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Review Article

Solid Lipid Nanoparticles as Novel Carriers for Enhancing Classical Antifungal Therapies

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A B S T R A C T

Fungi are increasingly recognized as significant human pathogens, making effective diagnosis and treatment crucial. While the introduction of new antifungal agents over the past two decades has advanced treatment options, rising drug resistance presents a challenge. Nanoparticles (NPs) have emerged as a promising solution for delivering antifungal drugs, offering greater inhibitory effects at lower concentrations compared to traditional antibiotics. Key issues such as reduced efficacy, limited tissue penetration, poor solubility, and decreased bioavailability often hinder antifungal treatments. Incorporating antifungal drugs into various NP delivery systems aims to overcome these limitations. This review discusses different types of NPs used for antifungal delivery and highlights their advantages over conventional drugs.

Keywords: Nanoparticles, SLNs, drug delivery, antifungal drug.

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INTRODUCTION

Fungal infections rank among the leading causes of skin disorders, impacting about 25% of the population. An estimated 40 million people in developing and underdeveloped countries experience these infections. According to a recent unpublished survey conducted by the International Foundation of Dermatology, which examined skin disease patterns in nine countries, superficial mycosis emerged as one of the three most prevalent skin conditions. The prevalence of superficial fungal infections tends to rise with changes in age, climate, and health status. Those on antibiotics, corticosteroids, immunosuppressants, or contraceptive therapies are especially at risk for developing fungal infections.[1]

Solid Lipid Nanoparticles:

Nanotechnology is a multidisciplinary field that emerged in the early 2000s, involving materials with dimensions typically between 1 nm and 1000 nm, applicable in various health products. Numerous researchers have investigated lipid-based nanocarriers, such as lipid nanocrystals, solid lipidnanoparticles (SLNs), and nanostructured lipid carriers (NLCs), to enhance drug penetration and extend release on the skin.[2]

Compared to various other materials, particularly polymers, lipids are regarded as a more compatible option with high biocompatibility. Solid lipid nanoparticles (SLNs) are particularly prominent in the fast-growing field of nanotechnology, offering significant potential for drug delivery, clinical applications, research, and other scientific fields.

Key features of SLNs include a solid core, a lipid matrix, nanoscale size, and biocompatibility. The solid core ensures stability and protects the encapsulated drugs, while the lipid matrix allows for controlled drug release. Their nanoscale size enhances cellular uptake and bioavailability, and their biocompatibility reduces the likelihood of toxicity and immune response.

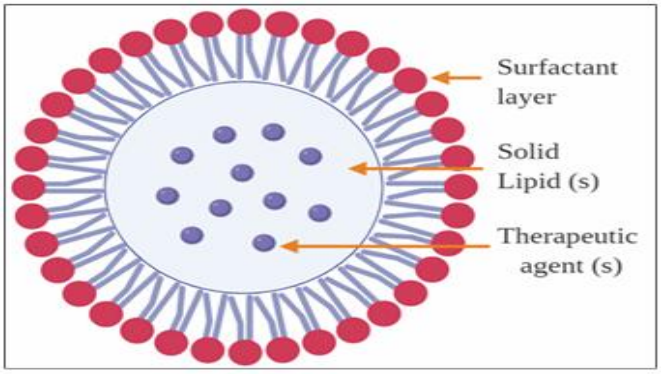


Figure 1: Structure of SLNs.

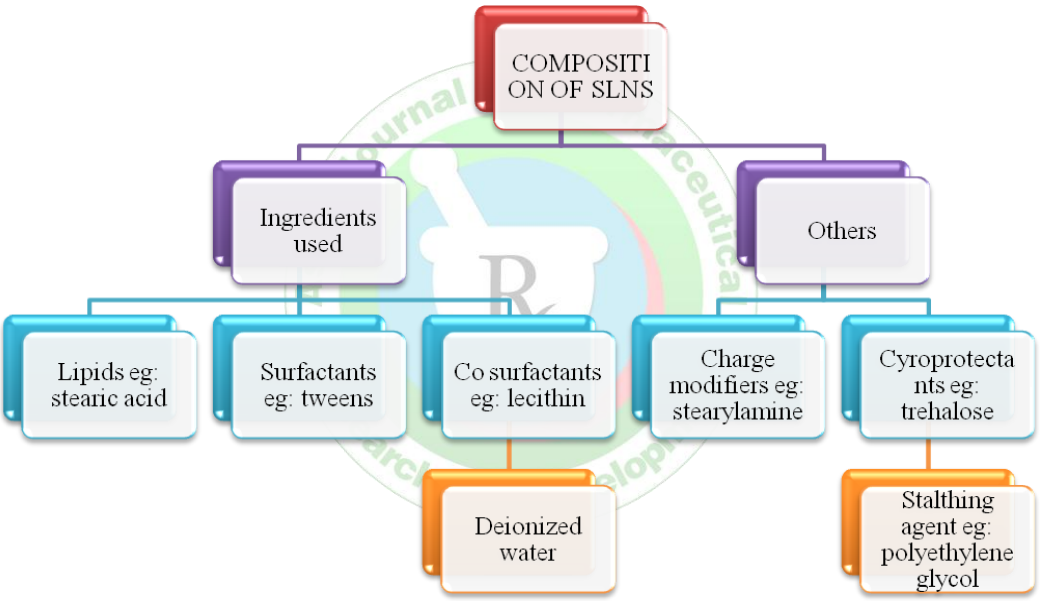
Advantages Solid Lipid Nanoparticles:

1. Improved drug solubility and bioavailability.
2. Enhanced stability and protection of sensitive drugs.
3. Targeted delivery to specific tissues or cells.
4. Reduced toxicity and side effects.
5. Potential for controlled release and sustained action.
6. Easy to manufacture than bipolymeric nanoparticles.
7. Lyophilization possible.[3]

Disadvantages of Solid Lipid Nanoparticles:

1. Limited drug loading capacity
2. Stability issues (e.g., agglomeration)
3. Challenges in predicting drug release kinetics
4. Complexity in manufacturing and scalability
5. Potential toxicity of lipid materials
6. Regulatory challenges and need for extensive clinical data
7. Drug expulsion after polymeric transition during storage

COMPOSITION OF SLNS



MODELS OF DRUG LOADING TO SLNS

There are mainly three models for drug loading in SLNs

a) Homogeneous matrix model.
b) Drug-enriched core model.
c) Drug-enriched shell model.(4)

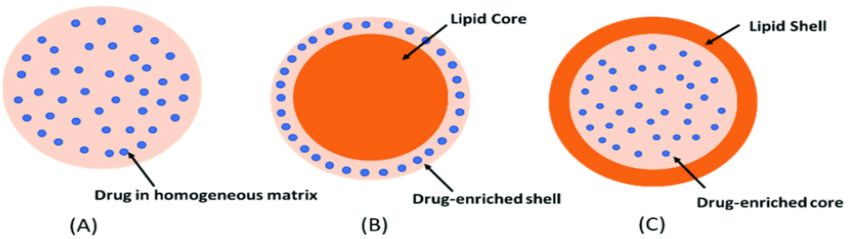


Figure: 2 Drug incorporation

SLNsphysicochemical properties influencing topical administration

Particle Size

Particle size is one of the most crucial parameters for successful penetration of SLNs through skin barrier layers along with its physical stability, which needs careful consideration when designing SLNs for topical application. Several studies have reported the effect of SLNs size on skin penetration. The results demonstrated that the SLNs in the sub 100 nm size range penetrated into the deeper dermis layer at a faster rate compared to larger SLNs. The reported optimum size range for topical administration is in between 100 to 500 nm. However, different sizes of SLNs will determine its deposition in different layers of the skin and the rate of penetration. The above few examples from the published literature clearly indicate that the size of SLNs is an important formulation parameter to consider as per the desired site of action. In general, smaller the particle size deeper is the penetration into the skin layers.[5]

Surface Charge

Surface charge of SLNs is another crucial parameter that dictates SLNs interaction with skin and thus influences its ability to penetrate the SC. Surface charge also determines the physical (colloidal) stability of the nanoformulation including its shelf life. Surface charge of SLNs is determined by zeta potential which can be measured by several techniques such as electrophoretic light scattering (Zetasizer), microelectrophoresis and high-performance capillary electrophoresis. The value of zeta potential is acceptable when it is less than -20 mV or more than +20 mV, as it ensures good long-term stability of SLNs. For topical administration, SLNs with positive surface charge have demonstrated high affinity towards skin permeation, as the skin carries overall negative surface charge due to the presence of phospholipids.[6]

Stability

SLNs are prepared from lipids, which are biocompatible, biodegradable and similar to physiological lipids and therefore have significantly low toxicity. SLNs have the ability to provide protection to the encapsulated drug against photolytic, oxidative, hydrolytic degradation. However, the physical instability of the carrier is a major concern. The physical instability is mainly due to the aggregation of the nanoparticles during the storage period. During aggregation, SLNs dispersed in the liquid phase stick to each other, and spontaneously form irregular nanoparticle clusters, flocs, or aggregates, resulting in increased particle size, influencing skin permeation. Another stability problem which is observed with SLNs is the possibility of drug leakage during the storage of SLNs; this is mainly due to the polymorphic transformation of the lipids. Therefore, stabilization of the lipid crystal lattice structure of the SLNs is also important to enhance the stability of the formulations.[7]

PRINCIPLE OF DRUG RELEASE FROM SLN

The general standards of medication discharge from lipid nanoparticles are as per the following:

1. Higher surface territory because of little molecule measure in nanometer extent gives higher medication discharge.
2. Slow medication discharge can be accomplished when the medication is homogenously scattered in the lipid framework. It depends on sort and medication entanglement model of SLN.
3. Crystallization conduct of the lipid carrier and high portability of the medication lead to quick medication discharge.
4. Fast initial drug release in the first 5 min in the drug – enriched shell model as a result of the outer layer of particle due to larger surface area of drug deposition on the particle surface.
5. The burst release is reduced with increasing particle size and prolonged release could be obtained when the particles were sufficiently large, i.e., lipid macromolecules.
6. The type of surfactant and its concentration, which will interact with the outer shell and affect its structure, should be noted as the outer factor which is important, because a low surfactant concentration leads to a minimal burst and prolonged drug release.[8]
7. The particle size affect drug release rate directly depends on various parameters such as composition of SLN formulation (such as surfactant, structural properties of lipid, drug) production method and conditions (such as production time, equipment, sterilization and lyophilization.

METHODS OF PREPARATION:

1. High pressure homogenization
   a) Hot homogenization
   b) Cold homogenization
2. Ultrasonication/high speed homogenization
   a) Probe ultrasonication
   b) Bath ultrasonication
3. Solvent evaporation method
4. Solvent emulsification-evaporation method
5. Supercritical fluid method
6. Microemulsion based method
7. Spraydryingmethod
8. Precipitation technique
9. Film-ultrasound dispersion

High Pressure Homogenization (HPH):

HPH is a reliable and suitable method for the preparation of SLN, NLC and LDC and can be performed at elevated temperature (hot HPH technique) or at or below room temperature (cold HPH technique). SLNs made from solid lipids or lipid blends produced by high pressure homogenization of melted lipids disperse in an aqueous as outer phase stabilized by surfactant as tween80, SDS, lecithin etc.

- High pressure homogenization pushes a liquid with high pressure (100-2000 bar) through a narrow gap. The fluid accelerates on a very short distance to very high velocity (over 100 km / hr)
- Very high shear stress and cavitation forces disrupt the particles down to the submicron range.

- Generally, 5-10% lipid content is used but up to 40% lipid content has also been investigated.[9]

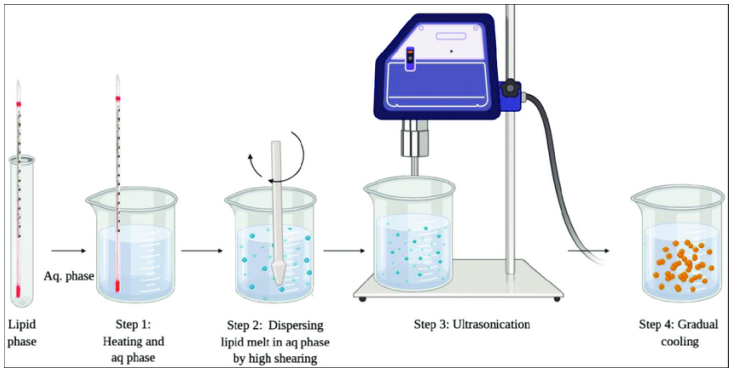


Figure 3: High Pressure Homogenization

Steps	Hot Homogenization Technique	Cold Homogenization Technique
Steps 1.	Melt lipid; dissolve or solubilize active ingredients in the lipid.	
Steps 2.	Disperse melted lipid in hot aqueous surfactant solution.	Cooling and recrystallization of the active lipid mixture using liquid nitrogen or dry ice.
Steps 3.	Preparation of a pre-emulsion by means of a rotor-stator homogenizer.	Milling of the active lipid mixture by means of a ball mill or a jet mill.
Steps 4.	High-pressure homogenization above the melting point of the lipid.	Disperse lipid microparticles in cold aqueous surfactant solution.
Steps 5.	Cooling and recrystallization.	High-pressure homogenization at or below room temperature.

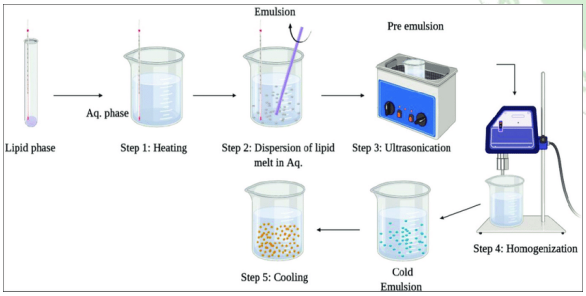


Figure 4: Hot Homogenization Technique

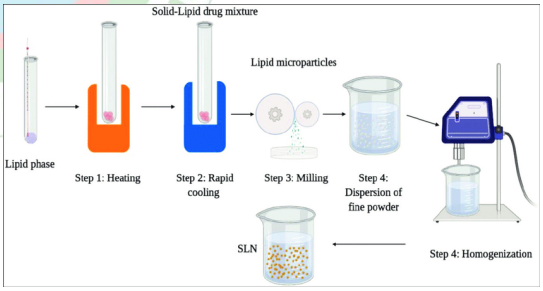


Figure 5: Cold Homogenization Technique

Ultrasonication or High-Speed Homogenization

The ultrasonication method is a dispersing technique originally developed for creating solid lipid nanodispersions. This approach relies on the principle of cavitation. Initially, the drug is incorporated into the melted solid lipid. Next, an aqueous phaseheated to the same temperature as the lipidis introduced. This can be done either through probe sonication, high-speed stirring, or by gradually adding the aqueous phase to the lipid while stirring magnetically.

The resulting pre-emulsion is then processed using a probe sonicator in a water bath maintained at 0°C. To avoid recrystallization during this process, the production temperature is kept at least 5°C above the lipid's melting point. The nanoemulsion (oil-in-water) produced is subsequently filtered through a 0.45 µm membrane to eliminate any impurities that may have been introduced during ultrasonication. The solid lipid nanoparticles (SLNs) are then stored at 4°C. To enhance the stability of the formulation, the product is often lyophilized, yielding a freeze-dried powder, with mannitol (5%) sometimes added as a cryoprotectant.

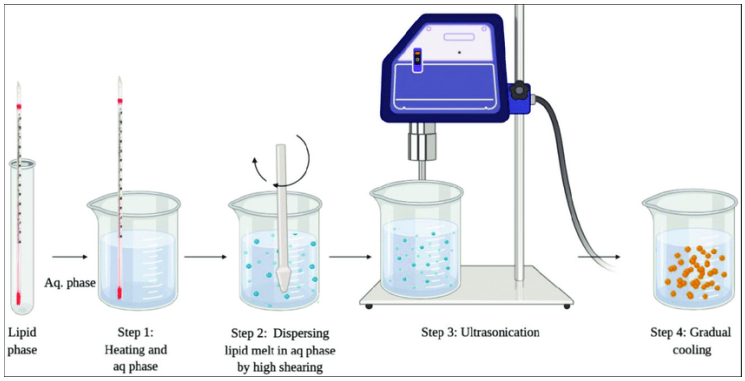


Figure 6: Ultrasonication or High-Speed Homogenization

Solvent emulsification evaporation method

In this approach, the lipid phase is first dissolved in an organic solvent, such as acetone, creating the organic phase. This organic phase is then introduced into an aqueous surfactant solution while maintaining continuous stirring at a temperature of 70-80 °C. Stirring is sustained until the organic solvent has completely evaporated. After the nanoemulsion is formed, it is cooled to a temperature below 5 °C to facilitate the solidification of the lipid nanoparticles.[10]

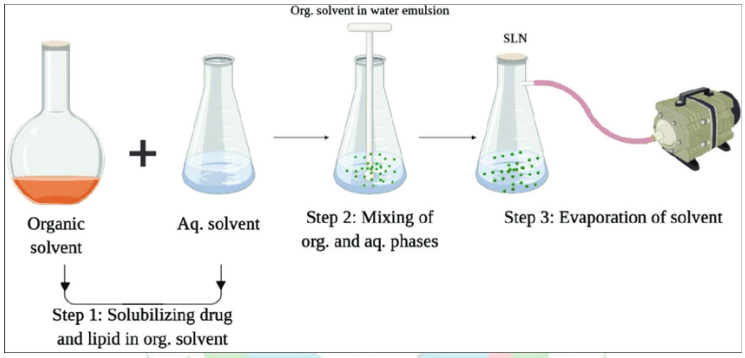


Figure 7: Solvent emulsification evaporation method

Super critical fluid method

In this technique, solid lipid nanoparticles (SLNs) are produced from gas-saturated solutions (GSS), which allows for processing without solvents. The formation of SLNs occurs through the rapid expansion of supercritical carbon dioxide solutions. GSS aids in melting the lipid material, which then dissolves in the supercritical fluid (SCF) under pressure. The saturated solution is then sprayed through a nozzle or atomizer, causing the SCF to expand rapidly and escape, resulting in fine, dry lipid particles. This method's lack of organic solvents and the extensive miscibility of lipids in SCF make it advantageous.

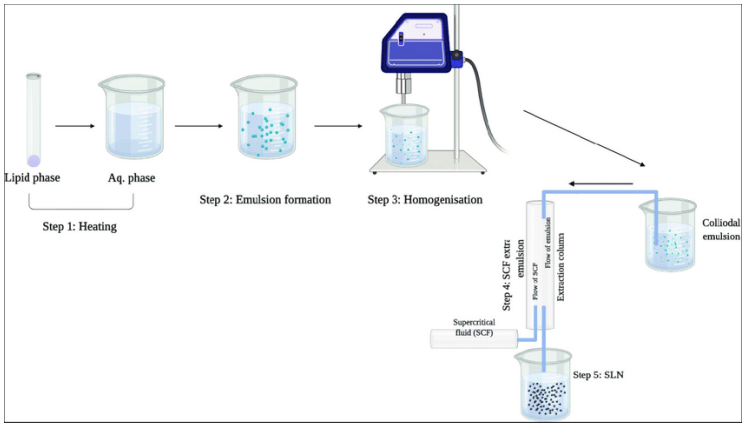


Figure 8: Super critical fluid method

Microemulsion based method

This method involves diluting a microemulsion to achieve lipid precipitation. Solid lipid nanoparticles (SLNs) are formed by stirring a clear mixture containing a low melting fatty acid, emulsifier, coemulsifiers, and water at 65–70 °C. Afterward, the hot microemulsion is added to cold water while stirring. The typical volume ratios of hot microemulsion to cold water range from 1:25 to 1:50. The specific composition of the microemulsion plays a crucial role in the dilution process. Finally, gentle mechanical mixing in a cold aqueous medium lead to the precipitation of the lipid phase into SLNs.

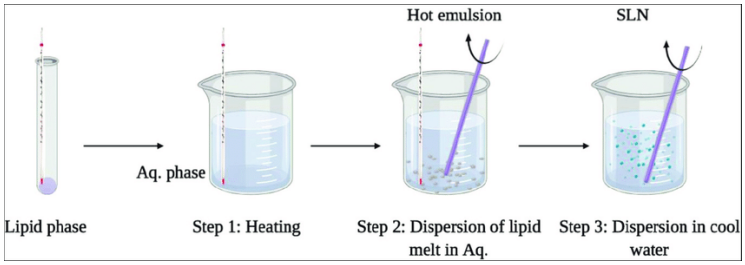


Figure 9: Microemulsion based method

Spray drying method

The spray drying technique is an alternative process for converting an aqueous dispersion of solid lipid nanoparticles (SLNs) into a final drug product. Although it is infrequently used for SLN formulations, it offers a more affordable option than lyophilization. However, this method has certain drawbacks, such as particle aggregation due to elevated temperatures and shear forces, as well as the risk of partial melting of the particles. Additionally, it requires lipids with a melting point above 70°C.[11]

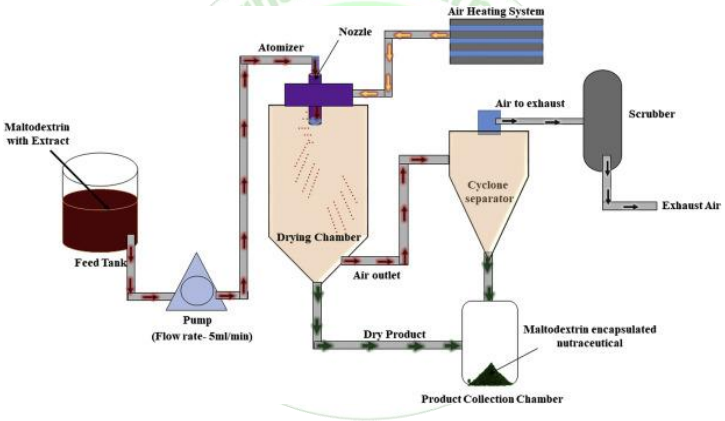


Figure 10: Spray drying method

Double emulsion method

This technique is utilized for creating hydrophilic drug-loaded solid lipid nanoparticles (SLNs) through a solvent emulsification-evaporation process. The drug is first dissolved in an aqueous solution, which is then combined with a liquid lipid melt. To stabilize the primary emulsion, a stabilizer is incorporated, and this emulsifier is dispersed in an aqueous phase containing a hydrophilic emulsifier. The resulting double emulsion is blended and subsequently separated by sifting. Poly (lactic-co-glycolic acid) (PLGA) is essential for the emulsification of the primary water-in-oil (w/o) emulsion. Research shows that increasing the concentration of PLGA improves the loading capacity, stability of the w/o emulsion, and encapsulation efficiency. However, PLGA does not significantly influence the particle size of the SLNs, and higher concentrations lead to a marked reduction in zeta potential.[12]

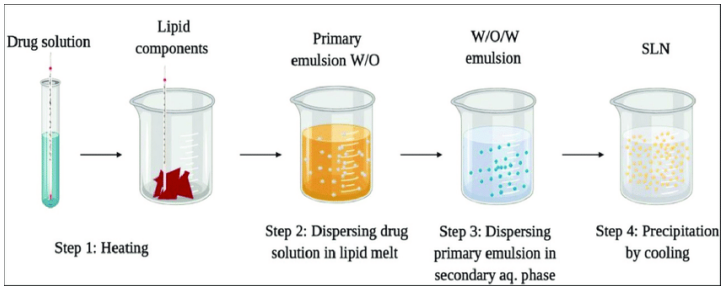


Figure 11: Double emulsion method

SLNS FOR TOPICAL USE

Corticosteroids are commonly used therapeutic agents for treating skin disorders such as eczema and psoriasis. Topical formulations using solid lipid nanoparticles (SLNs) hold great promise for effectively delivering corticosteroids directly to affected areas, reducing systemic absorption. By applying these medications at the site of the condition, localized treatment becomes more efficient. SLNs have been explored for various drugs, including anticancer therapies, vitamin A, isotretinoin, and flurbiprofen. For instance, nanoparticles loaded with vitamin A can be formulated using glyceryl behenate, which enhances skin penetration and allows for sustained release. Similarly, isotretinoin-loaded lipid nanoparticles have been created for topical administration. Flurbiprofen-loaded SLN gels provide the benefit of delivering concentrated doses directly to the target site. Additionally, delivering doxorubicin (Dox) through the skin could optimize its effectiveness against skin cancer while minimizing adverse effects.[13]

CHARACTERIZATION OF SLNS

1. **Particle Size Measurement**
   - **Photon Correlation Spectroscopy (PCS)**: Measures particle size based on dynamic light scattering from Brownian motion, suitable for particles ranging from 3 nm to 3 mm.
   - **Laser Diffraction (LD)**: Another method for assessing particle size, particularly for larger particles.
2. **Shape and Morphology**
   - **Electron Microscopy**: Provides direct visual information about particle shape and surface characteristics, complementing size measurements.
3. **Zeta Potential (ZP)**
   - Measures the surface charge of particles, indicating stability in colloidal dispersions. A higher absolute ZP suggests reduced aggregation and greater stability over time.
4. **Physical Stability**
   - Optimized SLN dispersions typically maintain stability for over 12 months, ensuring effective drug delivery.[14]

CONCLUSION

Solid lipid nanoparticle (SLN) drug delivery technology offers significant potential for enhancing medical therapeutics, yet much of this potential remains untapped. Key advantages of SLNs include their favorable composition, efficient production processes suitable for large-scale manufacturing, and the ability to achieve higher encapsulation efficiency. However, a major challenge is their limited capacity to load hydrophilic drugs, primarily due to partitioning effects during production.

Improving the bioavailability of drugs is critical in drug formulation, particularly for commonly used azole antifungal agents such as clotrimazole, miconazole, fluconazole, and others, which are often hydrophobic and poorly soluble in aqueous environments. Developing lipid-based nanocarrier systems could effectively enhance solubility and bioavailability, addressing these challenges and unlocking the full therapeutic potential of SLNs.

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