A Review on Solubility Enhancement of Antifungal Drugs

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Abstract:

Fungal infections pose a significant threat to immunocompromised individuals, yet the efficacy of antifungal therapies is often hindered by the poor aqueous solubility of many antifungal agents, particularly azoles. Enhancing solubility is essential for improving bioavailability and achieving effective drug concentrations at the site of infection. This review comprehensively explores contemporary formulation strategies aimed at increasing the solubility of poorly water-soluble antifungal drugs. Various techniques are discussed, including solid dispersions, cyclodextrin complexation, nanosuspensions, lipid-based systems (SLNs, liposomes, and niosomes), self-emulsifying drug delivery systems (SEDDS), microemulsions, salt formation, co-crystallization, and cosolvency. The article evaluates each method's mechanism, advantages, formulation considerations, and potential limitations. Emphasis is placed on the need for tailored approaches that integrate physicochemical drug properties with delivery goals to optimize antifungal efficacy and patient outcomes.

Keywords: antifungal drugs, solubility enhancement, low water solubility, formulation strategy, poorly water-soluble drugs**.**

مراجعة حول تعزيز قابلية ذوبان الأدوية المضادة للفطريات

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الخلاصة:

تشكل العدوى الفطرية تهديدًا كبيرًا للأشخاص الذين يعانون من ضعف في الجهاز المناعي، إلا أن فعالية العلاجات المضادة للفطريات غالبًا ما تُقيد بسبب ضعف ذوبان العديد من مضادات الفطريات، لا سيما الأزولات، في الماء. ويُعد تعزيز الذوبانية أمرًا ضروريًا لتحسين التوافر الحيوي وتحقيق تراكيز دوائية فعّالة في موقع العدوى. تستعرض هذه المراجعة استراتيجيات التركيب الحديثة التي تهدف إلى زيادة ذوبانية مضادات الفطريات ضعيفة الذوبان في الماء. وتشمل التقنيات التي تمت مناقشتها: التشتت الصلب، تكوين معقدات السيكلوديكسترين، المعلقات النانوية، أنظمة التوصيل المعتمدة على الدهون (مثل الجسيمات الدهنية الصلبة، الليبوسومات، والنيزومات)، أنظمة التوصيل الذاتي الاستحلابي، الميكرو-مستحلبات، تكوين الأملاح، تكوين البلورات المشتركة، وتقنية المذيب المشترك. وتُقيّم المراجعة آلية كل طريقة، مزاياها، اعتبارات التحضير،

والقيود المحتملة، مع التركيز على أهمية اختيار النهج المناسب استنادًا إلى الخصائص الفيزيائية والكيميائية للدواء بهدف تعزيز الفعالية العلاجية وتحسين نتائج المرضى.

الكلمات المفتاحية: الأدوية المضادة للفطريات، تعزيز الذوبان، انخفاض الذوبان في الماء، استراتيجية الصياغة، الأدوية قليلة الذوبان في الماء.

Introduction

Fungal diseases in humans emerge through superficial disorders of the skin layers and tissues or, more seriously, as infections that are both invasive and systemic, impacting the internal organs. Patients' appointments with dermatologists are mainly due to infection of the superficial type. severe mycotic infections are increasingly acknowledged as a significant etiology of morbidity and mortality, especially in individuals afflicted by acquired immunodeficiency syndrome (AIDS), haematologic tumors, severe aplastic anemia, myelodysplasia, illnesses that impair the immune system, individuals who have received organ transplants, premature newborns, and the elderly. [1, 2]. Numerous antifungal medications, as mentioned below, have hydrophobic characteristics, which result in inadequate solubility in water, poor oral bioavailability, and a restricted range of formulation options. commonly employed azole antifungal drugs, such as clotrimazole, miconazole, econazole, oxiconazole, ketoconazole, tioconazole, and sertaconazole.

The Biopharmaceutical Classification System (BCS) comprises four categories determined by solubility and permeability; the two BCS Class II and Class IV drugs exhibit restricted solubility[6]. Many new drug candidates, especially antifungal agents, have poor water solubility, which remains a major challenge in pharmaceutical development. Therefore, active pharmaceutical ingredients (APIs) that are not very soluble are subject to intense research into improved formulation techniques in the hopes of increasing their solubility and/or dissolution rate.

Despite the availability of numerous formulation strategies, as depicted in Table 1, no single technique universally addresses the solubility challenges posed by all antifungal drugs, particularly azoles and polyenes. Most studies focus on general drug delivery or solubility enhancement without giving specific attention to antifungal drugs and the unique challenges posed by fungal biofilms, tissue targeting, and localized delivery needs. Therefore, there remains a critical gap in consolidating and comparing current solubility enhancement strategies, specifically in the context of antifungal agents.

This review aims to systematically explore and compare various solubility enhancement approaches applied to antifungal drugs, with a particular emphasis on their formulation principles, mechanisms, and therapeutic implications. It highlights the advantages and limitations of each method, identifies research trends, and provides a focused analysis of promising techniques such as solid dispersion, nanosuspension, cyclodextrin inclusion complexes, and lipid-based carriers. The ultimate goal is to guide formulation scientists toward rational selection of solubility-enhancing strategies tailored for antifungal pharmacotherapy.

Table 1. Major techniques for solubility enhancement of antifungals.

Type	Name of technique	Advantages	Examples and references
Chemical alteration	Co Crystallization	Drug solubility, bioavailability, and stability are just a few examples of physical attributes that can be improved with their help, all without changing the chemical composition of APIs.	Ketoconazole-fumaric acid coccrystal[7]
Chemical alteration	formation of salt	The strategy most often used to increase solubility and the one most often recommended for developing liquid formulations. Speeds up the drug's dissolution by making its apparent inherent solubility seem higher. Facilitated synthesis while decreasing the expense of raw materials.	Miconazole nitrate[8]
Chemical alteration	Pro-drug synthesis	improved transporter-mediated absorption, lipophilicity, and drug solubility. has the capacity to distribute content according to a certain site.	amphotericin B[9]
Reduction of particle size	Micronization and nanoscale pharmaceuticals	Micronization enhances the dissolving rate of pharmaceuticals by augmenting surface area, but it does not improve equilibrium solubility.	Micronized itraconazole[10]
Amorphization	Solid dispersion	Because of its molecular dispersion and steric hindrance interactions within the polymeric matrix, it prevents the aggregate formation and crystals of medicinal compounds and has enhanced dissolution rate and solubility compared	Posaconazole[11]

		to standard crystal behavior modification.	
Solvent Composition	pH modification	An efficient and direct method for modifying the solubility of ionizable medicines. The ionization level of the drug candidates enables full solvation of the intended medicinal dosage.	itraconazole[12]
Solvent Composition	Co- ssolvent	Reduces solvent polarity, making nonpolar medications more soluble. In cases when pH manipulation falls short, it is possible to combine the solution with a cosolvent in order to enhance the solubility of the drugs.	clotrimazole[13]
Drug carrier systems	Micelles	The hydrophobic core functions as a reservoir for lipophilic pharmaceuticals. Enables chemical modification and demonstrates responsiveness to stimuli.	posaconazole[14]
Drug carrier systems	Cyclodextrins	Supersaturated pharmaceutical solutions are best made with this. Extend the time that medications remain effective by making them more physically and chemically stable.	difenoconazole[15]
Drug carrier systems	Lipid-based formulations (SLN, liposomes, SEDDDS)	Non-immunogenic, biocompatible vesicles and micelles that enhance medication absorption	Itraconazole liposomes[16]

Methods with rationale to improve the solubility of antifungal medications

There are several different approaches that can be taken in order to improve the solubility of drugs.

Self-emulsifying drug delivery systems

Systems that self-emulsify or self-microemulsify leverage the idea of in situ emulsion formation in the intestines. Transparent (it is clear, not cloudy or turbid, which indicates complete solubilization of all components, including the drug), isotropic (it is physically and chemically homogeneous) solutions are produced by combining oil with surfactant, co-surfactant, and co-solvents, as well as one or more hydrophilic solvents. As seen in Figure 1, an illustration of the self-emulsifying drug delivery system (SEDDS) is shown. By eliminating the need for pre-absorptive dissolution, SNEDDS have demonstrated enhanced bioavailability for medicines, particularly those classified as BCS II and IV. A combination of oil, surfactant, and co-solvent excipients is utilized in these systems in order to dissolve the medication. This is accomplished through the utilization of an isotropic mixture. [17].

Their thermodynamic stability and the fact that they spontaneously form when components are mixed with little agitation make SEDDS an attractive option for use in production and scaling. SEDDS provide a number of advantages over ordinary oily solutions, one of which is that they offer a broad interfacial area for the medication to partition between the oil and the water. Thus, these approaches have the potential to increase the rate and extent of lipophilic medicine absorption, which is limited by dissolution. High surfactant concentrations are the drawbacks of this method. Gastrointestinal side effects can be caused by the high surfactant content (30-60%) found in self-emulsifying formulations[18].SEDDS are presented in Table 2.

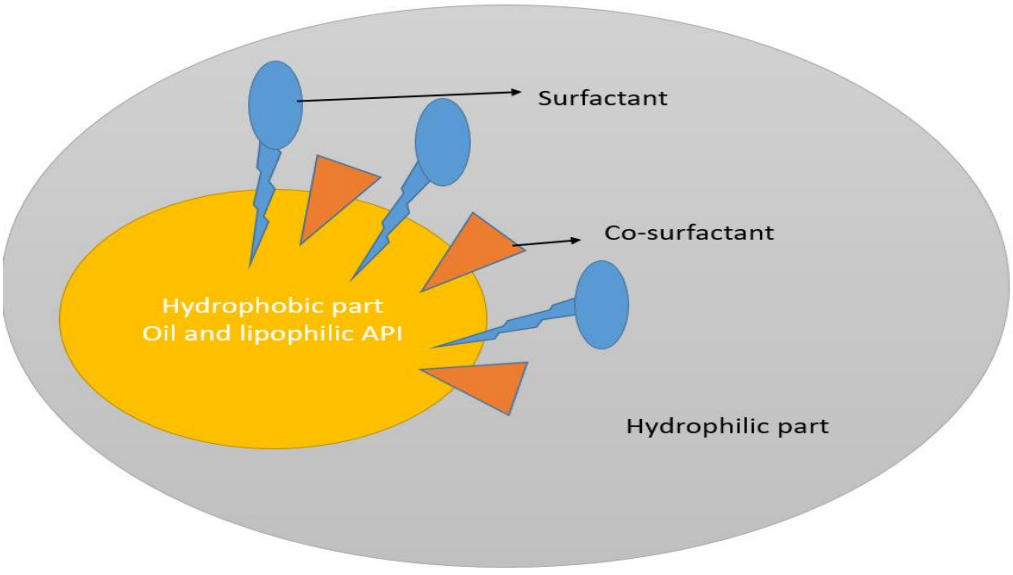

Figure 1. Various parts of a self-emulsifying medication delivery system.

Table 2. Examples of SEDDS.

Drug	Composition	Reference
Nystatin as an oral candidiasis therapy agent	The following ingredients were used: oleic acid (oil), surfactants Tweeen®20 (Tw20) and Tween®40 (Tw40), sulfoxide (DMSO), and propylene glycol (PG) (co-surfactants).	[19]
Amphotericin B(orally) For leishmaniasis	The non-ionic emulsifying agent chosen was Kolliphor RH "Hydrogenated Ricinus" 40. In contrast, the oil phase contained Captex 355, a medium-chain triglyceride that could enhance intestinal absorption. As a co-solvent, propylene glycol (PG) was selected as co-solvent.	[20]
Clotrimazole gel	Oleic acid, tween 80, and polyethylene glycol 400 were used to prepare clotrimazole SEDDS to be prepared as a gel.	[21]

Formation of drug/cyclodextrin complexes

Increasing a drug's solubility and rate of dissolution through complexation with cyclodextrins is an efficient method. A new class of complexing agents called the cyclodextrin family is only starting to emerge. In contrast to the hydrophobic interior cavity, the ring's surface is hydrophilic. Soluble inclusion complexes can be formed by incorporating lipophilic chemicals into the ring, as outlined in Figure 2. Because of their hydrophilic surface, CDs dissolve in water. In the meanwhile, the nonpolar medicament can be "masked" and its molecular dispersion in water improved by hosting it in the less polar interior through noncovalent interactions. Therefore, the water solubility of medications is significantly enhanced when they are integrated into cyclodextrins.

It is possible to provide a more accurate explanation for the solubility-enhancing capabilities of cyclodextrins by utilizing a dynamic inclusion mechanism. This mechanism involves the formation of a complex between lipophilic molecules and the interior cavity of the cyclodextrins. Additionally, cyclodextrins can solubilize molecules via non-complex-related methods, including the application of drug-cyclodextrin aggregation[22, 23]. β-CD is notable for its ability to form complexes, due to its accessibility, cost-effectiveness, and high efficiency; nevertheless, it also has several disadvantages, including nephrotoxicity caused by its reactions with lipid membrane components.

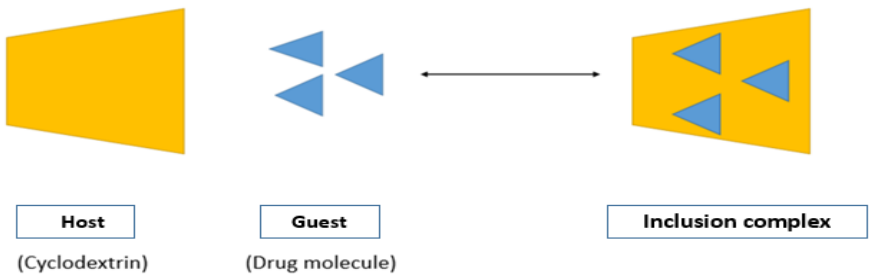

Figure 2. Cyclodextrin Complex Formation.

Table 3. Examples of CD complexes.

Drug	Composition	Reference
fluconazole-CD inclusion complexes	Fluconazole: β-CD inclusion complexes in a molar ratio of 1:1 and 1:2	[24]
Itraconazole	Itraconazole: cyclodextrin at a molar ratio of 1:3.	[25].
Miconazole	methyl-beta-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin	[26]
Nystatin	Complexes of Nystatin: βCD with ratios of 1:1, 1:2, and 2:1	[27]

Salt Formation

Salt generation is a neutralization reaction between acids and bases. Salt generation was utilized for pharmaceuticals that can be ionized to improve solubility. Ionic bonding in salts can form and be stable if the difference in pKa between acids and bases (ΔpKa) is greater than 3[28]. To produce salt, active pharmacological components must be protonated or must experience protonation from an ionizable functional group configuration, as evidenced by Figure 3 and Table 4. The synthesis of salt is uncomplicated and involves the supramolecular complexation of a therapeutic molecule of interest with an appropriate and biocompatible coformer. Carboxylic acids are acknowledged as proficient electron acceptors and donors, often participating in supramolecular processes, so acting as potential salt formers with an active pharmaceutical ingredient (API)[29, 30].

The selectivity of coformers is essential for modifying the characteristics of novel drug formulations, and this choice depends on functional compatibility, which is influenced by the tendency for hydrogen bonding and the configuration of functionalities to form a strong complex. [31]. This is a common pharmaceutical strategy to improve solubility, enhance stability, and boost bioavailability [32].

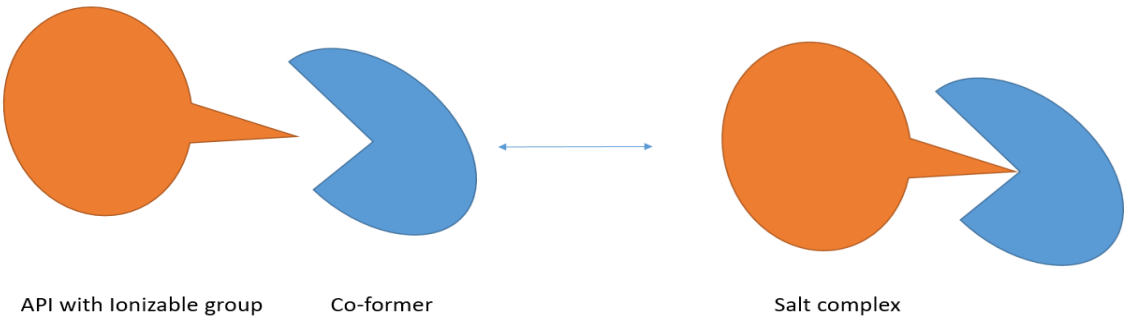

Figure 3. Illustrates the requirements to form a salt

Table 4. Examples of salt complexes.

Drug	Composition	Reference
miconazole and ketoconazole	naphthalene disulfonic acid	[33]
Itraconazole	hydrochloride, mesylate, and besylate	[34]
Ketoconazole	oxalic acid and fumaric acid	[35]

Nanosuspension

Nanosuspensions are colloidal dispersions of nanoscale drug particles stabilized by surfactants, see Figure 4. They can also be characterized as a biphasic system including pure drug particles dispersed in an aqueous medium, where the diameter of the suspended particles is smaller than 1 µm. The reduction of drug particles to the nanoscale results in an improved dissolution rate due to both the increased surface area and the greater saturation solubility.

For manufacturing nanosuspensions, there are two converse methods, "Top-down process technology" and "Bottom-up process technology". The top-down process follows a disintegration approach from large particles, microparticles, to nanosized particles. Examples are high-pressure homogenization, nanoedge, and media milling. The bottom-up process is an assembly method that forms nanoparticles from molecules. Examples include the solvent-antisolvent method, supercritical fluid process, Emulsification, Solvent evaporation technique, lipid emulsion/micro-emulsion template.

Particles form crystals and clump together when their size decreases, which is the main drawback of using stabilizers to keep the system from becoming unstable. The use of surfactants like ionic sodium lauryl sulphate (SLS) and nonionic polysorbate (Tween 80) in conjunction with polymers like hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP K30) is common as stabilizers. Some antifungal APIs formulated as nsnosuspension, as depicted in Table 5.

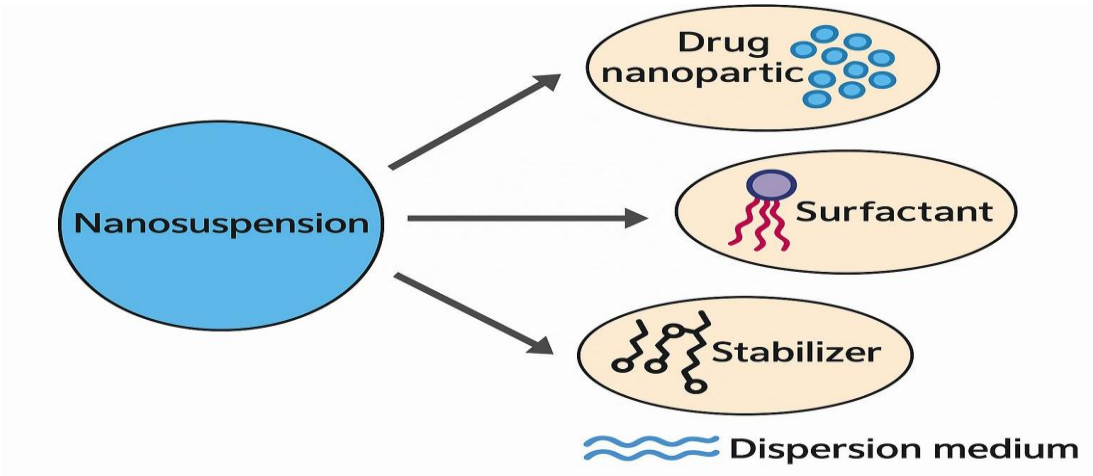

Figure 4. Schematic illustration of components of a nanosuspension

Table 5. Nanosuspension formulated antifungal API.

Drug	Composition	Reference
Posaconazole ophthalmic nanosuspension	Aqueous solutions of surfactants: Tween 20, Tween 80, Propylene glycol, and Pluronic 127	[37]
Amphotericin B (AmB)	0.18% (weight/volume) AmB nanosuspensions in aqueous γCD eye drop with either 0.25% (weight/volume) chitosan or 0.10% (weight/volume) phospholipids (PL).	[38]
Fluconazole	Low-viscosity hydroxypropyl methylcellulose (LV HPMC, grade E3), Kollicoat IR (KL), Pluronic F127 (PLF127), xanthan gum (XG)	[39]
Clotrimazole	A variety of stabilizers, including chitosan derivatives and Tween 80, were used to produce the clotrimazole nanosuspension.	[40]

Cocrystal

Cocrystallization represents an advanced crystal engineering strategy used to improve the therapeutic performance of pharmaceutical compounds by controlling the characteristics of active pharmaceutical ingredients (APIs) when they are in their solid state. Cocrystallization significantly expands the accessibility of innovative solid forms with diverse architectures. The cocrystallization technique has proven to be a promising and innovative strategy for overcoming the challenges associated with poorly water-soluble drugs.[29] [41].

Cocrystals are solid entities consisting of two or more separate elements in a stoichiometric ratio at room temperature, bound by noncovalent interactions, primarily hydrogen bonds. Cocrystallization produces new crystalline structures that often surpass the quality of the individual components. Cocrystals improve drug solubility by lowering lattice energy and increasing solvent affinity. To employ supersaturation (spring and parachute effect) as a method for improving the solubility and dissolution rate of poorly soluble pharmaceuticals, two critical procedures must be maintained. The initial aspect pertains to the establishment of the metastable supersaturated state, whereas the subsequent aspect concerns the maintenance of that condition[42].

Cocrystallization formers (co-formers) and active pharmaceutical ingredients (APIs) are two components that are co-integrated inside the same crystal lattice to generate a cocrystal. The compounds used as additives in pharmaceuticals must not only be free of dangerous chemicals but also be considered safe for human consumption. Histidine, glycine, nicotinamide, valine, tyrosine, urea, saccharin, gallic acid, ascorbic acid, glutamic acid, and gallic acid are all coformers.

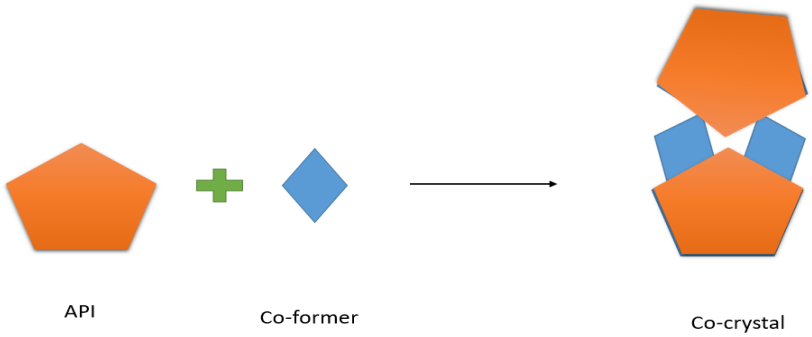

Figure 5. Component co-crystal system.

Table 6. APIs and their co-formers of some antifungal formulations.

Drug	Composition	Reference
Posaconazole	In comparison to the parent molecule, the glutamine, posaconazole-glutamine cocrystal exhibited a dissolving enhancement of 7.72 times and a solubility enhancement of 92.42 times.	[43]
Ketoconazole	cocrystal of Ketoconazole with the Fumaric acid coformer.	[7]
Fluconazole	fluconazole (FLC) and organosulfonate (NDSA-2H)	[44]

Solid Lipid Nanoparticles

To transport BCS Class II and IV medications, SLNs use a high-melting-point lipid as their solid core and encase them in an aqueous surfactant. Many different types of fatty acids, waxes, triglycerides, and partial glycerides are typically included when the word "lipid" is used. It is recommended to use solid lipids rather than liquid lipids in order to enhance the stability of chemically sensitive lipophilic compounds and to increase the control of release kinetics for encapsulated pharmaceuticals. A remarkable physical stability is displayed by solid lipid nanoparticles (SLNs), which maintain their solid state at both room temperature and physiological levels[45].

The drug delivery system benefits of solid lipid nanoparticles (SLNs) include increased drug loading capacity, longer drug release, better drug absorption, simplified biocompatibility, reduced adverse effects, and easy biodegradability. It is also easy to produce on a large scale[46].

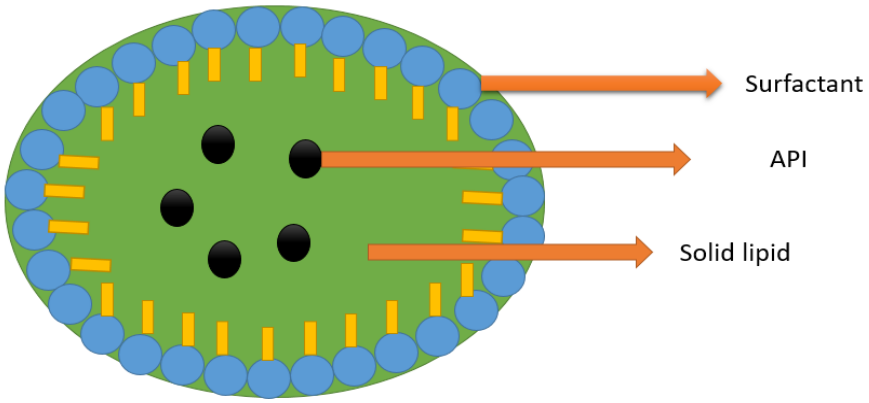

Figure 6. Typical representation of SLN.

Because of their properties, SLNs are a better choice for improving the bioavailability of medications that are sparingly water-soluble. To improve the diffusion of medications contained in nanoparticles across membranes, they may alter their transmembrane transport. Solid lipids, emulsifiers, co-emulsifiers, and water are the main excipients used in SLN formulations. A wide variety of substances can be considered lipids, including triglycerides (like tristearin), partial glycerides (like Imwitor), fatty acids (like stearic acid), steroids (like cholesterol), and waxes (like cetyl palmitate). To stabilize lipid dispersion, emulsifiers of various types have been used, including those involving charge (this means some emulsifiers stabilize particles by giving them an electrical charge (positive or negative) on their surface). When droplets have the same surface charge, they repel each other (electrostatic repulsion), reducing the chance of coming together, and molecular weight (this refers to emulsifiers that stabilize dispersions through their large molecular size, usually polymer-based. Large molecules (with high molecular weights) create a thick steric barrier around droplets. This steric hindrance physically prevents droplets from coming close enough to stick together).

Table 7. Some previously prepared SLNs.

Drug	Composition	Reference
Itraconazole	Lipids that are solid (stearic acid, fractionol 888, fractionol E ATO)	[47]
Miconazole	Precirol ATO5 (2%), and Lecinol (0.5%)	[48]
Sulconazole	The ingredients include glyceryl monostearate, phospholipon® 90 H, tween 20, and a surfactant.	[49]

Microemulsions

Surfactants and co-surfactants stabilize oil and water dispersions into microscopic emulsions, which are transparent, clear, and thermodynamically stable. Because of their small size, the oil-water droplets increase

the interfacial energy by creating a large surface area between the two liquids. It is crucial to include a secondary amphiphile in the formulation since it is typically impractical to achieve a low interfacial tension with a single surfactant to minimize the elevated interfacial energy. While not usually thought of as a surfactant, the secondary amphiphile—also called the co-surfactant—is usually a medium-chain-length alcohol that, by inserting itself between the surfactant molecules in the interfacial film surrounding the microemulsion droplets, successfully reduces interfacial tension. Their thermodynamic stability, ease of production, and suitability for hydrophilic and lipophilic medications are all notable characteristics[50].

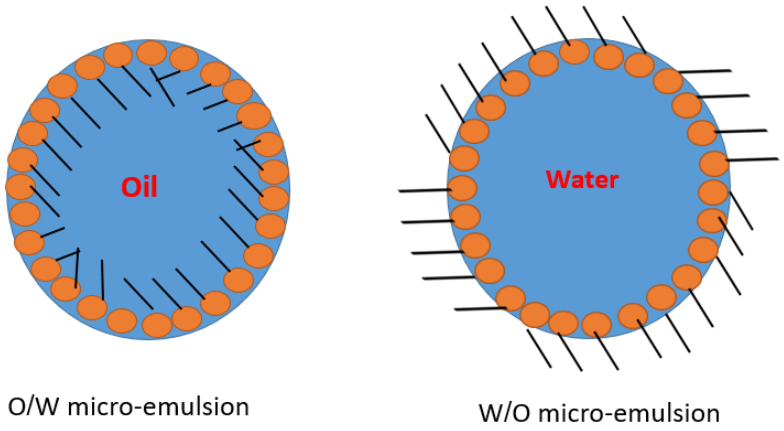

Figure 7. The two common types of microemulsions.

Table 8. Examples of micremulsions previously prepared of antifungals and their compositions.

Drug	Composion	Reference
Fluconazole	Capryol90, Cremophor EL Benzyl alcohol, Chlorocresol	[51]
Ketoconazole	Tween 20 (Polyethylene glycol sorbitan monolaurate) and Tween 80 (Polyethylene glycol sorbitan monooleate), rose essential oil. Cremophor EL, Span 20, and Span 80	[52]
Miconazole nitrate	Tween 80, Span 60, Span 80, Cremphore RH 40, Cremophore EL, PEG 400, Propylene glycol, Soyabean oil, Sweet almond oil	[53]

Niosomes (Non-ionic surfactant-based vesicles)

Niosomes are a novel class of drug delivery systems characterized by a bilayer structure. They are produced by the self-assembly of cholesterol and nonionic surfactants in aqueous media. In addition to being biodegradable and biocompatible, niosomes are also non-immunogenic. These products have a long shelf life, are very stable, and allow for the controlled and continuous release of medications with great precision[54].

There are a variety of nonionic surfactants that have the ability to form niosomes. This allows for the encapsulation of various medications with different solubility properties. It is possible to improve the drug delivery efficacy of niosomes by modifying their composition, size, quantity of lamellae, and surface charge[55, 56].

An aqueous medium, nonionic surfactants, and lipids (including cholesterol) make up niosomes. Nonionic surfactants have hydrophobic tails and hydrophilic head groups. At the water interface, the hydrophobic tails tend to aggregate due to interfacial tension with water, while the hydrophilic heads orient outward to interact with the aqueous environment. This orientation is stabilized by steric and hydrophilic repulsion between the head groups.

Their low toxicity and improved biocompatibility are a result of their nonionic characteristics. Niosomes' one-of-a-kind structure makes them ideal building blocks for efficient drug delivery systems that can accommodate hydrophilic and lipophilic drugs.

The niosome's aqueous core encases hydrophilic drugs, whereas the bilayer of its membrane incorporates lipophilic substances. The capacity of niosomes to release drugs is due in large part to their fluid membrane, which allows for membrane deformation without compromising vesicle stability or bilayer integrity.

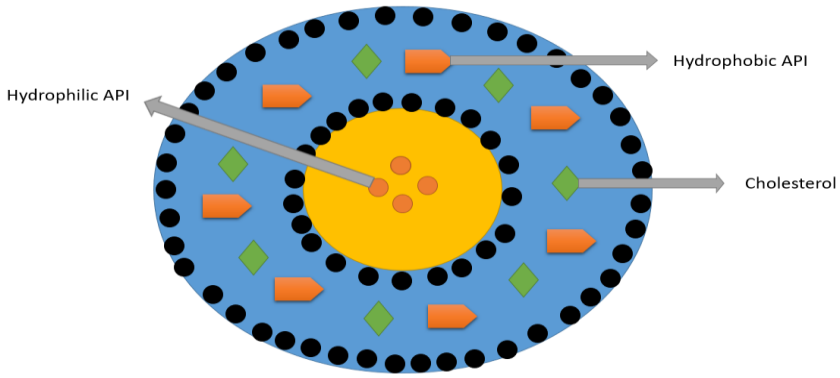

Figure 8. Typical constituents of niosomes.

Table 9. Examples of some antifungal API niosomal preparations.

Drug	Composition	Reference
Luliconazole niosomal topical gel	nonionic surfactant (Span 60), cholesterol, chloroform	[57]
Itraconazole	Span 60, Cholesterol AR, ethanol	[58]
Fluconazole-Niosome-Laden Contact Lens	Cholesterol, span 60, chloroform	[59]
Nystatin	(Span 60), (Span 40), cholesterol from lanolin	[60]

Solid dispersion

For medications that are not very soluble in water, solid dispersion has emerged as a great formulation option. There has been a lot of interest in using solid dispersions with water-soluble carriers to increase the dissolution rate and bioavailability of hydrophobic medicines. There are many ways[61],[62] to make solid dispersions as shown in Figure 9.

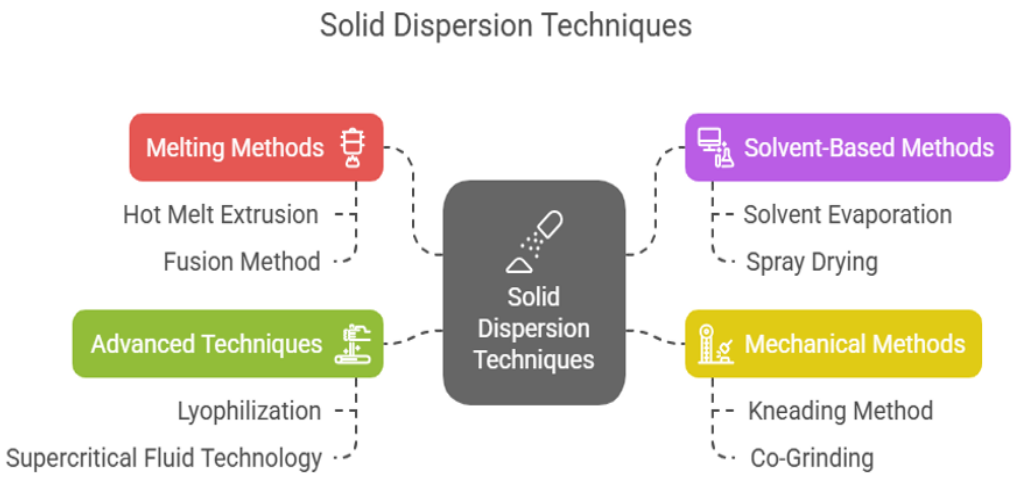

Figure (9). A commonly used technique for solid dispersion preparation

A range of carriers has been examined to improve the dissolution properties and bioavailability of poorly water-soluble drugs as shown in Figure (10).

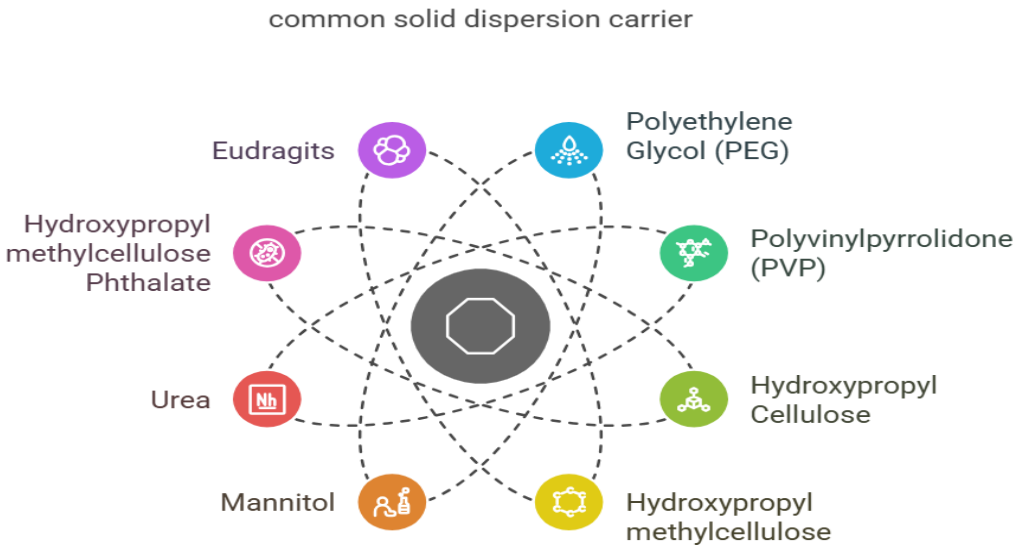

Figure (10). Commonly used carriers in solid dispersion.

The advantage of solid dispersion is its ability to achieve an even dispersion of drug molecules within carriers, which enhances the wetting ability of the drug molecules and subsequently improves drug solubility (65). Amorphous chemicals demonstrate higher apparent solubility compared to their crystalline counterparts due to their increased energy state and disordered structure, which removes the requirement to disrupt the crystal lattice during the dissolution process. By adjusting the characteristics of the carrier and the solid dispersion particles, it is possible to vary the drug release profiles using solid dispersions. The dissolution and bioavailability can be effectively optimized by managing characteristics including carrier molecular weight and composition, drug crystallinity, particle porosity, and wettability[63] [64].

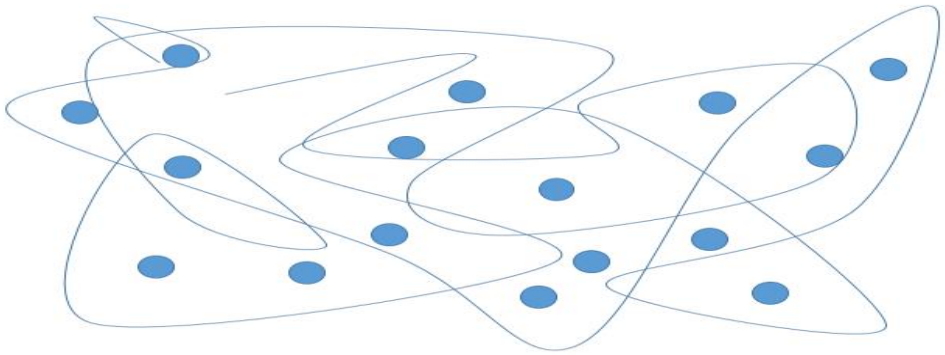

Figure 11. Molecular dispersion of API in the polymer matrix.

Table 10. Solid dispersion research of antifungal API with their respective compositions.

Drug	Composition	Reference
Itraconazole	Kollidon1 VA 64 (Copovidone, PVPVA64)	[65]
Voriconazole	Soluplus, Kollidone VA64	[66]
Amphotericin B	mimixture of poly(vinyl alcohol) and poly(vinylpyrrolidone) polymers	[67]
Griseofulvin	silica, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methylcellulose acetate succinate (HPMCAS)	[68]
Natamycin	Ethyl cellulose, PVA and Chitosan	[69]

Co-solvency/Solvent Blending

It is possible for water-miscible solvents to improve the solubility of drugs that are poor water-soluble. This is accomplished by lowering the interfacial tension that exists between the water and the hydrophobic substances. The aqueous solubility of non-ionizable pharmaceuticals is often improved by a cosolvent, since pH adjustment cannot increase their solubility. 'Like dissolves like' is a principle that states that polar pharmaceuticals are more likely to dissolve in polar solvents, whereas nonpolar medications are more likely to dissolve in nonpolar solvents. As a result, nonpolar drugs demonstrate low solubility in water, which is a polar solvent. Reducing the polarity of water can enhance the solubility of these medications. A third component, such as a low-polarity, water-miscible organic solvent, can facilitate this process. In this context, the liquid is termed a cosolvent.

When compared to the water solubility of the drug on its own, the solubility of co-solvents can increase the solubility of chemicals that are only weakly soluble by a factor of several times. Glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol are some of the cosolvents that are utilized rather frequently [5, 70].

Table 11. Co-solvent-based antifungal preparations.

Drug	Composition	Reference
Ketoconazole	Super critical carbon dioxide, menthol	[71]
Itraconazole	ethanol/isopropanol/DMSO/methanol	[72]
fluconazole	ethanol, water	[73]
Clotrimazole	propylene glycol, water	[74]

Liposomes (Phospholipid-based vesicles)

The spherical vesicles known as liposomes have an aqueous core and a bilayer membrane. While phospholipids are the most prevalent type of amphiphilic lipid utilized in liposome formation, any number of manufactured or naturally occurring lipids can serve as bilayer membrane components. When lipids with hydrophilic head groups and hydrophobic chains at opposite ends are exposed to water, they create liposomes.

The characteristics of liposomes differ markedly according to lipid composition, surface charge, size, and the manufacturing process employed. Liposomes are capable of encapsulating both hydrophobic and hydrophilic substances, thereby preventing the degradation of the encapsulated compounds and facilitating their release at targeted locations[75]. Lipid bilayers merge with other cellular bilayers to transport essential medication substances to the site of action, thereby discharging the liposomal contents. The size, hydrophobic and hydrophilic properties, and biological compatibility of liposomes make them an attractive candidate for drug delivery vehicles.

Liposomes have many benefits, such as being safe for both intravenous and topical use, easily manipulated, biocompatible, biodegradable in whole, and not causing immune responses. Potential phospholipid oxidation and hydrolysis, drug or chemical leakage or fusion, and increased production costs are some of the drawbacks of liposomes[76].

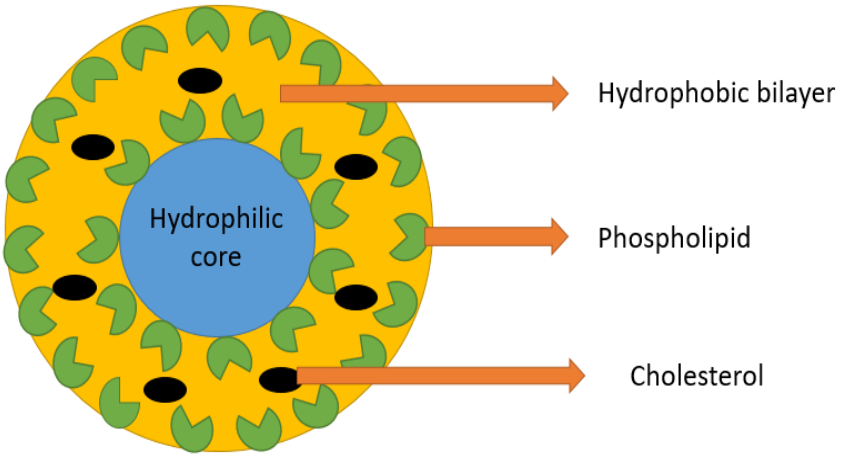

Figure 12. A schematic represented the components of a liposome.

Table 12. Liposomal-formulated antifungal drugs.

Drug	Compositions	Reference
Voriconazole	Cholesterol, soybean phosphatidylcholine, alpha-tocopherol, chloroform	[77]
itraconazole	The following substances were dissolved in chloroform or a 1:1 v/v mixture of chloroform and methanol: phospholipon 90G (PL90G), stearylamine, cholesterol, and ITZ.	[78]
Amphotericin B	Soy phosphatidylcholine and Tween-80	[79]

Conclusions

This review provides an extensive overview of enhancing the solubility of antifungal drugs, such as solid particle techniques, crystal engineering, micronization, solid dispersions, methods for reducing particle size, nanosizing, cyclodextrins, drug complexation, emulsion formation, micelles, microemulsions, cosolvents, pharmaceutical salts, and drug nanocrystals. Formulation development for therapeutic efficacy and improving the bioavailability of the active pharmaceutical ingredient relies on methods for improving the solubility of medications that are poorly water-soluble. Overall, enhancing the solubility of antifungal drugs is a pivotal strategy for overcoming dissolution-related limitations that hinder their clinical effectiveness. By improving aqueous solubility, these formulations can achieve higher local and systemic bioavailability, ultimately maximize therapeutic outcomes and reduce treatment failure.

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