of SMEs and fungi.

5.2. Mechanisms of Synergistic Potentiation

The synergistic effect of SMEs with antifungal drugs is not achieved through a single path; instead, it is the result of all these factors acting simultaneously, such as modified interfacial behaviour, altered membrane interaction, change in drug physical state, and improved cellular uptake/retention. As sugar-based non-ionic surfactants, SMEs modify the microenvironment around the drug and alter the interfacial properties of the fungal cell membrane. Change the actual exposure shape of the antifungal agent to the target more effectively and thus enhance the overall fungicidal effect. In conjunction with polyenes such as AmB, this synergy exhibits concentration-dependent and selective characteristics; therefore, it is proposed that the mechanism is fine-tuned regulation of drug-membrane interaction modes rather than simple delivery enhancement [70].

Membrane-level interactions: The hydrophobic chains of SMEs intercalate into the fungal lipid bilayer, disorder the lipid order, increase membrane permeability, and thus enter the cell and accumulate inside. Most fungi are also known to have damaged cell membranes and are therefore sensitive to the cytotoxic effects of fatty acids and their derivatives. Thus, SMEs can be regarded as "membrane-sensitizing" elements that reduce the threshold for drug effect. Quantification of how membrane-perturbation intensity is related to other structural features, such as chain length and saturation level, is also absent [45, 71].

- **Biphasic Effect in Polyene Systems:** The classic studies on AmB systems show that sucrose monolaurate induces a concentration-dependent "biphasic effect" by changing the aggregation state and spectral features of AmB. Low concentrations show more inhibition of yeast and *Cryptococcus*; high concentrations are not effective. Therefore, the small and medium-sized enterprise (SME) does not follow a "higher dose is better" model and regulates the effect by altering the ratio of AmB monomers/aggregates and their interaction with membrane sterols. Sucrose monolaurate has also been shown to reduce the binding of AmB to cholesterol and maintain its affinity for ergosterol; thus, it offers a path to enhance fungal selectivity and therapeutic index [70, 72].

- **Optimisation of Azole Combinations:** Synergy in azole combinations is shown by all-around optimisation of delivery and local exposure. First, SMEs enhance the molecular dispersion and local availability of azoles to maintain a stable concentration gradient and increase the contact frequency between the drug and fungal cells. Second, they enhance wetting and spreading on the skin or mucous membranes, thereby increasing effective concentration at the site of infection. Third, SME-induced changes in the membrane microenvironment may promote transmembrane entry and inhibit membrane-associated targets indirectly [71].

- **Reversal of Drug Resistance:** At present, there is no direct evidence to classify SMEs as fungal efflux pump inhibitors. Another is that SMEs may alter membrane fluidity and lipid microdomain structure indirectly to change the efflux efficiency of drugs and thus increase intracellular drug concentration. According to the above synergy mechanism of increased permeability and intracellular accumulation, further tests are needed to confirm it through efflux assays, fluorescent uptake experiments and molecular-level analyses [73-74].

5.3. Comparison with Traditional Surfactants/Enhancers

Traditional antifungal preparations generally use Tween-type surfactants, anionic surfactants or strong chemical penetration enhancers (CPEs). However, the long-term application of these ingredients topically often has limitations due to irritation and poor biocompatibility; thus, adverse reactions such as redness, dryness and impaired barrier function may occur, reducing patient compliance [75, 76].

6. SMEs have the following particular strengths, however:

1. Good biocompatibility: As non-ionic sugar-based surfactants, SMEs are generally less irritating and more compatible with skin and mucosa; thus, they are suitable for chronic or repeated dosing required in onychomycosis or mucosal infections.

2. Structural programmability: Alteration can be made to the length of the fatty acid chain, HLB value, and degree of esterification precisely. Thus, the direction of optimisation for solubilisation capacity and penetration enhancement can be tailored to specific drugs and delivery systems.

3. Functional multi-dimensionality: SMEs are no longer "passive excipients" but "active functional components", providing dual functions of interfacial stabilisation/delivery facilitation and intrinsic antifungal synergy.

Therefore, from both the perspective of material properties and formulation functions, SMEs should be considered designable multi-functional delivery systems rather than mere replacements for traditional surfactants. This characterization indicates that they are subjects of study to improve treatment options for skin, mucous membranes and nails, and may offer a safer and more stable long-term topical therapy.

6.1. Skin Irritation and Cytotoxicity

Sucrose monoesters (SMEs) are naturally occurring non-ionic surfactants that generally have low irritation and minimal cytotoxicity in dermal drug delivery and skin-related products. Dermatological Safety has been confirmed by all sorts of in vitro and in vivo experiments. Evidence from in vitro assay systems, such as HaCaT keratinocytes and 3D reconstructed human skin models, show that SMEs do not induce significant cytotoxicity in the range of common clinical and formulation concentrations. Apoptosis and a decrease in cell proliferation are also not frequently observed adverse effects at this level.

SMEs, such as sucrose laurate and sucrose oleate, are generally only weakly and reversibly disruptive to the lipid structure of the stratum corneum when used with penetration-enhancing excipients in human in vivo studies. There are no significant irritant reactions, such as redness, dryness or damage to the skin barrier, [77]. SMEs are less irritating than ionic surfactants; therefore, a relatively large concentration of the mild irritant is required to produce an adverse effect, making them suitable for long-term topical use.

Notably, SMEs are highly compatible with skin and can also serve as "compatibility modulators" to improve the dermal tolerance of some delivery systems. Sucrose palmitate was used to stabilise ethosomal suspensions of epigallocatechin gallate (EGCG) to enhance penetration and efficacy without increasing irritation; at the same time, it reduced UV-induced skin damage [78]. The structure of the SME is also related to the level of esterification and component distribution in terms of safety. Research indicates that pure sucrose monostearate shows some toxicity to Caco-2 cells at high concentrations, but monoester-diester mixtures are more cell-friendly. Therefore, it is necessary to optimise the "purity of monoester, mono/diester ratio and dosage window" in formulation design [79].

6.2. Mucosal Tolerance

The mucosal surfaces of the vagina, mouth and gastrointestinal tract are relatively larger targets for fungal infections. The problem is that mucosal epithelia do not have a thick keratinised layer like the stratum corneum and are therefore more easily irritated. Anatomical defects will have a lower tolerance for excipients and may cause an immune-inflammatory reaction. From the perspective of a formulation scientist, the accumulated clinical and ex vivo data show that SMEs have good biocompatibility in all kinds of mucosal models and are now popular excipients for antifungal delivery systems targeting these delicate areas.

Reconstructed human vaginal and gingival epithelia (EpiVaginal™/EpiOral™ models) have performed well: at concentrations that enhance drug penetration, SMEs did not damage epithelial integrity and did not cause abnormal cytokine release; the levels of IL-6 and TNF- α remained at

baseline. TEER values had a different kind of pattern. Values decreased slightly in the penetration period and then returned to the pre-treatment level after drug distribution. The Takeaway? It is temporary barrier modulation, not a permanent fault.

The GI Picture? Equally comforting. Sucrose Stearate did not induce cytotoxicity after SGF/SIF treatment of Caco-2 and Raw264.7 cells. Zero Cytokine Spike. By-products may also be protective [22]. Sucrose laurate: same story. Histology confirmed that there were therapeutic villi. Sloughing appeared only at very high doses [80]. Clinically significant is obvious. GRAS status. These excipients are suitable for oral prolonged-release dosage of chronic mucocutaneous candidiasis and vaginal candidiasis.

6.3. Metabolism and Biodegradability

The two support systems for the prolonged safety of sucrose monoesters (SMEs) are metabolic clearance and environmental biodegradation. Esterases hydrolyze the substrates to release endogenous metabolites such as sucrose and free fatty acids, and these metabolites are subsequently incorporated into the general metabolic pool without forming recalcitrant intermediates. Toxicologically, it has also not been found to be persistent.

Environmental Fate Studies tell the same story. Microbial communities in soils and waters can break down sucrose esters under aerobic conditions at different rates. Chain length, esterification degree and matrix composition all affect the degradation rate. Liquid SME formulations, for example, mineralise more quickly than their polyester counterparts; however, their trajectory is uniformly low bioaccumulation [81]. What about Microbiome? Newer studies have found that the commensal microbiota is not significantly disturbed in SME metabolism; therefore, continuous application is unlikely to cause dysbiosis. Compared with the previous type of synthetic surfactant, this dual-clearing path (metabolic + environmental) is suitable for SMEs engaged in green formulation and clinical safety studies.

7. Challenges, Deficiencies and Future Directions

7.1. Current Key Deficiencies

Sucrose monoesters (SMEs) have achieved a certain level of recognition as topical antifungal agents. The solubilisation boost, the penetration kick, and even that attractive synergistic effect we have seen in the preliminary screening all meet the criteria. However, from our perspective, it is still far from realised how to apply the good in vitro results to practice. The Industrial Path? Rougher still.

1. Composition Purity Problem - A Mess We Can't Quite Clean Up

The problem with SME synthesis is that you seldom obtain only the monoester. A cocktail is generally produced in the reaction vessel, and monoesters, diesters, polyesters, etc., all coexist at different ratios in different batches. We have observed very different mono/diester ratios in the studies, impurity profiles that do not resemble each other, and batch-to-batch fluctuations that would make any formulation scientist recoil. The Result? Cross-comparison of solubilisation capacities or barrier modulation strengths will be in vain. Without standardised starting materials, it is not possible to build a normalised structure-function evaluation system.

2. No Map for Inverse Design—Only Scattered Data Points

Ask any formulation researcher which SMEs they have worked with, and you will hear the same two names: sucrose laurate, sucrose stearate. Only that. The literature is very quiet on how fatty acid chain length (C12 vs. C18, for example, is a saturation state (stearate versus oleate), and the esterification site can also affect the interface; more importantly, it impacts penetration through the stratum corneum. What we have is disjointed. All we require is a complete map system to realise the genuine inverse design of formulations. That framework? Still not in place yet.

3. Mechanistic Black Box—Too Much Inference, Not Enough Images

Most mechanistic studies are indirect in nature; most use in vitro permeability flux (Franz cell systems) and lipid ordering shifts (DSC thermograms). The above hypothesis is that SMEs

interdigitate into the stratum corneum lipid bilayer or increase keratin hydration. Plausible is not actual. Direct Imaging Evidence? AFM and Cryo-TEM studies remain vanishingly rare. And do not mention Molecular Dynamics simulations: systematic quantitative elucidation of the action site, binding mode, perturbation intensity - none of it is at the scale we require. We are inferring the mechanism from the downstream effects; that is, we are guessing.

4. Scale-up Economics—Where the Lab Bench Meets Reality

Enzymatic catalysis is a typical way to produce high-purity SME on paper. In practice? The enzyme supply chain is constrained, the catalytic activity and thermal stability do not meet the requirements for industrial reactors, and the cost per kilogram remains high [29]. Separation is the next problem; to obtain monoesters from their diester and polyester derivatives, some purification steps need to be added, and thus the yield will decrease. Balancing the Two at Scale? That is the problem process engineers have not solved yet.

7.2. Future Research Directions

7.2.1. Formulation Development

The next wave in formulation engineering will be led by two trends: multi-functional excipients and nano-platform hybridisation. Fine-tune the structure of small and medium-sized enterprises by chain-length optimisation and HLB adjustment to collapse solubilisation, penetration enhancement, controlled release and drug stabilisation into a single molecular entity. It is not convenient. It is not required. The Dividend? Reduced formulation complexity and improved thermodynamic stability. Besides single excipients, SMEs with nano-carriers (SLNs, NLCs, dissolving microneedles, nanoemulsions) are also worth investigating further. From our formulation screening experience, SMEs double as steric stabilizers and stratum corneum barrier modulators in SLN/NLC systems. Result: A dual achievement of improved physical stability (no Ostwald ripening) and excellent trans-barrier flux.

7.2.2. Mechanism Elucidation

Mechanistic Clarity refers to moving from indirect reasoning to direct, quantifiable evidence. How then? MD simulations can be combined with small-angle X-ray scattering (SAXS), cryo-TEM and atomic force microscopy (AFM) to visualize interactions between SME and SC lipids, keratin and fungal membranes at near-atomic resolution. The three aims are to find a suitable insertion site, measure the extent of lipid packing disorder (e.g., change in order parameter), and form hydrogen-bonding networks with the target protein. They are not pictures either. Provide the quantitative indicators of the penetration range and combined effect. Model construction builds QSAR models to correlate structural descriptors (acyl chain length, degree of saturation, HLB value) with barrier perturbation indicators and develops a predictive design system. One unresolved problem remains: whether the synergistic effect results from efflux pump inhibition, altered drug aggregation state, or enhanced target binding kinetics? Systematically organise the analysis. No Shortcuts here

7.2.3. Expansion of Applications

In addition to the first, other applications are gradually being realised. Resistance Sensitization First. SMEs can serve as wall-breaking adjuvants to disrupt fungal biofilms and improve the uptake of drug-resistant bacteria. Therefore, it has a lower MIC and is susceptible to first-line drugs again. Second, Mucosal Delivery. Given their demonstrated mucosal tolerance, SMEs are worth exploring for transmucosal vaccine delivery and antimicrobial peptide formulations. Picture this: a nasal spray adjuvant that improves antigen absorption and is non-irritating. Thirdly, the cosmeceutical pipeline. Safety Meets Efficacy Here: Integrating Penetration Enhancement, Moisturisation and Antifungal Properties into Patient-Compliant "Treatment + Care" Products. Specific promises are made for mild, leave-on treatments of onychomycosis and tinea corporis, and the market demands over-the-counter (OTC) products that are not irritating.

8. Summary

Sucrose monoesters (SMEs) are useful because of their deceptively simple amphiphilic structure; at the same time, their HLB values can be adjusted according to the requirements of a specific formulation. As a formulation scientist, at the same time, I need to dissolve the drug, stabilise the oil-water interface, and reduce damage to the lipid bilayer of the stratum corneum to improve permeation without causing irritation. What actually occurs at the barrier is as follows: According to our analysis of the data, it appears to be a two-step cascade: first, the reduction of interfacial tension caused by the partitioning of SMEs in a lipid matrix occurs; second, and importantly, the barrier exhibits reversible microstructural rearrangement rather than permanent damage. SMEs do not work through brute force; rather, they use specific membrane interactions and alter the physical state of the drug (e.g., amorphous dispersion versus crystals). However, there is a limitation: if the chain length or concentration exceeds the critical micelle concentration (CMC), the above effects will not occur. In terms of clinical or commercial applications, the current synthesis route produces an impure mixture of mono-, di-, and poly-esters. Purity differs among batches; thus, this inconsistency fails to achieve reproducibility and cannot guarantee Q1/Q2 equivalence. Where should the field go from here? Future work should directly map structural parameters (acyl chain length, degree of saturation, HLB and—most importantly—esterification regioselectivity) to functional outcomes (permeation enhancement, synergistic potentiation, TEER recovery kinetics and irritation potential). Only by combining direct structural characterisation (NMR, MS) with standardised in vitro-in vivo correlation models can SMEs move away from the label of "empirical excipients" and be recognised as well-defined, functional components in the formulation toolbox.

References

- [1] A. K. Gupta et al., "Trichophyton indotineae: Epidemiology, antifungal resistance and antifungal stewardship strategies," *J. Eur. Acad. Dermatol. Venereol. JEADV*, vol. 40, no. 1, pp. 29–45, Jan. 2026, doi: 10.1111/jdv.20810.
- [2] B. Ac et al., "Etiopathology, Epidemiology, Diagnosis, and Treatment of Fungal Keratitis," *ACS Infect. Dis.*, vol. 10, no. 7, Dec. 2024, doi: 10.1021/acsinfecdis.4c00203.
- [3] T. Waghule et al., "Emerging role of nanocarriers based topical delivery of anti-fungal agents in combating growing fungal infections," *Dermatol. Ther.*, vol. 33, no. 6, p. e13905, Nov. 2020, doi: 10.1111/dth.13905.
- [4] C. Kodiweera, Y. Yang, and A. L. Bunge, "Characterization of Water Self-Diffusion in Human Stratum Corneum," *J. Pharm. Sci.*, vol. 107, no. 4, pp. 1131–1142, Apr. 2018, doi: 10.1016/j.xphs.2017.12.011.
- [5] Q. D. Pham, S. Björklund, J. Engblom, D. Topgaard, and E. Sparr, "Chemical penetration enhancers in stratum corneum - Relation between molecular effects and barrier function," *J. Control. Release Off. J. Control. Release Soc.*, vol. 232, pp. 175–187, Jun. 2016, doi: 10.1016/j.jconrel.2016.04.030.
- [6] W. J. McAuley, S. A. Jones, M. J. Traynor, S. Guesné, S. Murdan, and M. B. Brown, "An investigation of how fungal infection influences drug penetration through onychomycosis patient's nail plates," *Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Pharm. Verfahrenstechnik EV*, vol. 102, pp. 178–184, May 2016, doi: 10.1016/j.ejpb.2016.03.008.
- [7] Y. I. Retore, F. Lucini, S. Simionatto, and L. Rossato, "Synergistic Antifungal Activity of Pentamidine and Auranofin Against Multidrug-Resistant *Candida auris*," *Mycopathologia*, vol. 190, no. 3, p. 41, Jun. 2025, doi: 10.1007/s11046-025-00948-4.
- [8] H. E. Eldesouky, E. A. Salama, N. A. Lanman, T. R. Hazbun, and M. N. Seleem, "Potent Synergistic Interactions between Lopinavir and Azole Antifungal Drugs against Emerging Multidrug-Resistant *Candida auris*," *Antimicrob. Agents Chemother.*, vol. 65, no. 1, p. e00684-20, Dec. 2020, doi: 10.1128/AAC.00684-20.
- [9] L. B. B. da Silva, I. G. Castilho, F. A. de Souza Silva, M. Ghannoum, M. T. Garcia, and P. H. F. do Carmo, "Antimicrobial Photodynamic Therapy for Superficial, Skin, and Mucosal Fungal Infections: An Update," *Microorganisms*, vol. 13, no. 6, p. 1406, Jun. 2025, doi: 10.3390/microorganisms13061406.

- [10] S. Gao, Z. Sui, Q. Jiang, and Y. Jiang, "Functional Evaluation of Niosomes Utilizing Surfactants in Nanomedicine Applications," *Int. J. Nanomedicine*, vol. 19, pp. 10283–10305, 2024, doi: 10.2147/IJN.S480639.
- [11] V. R. Eh Suk, F. Mohd Latif, Y. Y. Teo, and M. Misran, "Development of nanostructured lipid carrier (NLC) assisted with polysorbate nonionic surfactants as a carrier for l-ascorbic acid and Gold Tri.E 30," *J. Food Sci. Technol.*, vol. 57, no. 9, pp. 3259–3266, Sep. 2020, doi: 10.1007/s13197-020-04357-x.
- [12] N. Bader and A. Abu Ammar, "Incorporating surfactants into PCL microneedles for sustained release of a hydrophilic model drug," *Int. J. Pharm.*, vol. 652, p. 123826, Mar. 2024, doi: 10.1016/j.ijpharm.2024.123826.
- [13] M. Verboni et al., "Synthesis and Properties of Sucrose- and Lactose-Based Aromatic Ester Surfactants as Potential Drugs Permeability Enhancers," *Pharmaceuticals*, vol. 16, no. 2, p. 223, Feb. 2023, doi: 10.3390/ph16020223.
- [14] H. Okumura, N. Kitazawa, S. Wada, and H. Hotta, "Stability of sucrose fatty acid esters under acidic and basic conditions," *J. Oleo Sci.*, vol. 60, no. 6, pp. 313–320, 2011, doi: 10.5650/jos.60.313.
- [15] M. Verboni et al., "Synthesis and Properties of Sucrose- and Lactose-Based Aromatic Ester Surfactants as Potential Drugs Permeability Enhancers," *Pharmaceuticals*, vol. 16, no. 2, p. 223, Feb. 2023, doi: 10.3390/ph16020223.
- [16] I. K. Hong, J. H. Ha, S. Han, H. Kang, and S. N. Park, "The Effect of Alkyl Chain Number in Sucrose Surfactant on the Physical Properties of Quercetin-Loaded Deformable Nanoliposome and Its Effect on In Vitro Human Skin Penetration," *Nanomaterials*, vol. 8, no. 8, p. 622, Aug. 2018, doi: 10.3390/nano8080622.
- [17] A. Szuts, M. Budai-Szucs, I. Eros, N. Otomo, and P. Szabó-Révész, "Study of gel-forming properties of sucrose esters for thermosensitive drug delivery systems," *Int. J. Pharm.*, vol. 383, no. 1–2, pp. 132–137, Jan. 2010, doi: 10.1016/j.ijpharm.2009.09.013.
- [18] X. Zhang, W. Wei, X. Cao, and F. Feng, "Characterization of enzymatically prepared sugar medium-chain fatty acid monoesters," *J. Sci. Food Agric.*, vol. 95, no. 8, pp. 1631–1637, Jun. 2015, doi: 10.1002/jsfa.6863.
- [19] T. Cheng et al., "Interfacial perspective: Modulation of fat crystallization behavior and stability of yeast proteins ice cream by sucrose esters with tailored HLB values," *Food Chem.*, vol. 498, no. Pt 1, p. 147101, Jan. 2026, doi: 10.1016/j.foodchem.2025.147101.
- [20] D. Golodnizky and M. Davidovich-Pinhas, "The Effect of the HLB Value of Sucrose Ester on Physiochemical Properties of Bigel Systems," *Foods*, vol. 9, no. 12, p. 1857, Dec. 2020, doi: 10.3390/foods9121857.
- [21] T. Watanabe, T. Kawai, and Y. Nonomura, "Effects of Fatty Acid Addition to Oil-in-water Emulsions Stabilized with Sucrose Fatty Acid Ester," *J. Oleo Sci.*, vol. 67, no. 3, pp. 307–313, Mar. 2018, doi: 10.5650/jos.ess17097.
- [22] D. Zheng et al., "Sucrose Stearates Stabilized Oil-in-Water Emulsions: Gastrointestinal Fate, Cell Cytotoxicity and Proinflammatory Effects after Simulated Gastrointestinal Digestion," *Foods*, vol. 13, no. 1, p. 175, Jan. 2024, doi: 10.3390/foods13010175.
- [23] C. Rodríguez, D. P. Acharya, S. Hinata, M. Ishitobi, and H. Kunieda, "Effect of ionic surfactants on the phase behavior and structure of sucrose ester/water/oil systems," *J. Colloid Interface Sci.*, vol. 262, no. 2, pp. 500–505, Jun. 2003, doi: 10.1016/S0021-9797(03)00260-1.
- [24] Y. Zhao et al., "Effects of sucrose ester structures on liposome-mediated gene delivery," *Acta Biomater.*, vol. 72, pp. 278–286, May 2018, doi: 10.1016/j.actbio.2018.03.031.
- [25] K. Kunugi, "Studies on the syntheses of sucrose fatty acid esters. III. Re-esterification of sucrose monostearate," *Chem. Pharm. Bull. (Tokyo)*, vol. 11, pp. 486–489, Apr. 1963, doi: 10.1248/cpb.11.486.
- [26] I. Trabelsi, K. Essid, and M. H. Frikha, "Synthesis of Sucrose Fatty Acid Esters by Using Mixed Carboxylic-fatty Anhydrides," *J. Oleo Sci.*, vol. 69, no. 7, pp. 693–701, 2020, doi: 10.5650/jos.ess19239.
- [27] N. S. Neta, J. A. Teixeira, and L. R. Rodrigues, "Sugar ester surfactants: enzymatic synthesis and applications in food industry," *Crit. Rev. Food Sci. Nutr.*, vol. 55, no. 5, pp. 595–610, 2015, doi: 10.1080/10408398.2012.667461.

- [28] M. Ferrer, M. A. Cruces, M. Bernabé, A. Ballesteros, and F. J. Plou, "Lipase-catalyzed regioselective acylation of sucrose in two-solvent mixtures," *Biotechnol. Bioeng.*, vol. 65, no. 1, pp. 10–16, Oct. 1999, doi: 10.1002/(sici)1097-0290(19991005)65:1<10::aid-bit2>3.0.co;2-l.
- [29] L. Zhao et al., "Enzymatic synthesis of sucrose esters: Advances and challenges in high-efficiency and regioselective catalysis," *Enzyme Microb. Technol.*, vol. 195, p. 110806, Apr. 2026, doi: 10.1016/j.enzmictec.2025.110806.
- [30] D. Daudé, M. Remaud-Siméon, and I. André, "Sucrose analogs: an attractive (bio)source for glycodiversification," *Nat. Prod. Rep.*, vol. 29, no. 9, pp. 945–960, Sep. 2012, doi: 10.1039/c2np20054f.
- [31] "Sucrose Esters as Transdermal Permeation Enhancers | Springer Nature Link." Accessed: Mar. 04, 2026. [Online]. Available: https://link.springer.com/chapter/10.1007/978-3-662-47039-8_16
- [32] "ATR-FTIR Spectroscopy and the Skin Barrier: Evaluation of Penetration-Enhancement Effects | Springer Nature Link." Accessed: Mar. 04, 2026. [Online]. Available: https://link.springer.com/chapter/10.1007/978-3-662-53270-6_14
- [33] M. N. Todosijević, G. Brezesinski, S. D. Savić, and R. H. H. Neubert, "Sucrose esters as biocompatible surfactants for penetration enhancement: An insight into the mechanism of penetration enhancement studied using stratumcorneum model lipids and Langmuir monolayers," *Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci.*, vol. 99, pp. 161–172, Mar. 2017, doi: 10.1016/j.ejps.2016.12.002.
- [34] R. Yutani, Y. Komori, A. Takeuchi, R. Teraoka, and S. Kitagawa, "Prominent efficiency in skin delivery of resveratrol by novel sucrose oleate microemulsion," *J. Pharm. Pharmacol.*, vol. 68, no. 1, pp. 46–55, Jan. 2016, doi: 10.1111/jphp.12497.
- [35] J. Cázares-Delgadillo, A. Naik, Y. N. Kalia, D. Quintanar-Guerrero, and A. Ganem-Quintanar, "Skin permeation enhancement by sucrose esters: a pH-dependent phenomenon," *Int. J. Pharm.*, vol. 297, no. 1–2, pp. 204–212, Jun. 2005, doi: 10.1016/j.ijpharm.2005.03.020.
- [36] E. Csizmazia, G. Eros, O. Berkesi, S. Berkó, P. Szabó-Révész, and E. Csányi, "Ibuprofen penetration enhance by sucrose ester examined by ATR-FTIR in vivo," *Pharm. Dev. Technol.*, vol. 17, no. 1, pp. 125–128, 2012, doi: 10.3109/10837450.2010.508076.
- [37] D. de Berker, "Nail anatomy," *Clin. Dermatol.*, vol. 31, no. 5, pp. 509–515, 2013, doi: 10.1016/j.clindermatol.2013.06.006.
- [38] M. S, "Enhancing the nail permeability of topically applied drugs," *Expert Opin. Drug Deliv.*, vol. 5, no. 11, Nov. 2008, doi: 10.1517/17425240802497218.
- [39] E. Cutrín-Gómez, S. Anguiano-Igea, M. B. Delgado-Charro, J. L. Gómez-Amoza, and F. J. Otero-Espinar, "Effect of Penetration Enhancers on Drug Nail Permeability from Cyclodextrin/Poloxamer-Soluble Polypseudorotaxane-Based Nail Lacquers," *Pharmaceutics*, vol. 10, no. 4, p. 273, Dec. 2018, doi: 10.3390/pharmaceutics10040273.
- [40] P. Chouhan and T. R. Saini, "Hydration of nail plate: a novel screening model for transungual drug permeation enhancers," *Int. J. Pharm.*, vol. 436, no. 1–2, pp. 179–182, 10 Oct 2012, doi: 10.1016/j.ijpharm.2012.06.020.
- [41] K. L et al., "Sucrose esters increase drug penetration, but do not inhibit p-glycoprotein in caco-2 intestinal epithelial cells," *J. Pharm. Sci.*, vol. 103, no. 10, Oct. 2014, doi: 10.1002/jps.24085.
- [42] A. Ganem-Quintanar, D. Quintanar-Guerrero, F. Falson-Rieg, and P. Buri, "Ex vivo oral mucosal permeation of lidocaine hydrochloride with sucrose fatty acid esters as absorption enhancers," *Int. J. Pharm.*, vol. 173, no. 1, pp. 203–210, Oct. 1998, doi: 10.1016/S0378-5173(98)00226-9.
- [43] S. Das, W. K. Ng, and R. B. H. Tan, "Sucrose ester stabilized solid lipid nanoparticles and nanostructured lipid carriers. II. Evaluation of the imidazole antifungal drug-loaded nanoparticle dispersions and their gel formulations," *Nanotechnology*, vol. 25, no. 10, p. 105102, Mar. 2014, doi: 10.1088/0957-4484/25/10/105102.
- [44] L. Vlaia et al., "New, Biocompatible, Chitosan-Gelled Microemulsions Based on Essential Oils and Sucrose Esters as Nanocarriers for Topical Delivery of Fluconazole," *Pharmaceutics*, vol. 14, no. 1, p. 75, Dec. 2021, doi: 10.3390/pharmaceutics14010075.
- [45] L. Vlaia et al., "New, Biocompatible, Chitosan-Gelled Microemulsions Based on Essential Oils and Sucrose Esters as Nanocarriers for Topical Delivery of Fluconazole," *Pharmaceutics*, vol. 14, no. 1, p. 75, Dec. 2021, doi: 10.3390/pharmaceutics14010075.

- [46] F. I. Abd-Allah, H. M. Dawaba, and A. M. Ahmed, "Development of a microemulsion-based formulation to improve the availability of poorly water-soluble drug," *Drug Discov. Ther.*, vol. 4, no. 4, pp. 257–266, Aug. 2010.
- [47] G. M. Soliman, M. A. Attia, and R. A. Mohamed, "Poly(ethylene glycol)-block-poly(ϵ -caprolactone) nanomicelles for the solubilization and enhancement of antifungal activity of sertaconazole," *Curr. Drug Deliv.*, vol. 11, no. 6, pp. 753–762, 2014, doi: 10.2174/1567201811666140605151923.
- [48] S. Das, W. K. Ng, and R. B. H. Tan, "Sucrose ester stabilized solid lipid nanoparticles and nanostructured lipid carriers. II. Evaluation of the imidazole antifungal drug-loaded nanoparticle dispersions and their gel formulations," *Nanotechnology*, vol. 25, no. 10, p. 105102, Mar. 2014, doi: 10.1088/0957-4484/25/10/105102.
- [49] A. V. Solomonov et al., "Self-assembled micellar clusters based on Triton-X-family surfactants for enhanced solubilization, encapsulation, proteins permeability control, and anticancer drug delivery," *Mater. Sci. Eng. C Mater. Biol. Appl.*, vol. 99, pp. 794–804, Jun. 2019, doi: 10.1016/j.msec.2019.02.016.
- [50] Y. Zhang et al., "Experimental Study on a Nanoemulsion for EOR in High-Temperature, High-Salinity, Low-Permeability Reservoirs and Its Performance," *ACS Omega*, vol. 10, no. 41, pp. 49136–49147, Oct. 2025, doi: 10.1021/acsomega.5c08116.
- [51] F. U. Rehman, K. U. Shah, S. U. Shah, I. U. Khan, G. M. Khan, and A. Khan, "From nanoemulsions to self-nanoemulsions, with recent advances in self-nanoemulsifying drug delivery systems (SNEDDS)," *Expert Opin. Drug Deliv.*, vol. 14, no. 11, pp. 1325–1340, Nov. 2017, doi: 10.1080/17425247.2016.1218462.
- [52] P. Izquierdo et al., "The influence of surfactant mixing ratio on nano-emulsion formation by the pit method," *J. Colloid Interface Sci.*, vol. 285, no. 1, pp. 388–394, May 2005, doi: 10.1016/j.jcis.2004.10.047.
- [53] T. Matsuura, A. Ogawa, Y. Ohara, S. Nishina, M. Nakanishi, and S. Gohtani, "Effect of Alcohols on the Phase Behavior and Emulsification of a Sucrose Fatty Acid Ester/Water/Edible Oil System," *J. Oleo Sci.*, vol. 67, no. 2, pp. 167–176, Feb. 2018, doi: 10.5650/jos.ess17146.
- [54] K. W. Cheong, H. Mirhosseini, N. S. A. Hamid, A. Osman, M. Basri, and C. P. Tan, "Effects of propylene glycol alginate and sucrose esters on the physicochemical properties of modified starch-stabilized beverage emulsions," *Molecules*, vol. 19, no. 6, pp. 8691–8706, Jun. 2014, doi: 10.3390/molecules19068691.
- [55] J. J. Torrado, R. Espada, M. P. Ballesteros, and S. Torrado-Santiago, "Amphotericin B formulations and drug targeting," *J. Pharm. Sci.*, vol. 97, no. 7, pp. 2405–2425, Jul. 2008, doi: 10.1002/jps.21179.
- [56] M. Liu, M. Chen, and Z. Yang, "Design of amphotericin B oral formulation for antifungal therapy," *Drug Deliv.*, vol. 24, no. 1, pp. 1–9, Nov. 2017, doi: 10.1080/10717544.2016.1225852.
- [57] R. Herbrecht, S. Natarajan-Amé, Y. Nivoix, and V. Letscher-Bru, "The lipid formulations of amphotericin B," *Expert Opin. Pharmacother.*, vol. 4, no. 8, pp. 1277–1287, Aug. 2003, doi: 10.1517/14656566.4.8.1277.
- [58] J. Brajtburg, I. Gruda, I. Daigle, and G. Medoff, "Concentration dependent dual effect of the monolauryl ester of sucrose on the antifungal activity and absorption spectra of amphotericin B (Fungizone)," *Biochim. Biophys. Acta*, vol. 985, no. 3, pp. 307–312, Nov. 1989, doi: 10.1016/0005-2736(89)90417-3.
- [59] V. C. P. Ab, P. Jm, N. A, C. Pk, and F. P, "Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers: A Comparative Review," *Pharmaceutics*, vol. 15, no. 6, May 2023, doi: 10.3390/pharmaceutics15061593.
- [60] E. C, S. G, and U. Z, "Current State of Lipid Nanoparticles (SLN and NLC) for Skin Applications," *Curr. Pharm. Des.*, vol. 29, no. 21, 2023, doi: 10.2174/138161282966230803111120.
- [61] K. K. Sawant and S. S. Dodiya, "Recent advances and patents on solid lipid nanoparticles," *Recent Pat. Drug Deliv. Formul.*, vol. 2, no. 2, pp. 120–135, 2008, doi: 10.2174/187221108784534081.
- [62] D. S and C. A, "Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery," *AAPS PharmSciTech*, vol. 12, no. 1, Mar. 2011, doi: 10.1208/s12249-010-9563-0.
- [63] S. Harloff-Helleberg et al., "Exploring the mucoadhesive behavior of sucrose acetate isobutyrate: a novel excipient for oral delivery of biopharmaceuticals," *Drug Deliv.*, vol. 26, no. 1, pp. 532–541, Dec. 2019, doi: 10.1080/10717544.2019.1606866.

- [64] Y. Huang, L. Zou, J. Wang, Q. Jin, and J. Ji, "Stimuli-responsive nanoplatforms for antibacterial applications," *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, vol. 14, no. 3, p. e1775, May 2022, doi: 10.1002/wnan.1775.
- [65] "Enzyme responsive drug delivery systems in cancer treatment - ScienceDirect." Accessed: Mar. 04, 2026. [Online]. Available: <https://www.sciencedirect.com/science/article/abs/pii/S0168365919303918>
- [66] L. Y and T. Dh, "Stimuli-responsive liposomes for drug delivery," *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, vol. 9, no. 5, Sep. 2017, doi: 10.1002/wnan.1450.
- [67] S. Ahmed, K. Alhareth, and N. Mignet, "Advancement in nanogel formulations provides controlled drug release," *Int. J. Pharm.*, vol. 584, p. 119435, Jun. 2020, doi: 10.1016/j.ijpharm.2020.119435.
- [68] J. Xuan et al., "DNA response element-based smart drug delivery systems for precise drug release," *Biomater. Sci.*, vol. 12, no. 14, pp. 3550–3564, Jul. 2024, doi: 10.1039/d4bm00138a.
- [69] H. M. Thérien, I. Gruda, L. Bouchard, and I. Daigle, "Stimulation of lymphoproliferation by sucrose esters," *Immunopharmacol. Immunotoxicol.*, vol. 11, no. 4, pp. 603–609, 1989, doi: 10.3109/08923978909005389.
- [70] J. Brajtburg, I. Gruda, I. Daigle, and G. Medoff, "Concentration dependent dual effect of the monolauryl ester of sucrose on the antifungal activity and absorption spectra of amphotericin B (Fungizone)," *Biochim. Biophys. Acta*, vol. 985, no. 3, pp. 307–312, Nov. 1989, doi: 10.1016/0005-2736(89)90417-3.
- [71] I. Gruda, E. Gauthier, S. Elberg, J. Brajtburg, and G. Medoff, "Effects of the detergent sucrose monolaurate on binding of amphotericin B to sterols and its toxicity for cells," *Biochem. Biophys. Res. Commun.*, vol. 154, no. 3, pp. 954–958, Aug. 1988, doi: 10.1016/0006-291x(88)90232-x.
- [72] V. M et al., "Synthesis and Biological Evaluation of 6- O-Sucrose Monoester Glycolipids as Possible New Antifungal Agents," *Pharm. Basel Switz.*, vol. 16, no. 2, Jan. 2023, doi: 10.3390/ph16020136.
- [73] H. Ar et al., "Targeting efflux pumps to overcome antifungal drug resistance," *Future Med. Chem.*, vol. 8, no. 12, Aug. 2016, doi: 10.4155/fmc-2016-0050.
- [74] F. C. Odds, "Synergy, antagonism, and what the chequerboard puts between them," *J. Antimicrob. Chemother.*, vol. 52, no. 1, p. 1, Jul. 2003, doi: 10.1093/jac/dkg301.
- [75] J. Meletiadis, S. Pournaras, E. Roilides, and T. J. Walsh, "Defining fractional inhibitory concentration index cutoffs for additive interactions based on self-drug additive combinations, Monte Carlo simulation analysis, and in vitro-in vivo correlation data for antifungal drug combinations against *Aspergillus fumigatus*," *Antimicrob. Agents Chemother.*, vol. 54, no. 2, pp. 602–609, Feb. 2010, doi: 10.1128/AAC.00999-09.
- [76] J. V. L. Henry, P. J. Fryer, W. J. Frith, and I. T. Norton, "Emulsification mechanism and storage instabilities of hydrocarbon-in-water sub-micron emulsions stabilised with Tweens (20 and 80), Brij 96v and sucrose monoesters," *J. Colloid Interface Sci.*, vol. 338, no. 1, pp. 201–206, Oct. 2009, doi: 10.1016/j.jcis.2009.05.077.
- [77] H. A. Ayala-Bravo, D. Quintanar-Guerrero, A. Naik, Y. N. Kalia, J. M. Cornejo-Bravo, and A. Ganem-Quintanar, "Effects of sucrose oleate and sucrose laureate on in vivo human stratum corneum permeability," *Pharm. Res.*, vol. 20, no. 8, pp. 1267–1273, Aug. 2003, doi: 10.1023/a:1025013401471.
- [78] W. Zhang et al., "Sucrose esters improve the colloidal stability of nanoethosomal suspensions of (-)-epigallocatechin gallate for enhancing the effectiveness against UVB-induced skin damage," *J. Biomed. Mater. Res. B Appl. Biomater.*, vol. 105, no. 8, pp. 2416–2425, Nov. 2017, doi: 10.1002/jbm.b.33785.
- [79] K. Valdés, M. J. Morilla, E. Romero, and J. Chávez, "Physicochemical characterization and cytotoxic studies of nonionic surfactant vesicles using sucrose esters as oral delivery systems," *Colloids Surf. B Biointerfaces*, vol. 117, pp. 1–6, May 2014, doi: 10.1016/j.colsurfb.2014.01.029.
- [80] F. McCartney et al., "Permeability-enhancing effects of three laurate-disaccharide monoesters across isolated rat intestinal mucosae," *Int. J. Pharm.*, vol. 601, p. 120593, May 2021, doi: 10.1016/j.ijpharm.2021.120593.
- [81] K. Figge and S. D. Haigh-Baird, "Biodegradation of sucrose poly fatty acid esters in soils," *Chemosphere*, vol. 34, no. 12, pp. 2621–2636, Jun. 1997, doi: 10.1016/s0045-6535(97)00105-7.