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SOLID LIPID NANOPARTICLES (SLNs): COMPREHENSIVE

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ABSTRACT

Solid lipid nanoparticles (SLNs) are nanoscale colloidal drug carriers composed of physiological lipids that remain solid at both room and body temperature. They were developed in the early 1990s by R. H. Müller and colleagues to overcome the major limitations of conventional carriers such as liposomes and polymeric nanoparticles, including physical instability, potential toxicity, and difficulties in large-scale production. This review provides a comprehensive evaluation of SLN formulation principles, physicochemical properties, preparation techniques, drug incorporation mechanisms, release kinetics, stability factors, regulatory considerations, clinical translation, and emerging applications. It presents an integrated analysis of the mechanistic, thermodynamic, kinetic, and industrial aspects of SLNs, linking pharmaceutical nanotechnology principles with modern biomedical applications. SLNs offer several advantages, including improved drug stability, controlled and sustained release, enhanced bioavailability, reduced systemic toxicity, and feasibility for industrial-scale manufacturing. Their applications extend across multiple therapeutic areas such as oncology, central nervous system disorders, antimicrobial therapy, gene delivery, and nutraceutical delivery. Although certain challenges remain, particularly polymorphic transitions of lipids and relatively limited drug loading capacity, SLNs continue to represent a promising and versatile nanocarrier platform with significant translational potential, especially in the fields of gene therapy and personalized nanomedicine.

KEYWORDS: *Solid Lipid Nanoparticles; Lipid Nanocarriers; Nanomedicine; Drug Delivery; Lipid Polymorphism; Controlled Release; Pharmacokinetics; Gene Delivery; Nanotechnology; Pharmaceutical Engineering.*

INTRODUCTION TO SOLID LIPID NANOPARTICLES

Nanotechnology has emerged as one of the most influential technological advancements in pharmaceutical sciences. It offers innovative strategies to improve drug delivery, enhance therapeutic efficacy, and reduce adverse effects. Traditional dosage forms such as tablets, capsules, and injections often face limitations including poor aqueous solubility, rapid degradation, non-specific distribution, short half-life, and systemic toxicity. These challenges reduce the bioavailability of many drugs and limit their therapeutic potential. Nanocarrier systems have been developed to overcome these drawbacks by modifying pharmacokinetic and pharmacodynamic properties of drugs fig 1

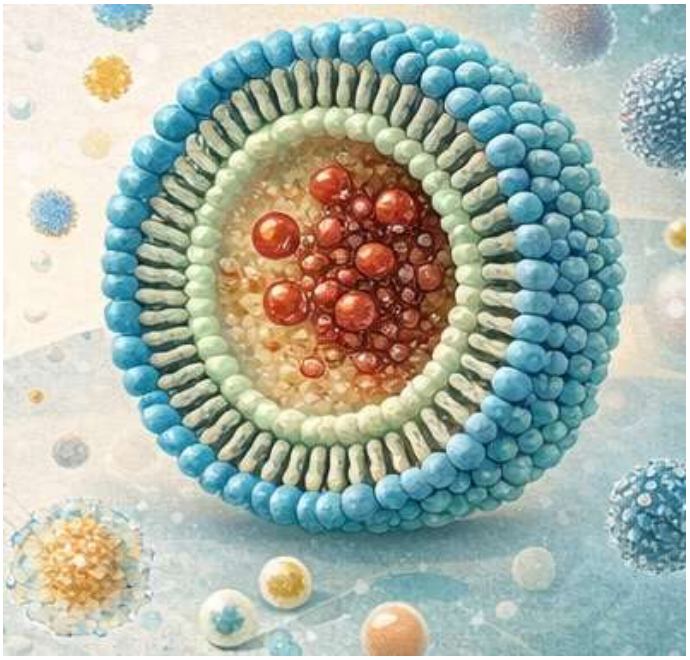


Figure:1: Nanocarrier

Among the various nanocarrier systems, Solid Lipid Nanoparticles (SLNs) have gained considerable attention as a promising drug delivery platform. SLNs are submicron colloidal carriers composed of physiological lipids that remain solid at both room and body temperatures. They combine the advantages of lipid emulsions, such as biocompatibility and low toxicity, with the stability of polymeric nanoparticles.

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Structurally, SLNs consist of three main components: a solid lipid core, a stabilizing surfactant layer, and the encapsulated drug molecule. The lipid matrix forms a crystalline or semi-crystalline structure that protects the drug from chemical and enzymatic degradation. The nanoscale size, typically ranging from 50 to 1000 nanometers, allows improved cellular uptake, enhanced permeability, and retention effects in tumor tissues. Over the last three decades, SLNs have been investigated for multiple routes of administration, including oral, parenteral, topical, pulmonary, nasal, and ocular delivery. Their production through scalable techniques such as high-pressure homogenization makes them suitable for industrial manufacturing.

Historical Evolution of Lipid Nanocarriers

The development of lipid-based nanocarriers has evolved through several generations, each addressing limitations of previous systems. The first generation consisted of liposomes, which are spherical vesicles composed of phospholipid bilayers. Although liposomes improved drug solubility and biocompatibility, they suffered from issues such as leakage of encapsulated drugs, poor physical stability, and high production costs.

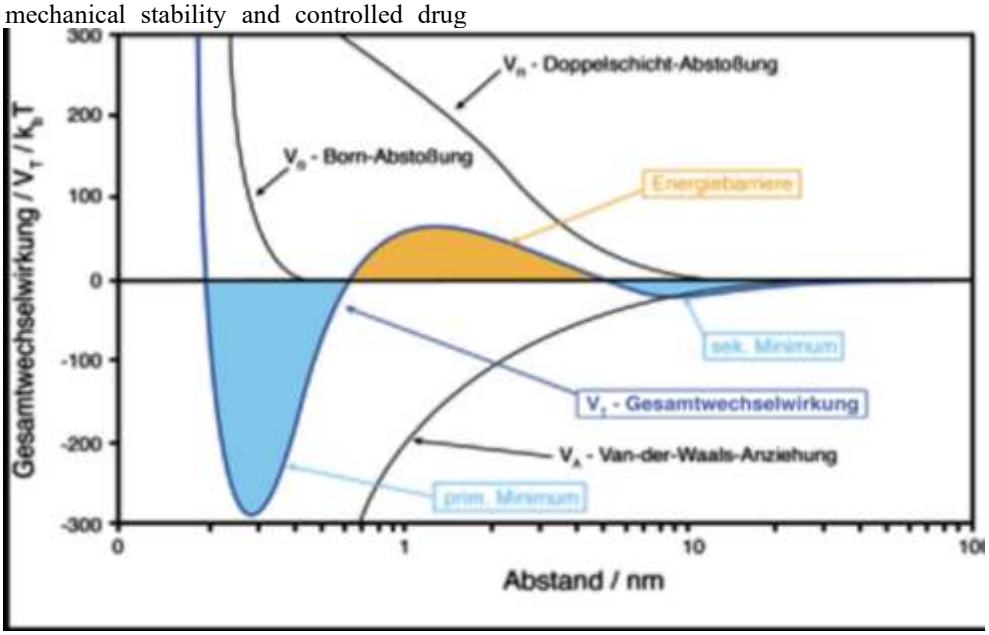
The second generation introduced polymeric nanoparticles made from synthetic or natural polymers. These systems offered improved mechanical stability and controlled drug release. However, concerns regarding polymer toxicity, residual solvents, and long-term safety limited their widespread acceptance.

The third generation led to the development of Solid Lipid Nanoparticles. SLNs were designed to combine the safety of lipid carriers with the stability of polymeric nanoparticles. They provided controlled drug release, protection of sensitive drugs, and improved biocompatibility.

However, SLNs exhibited certain limitations, particularly in terms of limited drug loading capacity and the possibility of drug expulsion during storage due to lipid crystallization. To address these issues, the fourth generation of lipid carriers, known as Nanostructured Lipid Carriers (NLCs), was developed. These systems contain a mixture of solid and liquid lipids, creating an imperfect crystal structure that allows higher drug loading and improved stability.

Physicochemical Principles of SLNs

SLNs function based on the principles of colloidal dispersion, lipid crystallization, and interfacial phenomena. The stability and performance of SLNs depend on several physicochemical parameters, including particle size, surface charge, lipid crystallinity, drug solubility, and interfacial tension between lipid and surfactant.



Particle size plays a crucial role in determining biodistribution, cellular uptake, and drug release behavior. Smaller particles offer larger surface area and improved interaction with biological membranes. Surface charge, expressed as zeta potential, influences colloidal stability. A high absolute zeta potential value provides electrostatic repulsion between particles, preventing aggregation.

The stability of SLNs is often explained using DLVO theory, which describes the balance between attractive van der Waals forces and repulsive electrostatic forces. When repulsive forces dominate, the dispersion remains stable. When attractive forces exceed repulsion, aggregation occurs.

Lipid Polymorphism and Crystallinity

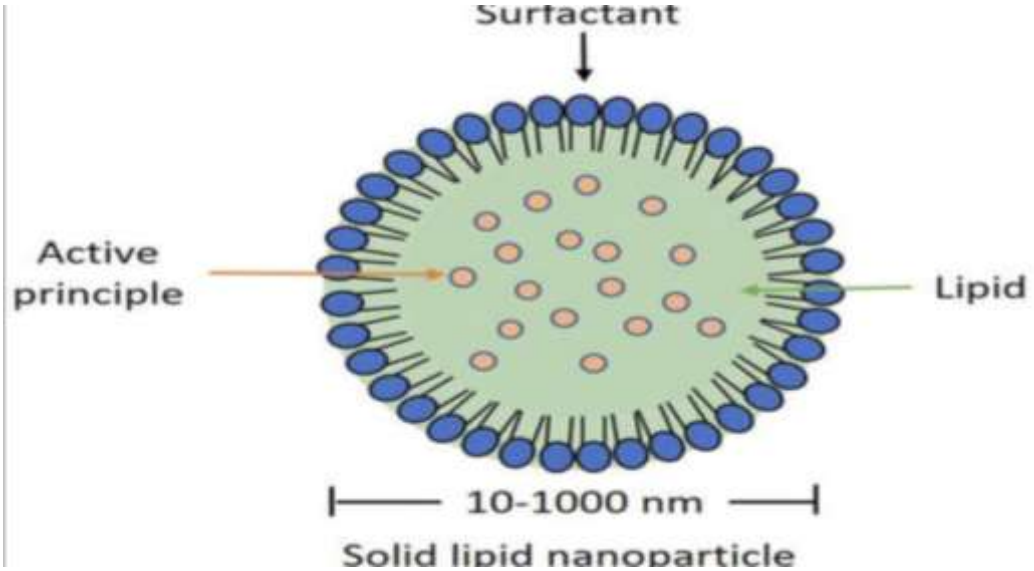
One of the most critical aspects of SLN stability is lipid polymorphism. Lipids can exist in different crystalline forms, including the alpha (α), beta-prime (β′), and beta (β) forms. The α-form is the least stable and has a loosely packed crystal structure. The β′-form is metastable and moderately ordered, while the β-form is the most stable and highly ordered crystalline state.

During storage, lipids tend to undergo polymorphic transitions from the α-form to the β′-form and eventually to the β-form. As the crystal structure becomes more ordered, the available space for drug molecules decreases, which may result in drug

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expulsion from the lipid matrix. This phenomenon reduces entrapment efficiency and affects drug release behavior.
Differential Scanning Calorimetry (DSC) is commonly used to monitor these polymorphic transitions. It provides information about melting points, crystallization behavior, and thermal stability of the lipid matrix.

Composition of SLNs
The composition of SLNs includes lipids, surfactants, co-surfactants, and the active pharmaceutical ingredient. The choice of lipid significantly influences the melting point, crystallinity, drug loading capacity, and release profile. Common lipids used in SLNs include glyceryl monostearate, stearic acid, tripalmitin, and cetyl palmitate.



Surfactants are essential for stabilizing the nanoparticle dispersion. They reduce surface tension, prevent aggregation, and control particle size. Common surfactants include polysorbates, poloxamers, lecithin, and sodium cholate.

Co-surfactants are sometimes added to improve emulsification efficiency and stability. The compatibility between the drug and lipid matrix determines entrapment efficiency and release characteristics. Drugs with higher solubility in the lipid phase exhibit better encapsulation.

Preparation Techniques
Several techniques are used to prepare SLNs, each based on different physicochemical principles.
High-pressure homogenization is the most widely used method. It involves forcing a hot or cold lipid dispersion through a narrow gap at high pressure. Mechanical shear and cavitation forces break down the droplets into nanosized particles. This method is scalable, solvent-free, and compatible with industrial production.

Solvent evaporation involves dissolving lipid and drug in an organic solvent, followed by emulsification in an aqueous phase. The solvent is then evaporated, causing lipid precipitation and nanoparticle formation. However, the presence of residual solvents is a major limitation.

Supercritical fluid technology uses supercritical carbon dioxide to dissolve lipids and drugs, followed by rapid expansion to form nanoparticles. This method reduces **solvent residues and is considered environmentally friendly.**

Characterization of SLNs
Characterization of solid lipid nanoparticles (SLNs) is a critical step to ensure their quality, stability, safety, and therapeutic performance. It provides essential information about the physical, chemical, and biological properties of the formulation, which directly influence drug release, bioavailability, and shelf life. Proper characterization also helps in optimizing formulation variables and ensuring reproducibility during large-scale production.

Particle size and size distribution are among the most important parameters, as they influence drug absorption, biodistribution, stability, and cellular uptake. These parameters are commonly measured using Dynamic Light Scattering (DLS), which determines the hydrodynamic diameter of nanoparticles in suspension. A narrow size distribution indicates uniformity and better stability of the formulation.

Morphological analysis is performed to examine the shape and surface structure of SLNs. Transmission Electron Microscopy (TEM) provides high-resolution images that reveal the internal and external structure of nanoparticles, while Scanning Electron Microscopy (SEM) gives information about surface morphology and particle shape. SLNs are generally observed to be spherical or slightly oval in shape.

Zeta potential analysis is used to determine the surface charge of nanoparticles, which is a key indicator of colloidal stability. High positive or negative zeta potential values (typically ±30 mV or greater) suggest good electrostatic repulsion between particles, preventing aggregation and enhancing stability during storage.

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X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC) are employed to study the crystalline structure of the lipid matrix and any polymorphic transitions. These techniques help determine whether the drug is present in crystalline or amorphous form and reveal interactions between the drug and lipid components. Changes in crystallinity can influence drug loading, release behavior, and long-term stability.

Atomic Force Microscopy (AFM) provides three-dimensional surface topography at the nanoscale. It allows visualization of surface roughness, particle shape, and aggregation behavior without the need for extensive sample preparation. Raman spectroscopy is used for chemical characterization, enabling identification of molecular interactions, drug distribution within the lipid matrix, and confirmation of encapsulation.

In vitro drug release studies are conducted to evaluate the release profile of the drug from SLNs over time. These studies are typically performed using dialysis membranes, Franz diffusion cells, or dissolution apparatus. The results help in understanding release kinetics, identifying burst or sustained release patterns, and predicting the in vivo behavior of the formulation. Such studies are essential for optimizing therapeutic efficacy and ensuring consistent drug delivery performance.

Drug Incorporation Models

Drug incorporation into SLNs depends on thermodynamic compatibility between the drug and lipid matrix. The process is governed by the Gibbs free energy equation. When the change in free energy is negative, drug encapsulation is thermodynamically favorable.

Three main models describe drug distribution within SLNs. In the homogeneous matrix model, the drug is uniformly distributed throughout the lipid matrix. In the drug-enriched shell model, the drug is concentrated near the outer layer of the nanoparticle. In the drug-enriched core model, the drug is concentrated at the center of the particle.

Each model produces different drug release patterns and stability characteristics.

Mechanisms of Drug Release

Drug release from solid lipid nanoparticles (SLNs) is governed by multiple mechanisms, primarily diffusion, erosion of the lipid matrix, or a combination of both processes. The release behavior depends on the internal structure of the lipid core, the location of the drug within the nanoparticle, and the physicochemical properties of the formulation. Understanding these mechanisms is important for designing SLNs with predictable and controlled therapeutic effects.

In diffusion-controlled release, the drug gradually migrates from the lipid matrix into the surrounding aqueous environment. This process occurs when the drug is molecularly dispersed within the lipid core or located near the particle surface. The rate of diffusion depends on the lipid crystallinity, the solubility of the drug in the lipid phase, and the thickness of the lipid matrix. Diffusion-controlled release is commonly observed in SLNs with less ordered or partially crystalline lipid structures.

In erosion-controlled release, the drug is released as the lipid matrix undergoes degradation. This degradation may occur through enzymatic action, especially in the gastrointestinal tract where lipases and other enzymes break down the lipid components. As the matrix erodes, the entrapped drug is gradually released into the surrounding medium. This mechanism is more significant in oral formulations and in biological environments where enzymatic activity is high.

In many cases, drug release from SLNs follows a combination of diffusion and erosion mechanisms. Initially, a burst release may occur due to drug molecules located on or near the particle surface. This is followed by a slower, sustained release phase as the drug diffuses through the lipid matrix or is released during lipid degradation.

Various kinetic models are used to describe and analyze the release behavior of drugs from SLNs. Zero-order kinetics represent a system where the drug is released at a constant rate over time, independent of drug concentration. This type of release is ideal for maintaining consistent therapeutic levels. First-order kinetics describe a release pattern that depends on the remaining drug concentration in the system, resulting in a faster release initially and a slower release as the drug content decreases.

The Higuchi model is commonly applied to diffusion-controlled systems. It describes drug release as a function of the square root of time, indicating that the release rate decreases over time as the diffusion path length increases. This model is often used for matrix-based delivery systems, including SLNs.

The Korsmeyer–Peppas model is a semi-empirical equation used to analyze drug release from polymeric and lipid systems when the mechanism is not purely diffusion or erosion. It helps identify anomalous or non-Fickian transport, where both diffusion and matrix relaxation or erosion contribute to the release process. The release exponent obtained from this model indicates the dominant mechanism.

The overall release mechanism from SLNs is influenced by several formulation and environmental factors. Lipid crystallinity plays a major role; highly crystalline lipids tend to retain the drug more tightly, resulting in slower and more sustained release, whereas less ordered lipids allow faster diffusion. Particle size also affects release, as smaller particles have a larger surface area, leading to faster drug release. Drug solubility in the lipid matrix determines how strongly the drug is retained within the core. Environmental conditions such as pH, temperature, enzymatic activity, and ionic strength can further influence lipid degradation, drug diffusion, and overall release kinetics. Proper control of these parameters enables the design of SLNs with desired release profiles for specific therapeutic applications.

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Stability Studies
SLNs may undergo instability due to aggregation, Ostwald ripening, polymorphic transitions, and oxidative degradation. Aggregation occurs when particles come together, increasing particle size. Ostwald ripening involves growth of larger particles at the expense of smaller ones.

Shelf-life prediction is performed using the Arrhenius equation, which relates degradation rate to temperature. Accelerated stability studies are conducted at elevated temperature and humidity to predict long-term stability.

Toxicology and Regulatory Aspects
Regulatory agencies require extensive evaluation of nanoparticle systems before approval. This includes physicochemical characterization, toxicokinetic studies, immunogenicity assessment, and batch-to-batch reproducibility.

Surface modification techniques such as PEGylation are often used to reduce recognition by the immune system and prolong circulation time.

Route-Specific Applications
SLNs are suitable for multiple routes of administration. Oral delivery improves solubility and enables lymphatic uptake. Parenteral delivery provides controlled systemic release. Intranasal delivery enables direct brain targeting. Pulmonary delivery benefits from the large surface area of the lungs. Ocular delivery increases drug residence time, and topical application enhances skin hydration.

Applications in Oncology
SLNs enhance drug accumulation in tumor tissues through the Enhanced Permeability and Retention effect. They reduce systemic toxicity and improve therapeutic efficacy. For example, doxorubicin-loaded SLNs reduce cardiotoxicity while maintaining anticancer activity.

CNS Applications
SLNs coated with surfactants such as polysorbate 80 can cross the blood–brain barrier through receptor-mediated transport. This makes them useful in treating neurological disorders such as Alzheimer's disease, Parkinson's disease, and epilepsy.

Antimicrobial Applications
SLNs improve intracellular penetration of antimicrobial agents and provide sustained drug release. They have shown improved efficacy against resistant pathogens and have been studied for tuberculosis, HIV, and fungal infections.

Gene Delivery Applications
SLNs are being explored as non-viral carriers for gene delivery. They can deliver siRNA, DNA, and mRNA with lower immunogenicity and improved stability compared to conventional viral vectors.

Clinical Translation
Although few SLN-based pharmaceutical products are approved, many formulations are under clinical investigation. Challenges include regulatory complexity and large-scale reproducibility.

Industrial Considerations
Industrial production of SLNs requires GMP-compliant equipment, sterile processing, and quality control systems. Lyophilization is commonly used for long-term storage.

Comparison of Major Nanocarrier Systems in Drug Delivery
Nanocarriers are nanoscale drug delivery systems designed to improve solubility, stability, targeting, and controlled release of drugs. The most commonly used nanocarriers include solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, polymeric nanoparticles, nanoemulsions, and dendrimers. Each system has unique structural features, advantages, and limitations.

Feature	Solid Lipid Nanoparticles (SLNs)	Nanostructured Lipid Carriers (NLCs)	Liposomes	Polymeric Nanoparticles	Nanoemulsions	Dendrimers
Basic Structure	Solid lipid core with surfactant	Mixture of solid and liquid lipids	Phospholipid bilayer vesicles	Polymer matrix or capsule	Oil-in-water or water-in-oil droplets	Highly branched polymer structures
Physical State of Core	Solid at room and body temperature	Imperfect solid matrix	Aqueous core surrounded by lipid bilayer	Solid polymeric matrix	Liquid oil core	Solid polymeric structure
Drug Loading Capacity	Moderate	High	High (both hydrophilic and lipophilic)	High	Moderate	High
Stability	High	Very high	Moderate (prone to leakage)	Very high	Moderate	High
Release Profile	Sustained release	Controlled and improved release	Rapid or controlled	Controlled release	Rapid release	Controlled or targeted release

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			depending on design			
Biocompatibility	Excellent (physiological lipids)	Excellent	Excellent	Moderate to good (depends on polymer)	Good	Variable (depends on generation and surface groups)
Toxicity	Very low	Very low	Low	Moderate (polymer-dependent)	Low	Can be higher at high generations
Scalability	Easy industrial scale-up	Easy scale-up	Difficult and expensive	Moderate	Easy	Complex synthesis
Cost	Low	Moderate	High	Moderate	Low	High
Typical Applications	Anticancer, oral delivery, topical	High-load drug delivery, improved stability	Vaccines, gene delivery, anticancer drugs	Controlled release, implants, targeted therapy	Parenteral and oral drug delivery	Gene delivery, targeted therapy

Future Prospects and Conclusion

Solid lipid nanoparticles (SLNs) represent a highly promising nanocarrier system that combines **biocompatibility, physical stability, controlled drug release, and targeted delivery**. They are composed of physiological lipids that remain solid at both room and body temperatures, which provides structural rigidity and enhances drug protection. This solid matrix enables **sustained and controlled release profiles**, reduces drug degradation, and improves therapeutic efficacy. Because the lipids used are generally recognized as safe (GRAS), SLNs show **low toxicity and good patient compliance**, making them suitable for oral, topical, parenteral, ocular, and pulmonary drug delivery.

Recent advancements in **lipid engineering** have significantly improved the performance of SLNs. By selecting appropriate combinations of solid lipids, emulsifiers, and co-lipids, scientists can optimize drug loading capacity, particle size, and release characteristics. The development of **nanostructured lipid carriers (NLCs)**, which incorporate both solid and liquid lipids, has further addressed limitations such as low drug loading and drug expulsion during storage. In addition, **surface modification techniques**, such as PEGylation or ligand attachment, have enhanced targeting efficiency, circulation time, and cellular uptake. These modifications allow SLNs to selectively deliver drugs to specific tissues, such as tumor cells or the central nervous system, thereby increasing therapeutic effectiveness while minimizing systemic side effects.

The integration of **artificial intelligence (AI) and machine learning** into formulation design is another emerging advancement. AI-based predictive models can optimize formulation parameters, such as lipid composition, surfactant concentration, and processing conditions, to achieve desired particle size, stability, and drug release profiles. This approach reduces trial-and-error experimentation, saves time and resources, and accelerates the development of SLN-based drug delivery systems. AI can also help predict **stability issues, polymorphic transitions, and drug–lipid interactions**, improving overall formulation reliability.

Despite these advantages, SLNs still face certain challenges. One major issue is **polymorphic instability**, where the lipid matrix undergoes structural rearrangement over time, leading to drug expulsion or changes in release behavior. Another limitation is the **restricted drug loading capacity**, especially for highly water-soluble drugs. Additionally, large-scale production and long-term storage stability remain areas requiring further research and optimization.

Nevertheless, ongoing innovations in **lipid chemistry, nanotechnology, surface functionalization, and AI-driven design** are expected to overcome these limitations. As a result, SLNs hold significant potential in various therapeutic areas, including **oncology, neurology, infectious diseases, and gene therapy**. Their ability to enhance drug bioavailability, reduce toxicity, and provide targeted and controlled delivery positions SLNs as an important platform in the future of advanced drug delivery systems.

REFERENCES

1. *Aulton ME, Taylor K. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 5th ed. London: Elsevier; 2018.*
2. *Allen LV. Pharmaceutical Dosage Forms and Drug Delivery Systems. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.*
3. *Ansel HC, Allen LV, Popovich NG. Pharmaceutical Calculations. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2014.*
4. *Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Mumbai: Varghese Publishing; 2009.*
5. *Martin A. Physical Pharmacy and Pharmaceutical Sciences. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.*
6. *Remington JP. Remington: The Science and Practice of Pharmacy. 22nd ed. London: Pharmaceutical Press; 2013.*
7. *Harry RG. Harry's Cosmeticology. 8th ed. New York: Chemical Publishing; 2000.*
8. *Butler H. Poucher's Perfumes, Cosmetics and Soaps. 10th ed. Dordrecht: Springer; 2000.*
9. *Barel AO, Paye M, Maibach HI. Handbook of Cosmetic Science and Technology. 4th ed. Boca Raton: CRC Press; 2014.*

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10. *Draelos ZD. Cosmetic Dermatology: Products and Procedures. 2nd ed. Oxford: Wiley-Blackwell; 2015.*
11. *Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. 9th ed. London: Elsevier; 2019.*
12. *Kokate CK, Purohit AP, Gokhale SB. Pharmacognosy. 56th ed. Pune: Nirali Prakashan; 2021.*
13. *Trease GE, Evans WC. Trease and Evans Pharmacognosy. 16th ed. London: Saunders Elsevier; 2009.*
14. *Wallis TE. Textbook of Pharmacognosy. 5th ed. New Delhi: CBS Publishers; 2011.*
15. *Tyler VE, Brady LR, Robbers JE. Pharmacognosy. 9th ed. Philadelphia: Lea & Febiger; 2008.*
16. *Indian Pharmacopoeia Commission. Indian Pharmacopoeia. Ghaziabad: IPC; 2022.*
17. *British Pharmacopoeia Commission. British Pharmacopoeia. London: TSO; 2022.*
18. *World Health Organization. WHO Monographs on Selected Medicinal Plants. Vol. 1. Geneva: WHO; 1999.*
19. *World Health Organization. WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants. Geneva: WHO; 2003*
20. *Prabu GR, Gnanamani A, Sadulla S. Guaijaverin – a plant flavonoid as potential antiplaque agent against Streptococcus mutans. J Appl Microbiol. 2006;101(2):487–95.*
21. *Chaieb K, Hajlaoui H, Zmantar T, Kahla-Nakbi AB, Rouabhia M, Mahdouani K, et al. The chemical composition and biological activity of clove essential oil. Phytother Res. 2007;21(6):501–6.*
22. *Subapriya R, Nagini S. Medicinal properties of neem leaves: a review. Curr Med Chem Anticancer Agents. 2005;5(2):149–56.*
23. *Biswas K, Chattopadhyay I, Banerjee RK, Bandyopadhyay U. Biological activities and medicinal properties of neem (Azadirachta indica). Curr Sci. 2002;82(11):1336–45.*
24. *Prashar A, Locke IC, Evans CS. Cytotoxicity of clove (Syzygium aromaticum) oil and its major components to human skin cells. Cell Prolif. 2006;39(4):241–8.*
25. *Addy M. Tooth brushing, tooth wear and dentine hypersensitivity – are they associated? Int Dent J. 2005;55(4 Suppl 1):261–7.*
26. *ten Cate JM. Contemporary perspective on the use of fluoride products in caries prevention. Br Dent J. 2013;214(4):161–7.*
27. *Joiner A. The bleaching of teeth: a review of the literature. J Dent. 2006;34(7):412–9.*
28. *Marsh PD. Dental plaque as a biofilm and a microbial community – implications for health and disease. BMC Oral Health. 2006;6(Suppl 1):S14.*
29. *American Dental Association Council on Scientific Affairs. Acceptance Program Guidelines: Toothpastes. Chicago: ADA; 2018.*
30. *U.S. Food and Drug Administration. Antiperspirant Drug Products for Over-the-Counter Human Use. Final Monograph. Washington DC: FDA; 2003.*