RESEARCH PAPER

Solid Lipid Nanoparticles (SLNs) for Oral Delivery of Biologics: A Comprehensive Review

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Abstract:
For the oral delivery of biologics, solid lipid nanoparticles (SLNs) have become a viable nanocarrier technology that addresses important issues such enzymatic degradation, low solubility, and restricted bioavailability of therapeutic proteins, peptides, and nucleic acids. While surface alterations enable targeted distribution to certain organs and enhanced absorption across biological barriers, their solid lipid matrix offers a protective environment that improves stability and permits regulated release. SLNs have the advantages of biocompatibility, biodegradability, and scalability over traditional carriers, which makes them appropriate for a variety of therapeutic uses. This thorough analysis examines recent preclinical and clinical data, assesses constraints including drug loading capacity and manufacturing difficulties, and highlights the design, formulation techniques, and mechanisms by which SLNs enhance oral administration of biologics. In order to offer SLNs as a flexible platform for upcoming oral biologic medicines, future prospects highlight their integration with cutting-edge biologics, such as monoclonal antibodies and RNA-based therapeutics.

Keywords: Oral delivery, biologics, nanocarriers, controlled release, bioavailability, protein therapeutics, peptide medicines, RNA therapeutics, solid lipid nanoparticles, and targeted drug delivery.

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Introduction:
Oral administration continues to be the most often used medication delivery modality. Significant issues still exist despite the oral route's widespread use and adaptability. Certain medication compounds do not have the physical, chemical, or biological properties required for an oral treatment to be effective. It is generally recognized that issues like inadequate permeability through biological membranes, low solubility or chemical stability in the gastrointestinal tract environment, or susceptibility to metabolism lead to the rejection of possible medication candidates. Drug delivery systems based on lipids have been suggested as a way to get beyond some of the more difficult physical or chemical barriers connected to poorly absorbed medications.[1]

Therefore, a number of different drug delivery methods are being explored to improve the oral BA of chemically unstable and poorly soluble medications. These delivery systems include: improving solubility through solid dispersions, complexation with cyclodextrins, and liquid solid compacts; increasing stability and prolonged residence time through floating systems, multiple floating systems, and increasing the mucoadhesive property; and reducing particle size through micronization using nanosuspensions, various colloidal carriers, transferosomes, nanoemulsions, and semisolid dispersions after first-pass metabolism with buccal drug delivery. Additionally, colloidal carrier systems shield delicate medications from deterioration in biological fluids. Because of their continuous release, they give the patient protection against gastrointestinal irritation and prolong the duration of the drug's activity. Moreover, medication targeting may be accomplished with colloidal carrier systems.[2]

There is more biological acceptance of colloidal carrier systems with compositions that resemble physiological structures. Furthermore, lipids can be readily converted into harmless metabolites. Colloidal systems made of biodegradable polymers have also been thoroughly studied and have shown themselves to be excellent options for oral medication delivery. The interaction with the reticulo endothelial system (RES) is the main issue with the parenteral delivery of colloidal particles. Phagocytic cells, which make up this system, efficiently and quickly eliminate unwanted particles from the bloodstream. As a result, methods for "masking" the colloids with hydrophilic macromolecules were developed.[3]

Numerous disadvantages of traditional medication delivery methods include nonspecific targeting, rapid degradation, severe side effects, and limited solubility.

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Because of their unique chemical and physical properties, nanoparticles provide a viable solution to these issues. They can facilitate longer-term release, improve drug payload stability, stop degradation, and facilitate drug distribution to specific tissues or cells. Numerous nanoparticle types, including liposomes, dendrimers, solid lipid nanoparticles, metallic nanoparticles, and polymeric nanoparticles, are used in drug delivery. Each type has special characteristics and may be tailored for certain applications.[4]

Nanoparticles have several advantages for drug administration, including the capacity to transport medications to previously inaccessible areas due to their ability to cross a range of biological barriers, including the blood-brain barrier. Nanoparticles can passively accumulate at the target location due to the increased permeability and retention (EPR) effect brought on by the leaky vasculature seen in tumors and inflammatory tissues. The effectiveness and selectivity of the nanoparticles can also be increased by functionalizing their surfaces with specific ligands or antibodies to actively target certain receptors or antigens. Chemotherapy is more effective when this precise and customized approach reduces off-target effects and damage to healthy tissues. Despite these promising advantages, there are still challenges in the development and widespread use of drug delivery systems based on nanoparticles. Issues including potential toxicity, immune system clearance, and scale-up for mass manufacturing must be carefully taken into account during their development and regulatory appr oval processes. In conclusion, the application of nanoparticles in drug delivery systems is a cutting-edge and ground-breaking technique that has great promise for improving medical treatment. As science and technology advance, nanoparticles might revolutionize the way we treat a range of illnesses by providing patients with safer, more accurate, and more efficient therapies.[5]

Solid lipid nanoparticles are colloidal systems composed of solid lipids that are stabilized by a layer of surfactant. Solid lipid nanoparticles (SLNs), which are advanced drug delivery vehicles, have attracted a lot of interest from the pharmaceutical and biomedical sectors. They were a major advancement in the field of drug delivery technology based on nanoparticles when Gasco and Muller initially introduced them in 1991. Overcoming the shortcomings of conventional liquid lipid-based delivery systems, such as liposomes and emulsions, was the main objective of SLN development. Drug leakage, instability, and potential deterioration may arise from emulsions' active component dissolving in the oily phase. On the other hand, liposomes, which are composed of phospholipids, usually have low drug encapsulation efficiency and early drug release.[1]

In contrast, solid lipid nanoparticles consist of solid lipids that combine to form a matrix that allows the active ingredient (such as drugs, therapeutic agents, or ingredients used in cosmetics) to be dissolved, entrapped, adsorbed, or attached. The encapsulated cargo is stabilized by this solid lipid matrix, which also inhibits leakage and degradation, improving drug delivery effectiveness and bioavailability. Solid lipid nanoparticles are usually spherical in form and range in size from 50 to 1000 nm. Despite these promising advantages, challenges still exist. Their huge surface area and tiny size enhance the loaded nanoparticles, facilitating cellular absorption, drug release, and diffusion. Issues including potential toxicity, immune system clearance, and scale-up for mass manufacturing must be carefully taken into account during their development and regulatory approval processes.[1] In summary, the application of nanoparticles in drug delivery systems is a cutting-edge and ground-breaking technology with tremendous promise for medical progress. As science and technology advance, nanoparticles have the potential to fundamentally alter how we treat a wide range of illnesses by providing patients with safer, more accurate, and more effective medicines.[5]

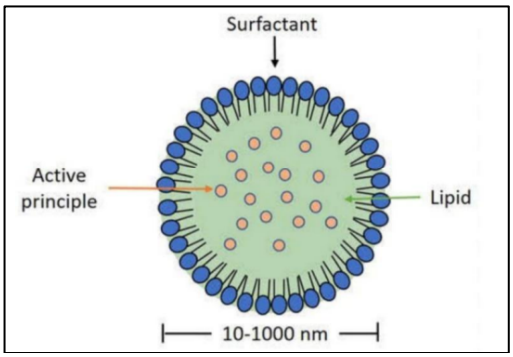

Figure 1: Structure of Solid Lipid Nanoparticles (NLCs)[54]

Because of their ability to produce stable and solid nanoparticles, their effective delivery mechanism, and their adaptability to different lipid matrices, emulsifiers, core materials, and manufacturing techniques, SLNs are the most often used models. Since their introduction in 1991, SLNs have outperformed traditional colloid systems as a carrier system. SLNs' simplicity of producing dispersion systems and sufficient entrapment effectiveness have made them an efficient and stable paradigm for encapsulating and delivery systems for

liposomes, emulsions, and polymer nanoparticles. The dispersion stability of SLNs can be improved by coating them with a liquid surfactant at a concentration of around 0.5–5%. SLNs are colloidal carrier systems made up of a lipid core with a high melting point.[6]

The primary components of SLNs are water or other solvents, solid lipids, and surfactants/emulsifiers. Solid lipids are employed as the dispersed phase because they act as a matrix material when encapsulated chemicals are introduced. Triglycerides, partial glycerides, free fatty acids, steroids, and waxes are some of the several forms of solid lipids. Since it may enhance control over the release kinetics of coated compounds and boost the stability of the generated lipophilic sites, the phase transition of liquid lipids to solid lipids offers additional advantages for SLN colloidal carrier systems.[7]

Compared to liquid lipids, the usage of solid lipids can preserve the stability of micronutrients against environmental factors such oxygen, light, and water while also better controlling the release of micronutrients trapped in lipids in the gastrointestinal tract.

Furthermore, a more sustainable or long-lasting release of the encapsulated substances is made possible by the thick lipid matrix's ability to slow down lipid breakdown. In order to create an O/W emulsion or a double emulsion (W/O/W), a liquid-type surfactant is utilized during the emulsifying phase. It can also serve as a stabilizer for SLN dispersion.[8]

Entrapment efficiency, particle size, stability, crystallinity, and pharmacokinetic characteristics like bioavailability, release time, and absorption stability of the coated drug or active ingredient are all impacted by the choice of lipids and surfactants used in the synthesis/fabrication process. High-speed homogenization in conjunction with ultrasonication, high-pressure homogenization at high or low temperatures, solvent emulsification, evaporation or diffusion, and supercritical fluid extraction of emulsions are among the techniques that may be employed to create SLNs.[9] To ensure that the application is appropriate for achieving the goals, the process for creating the chosen SLNs must be tailored to the properties of the active component to be encapsulated.

Drugs, vitamins, minerals, antibiotics, and other polar, semipolar, and non-polar antioxidant chemicals are among the active components that are encapsulated by SLNs. Because SLNs are highly efficient at boosting antioxidant activity, bioavailability, and regulated release for absorption in the gastrointestinal system, their development in antioxidant compounds has drawn interest. Lipid matrices, emulsifiers, and surfactants have all been used to effectively encapsulate a variety of antioxidant chemicals in SLNs. Because of their affinity and appropriate interactions between the lipid matrix and the core material, hydrophobic antioxidant chemicals are comparatively simple to convert into SLNs. Hydrophilic antioxidants, on the other hand, need certain procedures to be effectively encapsulated, particularly through the creation of emulsions, both single and double.[10]

Because of their superiority as a delivery vehicle for maximum absorption, antioxidant-loaded SLNs are gaining popularity in tandem with the growing need for well-protected antioxidant chemicals to enhance food stability and growing interest from the pharmaceutical sector. Furthermore, there are yet few explicit talks about the use of SLNs for antioxidant chemicals. In order to provide information on current research on SLNs, this review will begin with a summary of different fabrication techniques and their uses, particularly for the encapsulation and delivery systems for different active compounds, particularly antioxidant compounds, including both polar (hydrophilic) and non-polar (hydrophobic) antioxidants.[1]

Advancement of lipid nanoparticle technology in the form of Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs):

When it comes to the encapsulation of medications and active ingredients, lipid nanoparticle formulation (LNF) offers numerous advantages over other lipid-based vehicles, including liposomes and emulsions in colloidal nanocarrier systems, including kinetic stability and rigid structural morphology. It is possible to create a variety of LNFs, particularly in the form of SLNs and NLCs. In order to improve the bioavailability of micronutrients or active substances with limited solubility, SLNs are delivery methods that contain a solid lipid portion. For colloidal particles such emulsions, liposomes, micro-polymers, and nanoparticles, SLNs are excellent carriers. Solid lipids, surfactants, and active chemicals or medications make up the three primary components of SLNs.[11] Surfactants serve as a barrier between the particles and the lipid matrix outside of them. Triglycerides, mono- and diglycerides, free fatty acids, and other fatty acid esters that function as binders of active ingredients or medications in the lipid matrix are examples of solid lipids that can be utilized.

Surfactants, a thick lipid matrix at physiological temperatures, and occasionally other cosurfactants (such solvents) make up SLNs. Numerous techniques, including solvent emulsification/evaporation, cold and hot homogenization, high-pressure and high-shear homogenization, and ultrasound procedures, can be used to create SLNs. In order for the final combination to create a clear and thermodynamically stable microemulsion, the lipid mixture employed with surfactants and other ingredients must be optimized during the synthesis or manufacture of SLNs. However, SLN functionality might be impacted by preparation conditions and temperature. The stability of the active ingredients contained in SLNs may potentially be lowered by the application of high heat. Furthermore, the development of unstable lipid crystals and an impact on the entrapment efficiency might result from the use of high temperatures during the SLN preparation process and quick cooling during solidification.[12]

Particle size, release behaviour, stability during storage, and micronutrient loading can all be impacted by the choice of suitable lipids and surfactants. Glyceryl monostearate, tripalmitin, stearic acid, cetyl alcohol, Compritol 888, tristearin, and other biocompatible lipids are utilized in solid form at both body temperature and room temperature. In order for the hydrophilic groups that make up the surfactant's head and the lipophilic groups that constitute its tail to have an appropriate hydrophilic-lipophilic balance (HLB), surfactants that operate as emulsifiers must be able to lower the surface tension between the two phases. As systems for delivering micronutrients, SLNs cover vitamins, minerals, bioactive ingredients, and other active substances to shield them from harm while they travel through the intestines for absorption. SLNs are typically added to food items as a way to fortify them with micronutrient components that the body needs.[13]

SLNs' Strengths and Weaknesses:

Lipid nanoparticles, or SLNs, are an emulsion system that was created as a substitute carrier system for earlier techniques such emulsions, liposomes, and polymer nanoparticles. Due of their many benefits over other encapsulation methods, SLNs are encapsulation and delivery technologies that have been extensively developed. The SLN delivery method has several benefits, including the capacity to regulate the release of active chemicals, boost their stability, mix hydrophilic and lipophilic components, steer clear of hazardous drug carriers, and avoid using organic solvents.[14]

It is also technically and financially possible to create SLNs on a massive scale. SL Ns are less expensive than polymer carriers, dependable, lipid biodegradable, easy to produce, inexpensive, and offer chemical diversity. They are also easier to get permission for. Numerous physicochemical traits connected to the physicochemical parameters of the lipid phase are responsible for this possibly advantageous effect. First, because the active chemical moves more slowly in the solid lipid matrix than in the liquid matrix, its rate of degradation can be slowed. Second, by preventing the build-up of active compounds on the surface of lipid particles, degradation processes of active compounds are avoided. because the active chemicals and carrier lipids in the nanoparticles are separated and controlled. Third, following integration into SLNs7, some free active chemicals that are challenging to ingest are more readily absorbed.[15]

The features of SLNs are significantly influenced by the physical properties of solid lipids. Because of the high viscosity of the diffuse phase, SLNs with huge diameters can be formed by using lipids with high melting temperatures. The polydispersity index, which shows that the particle size of SLNs is not uniform, can also rise when solid lipids with high melting temperatures are used. The properties of the SLNs are also influenced by the length of the fatty acid chains in lipids. Using long-chain solid lipids can lower the zeta potential, which subsequently results in a decline in the dispersion system's stability. A drop in zeta potential can lead to SLN particles adhering to each other more readily, a process known as agglomeration, which increases particle size. The limited number of components that can be bound, the appearance of component damage or leakage during storage due to changes in the crystallinity of solid lipids, the low loading capacity for some active compounds, and the requirement for water in sufficient quantities to dissolve SLNs are some of the weaknesses of SLNs that necessitate further research and development.[16]

Agglomeration or coalescence between dispersed SLNs, unpredictable polymer transition dynamics, the establishment of a predisposition towards unpredictable gelation processes, and low binding capacity due to the dense lipid crystal structure can all cause lipid particle growth in SLNs. In order to improve the microstructure of the subsequent generation of nanoparticles—often referred to as nanostructured lipid carriers (NLCs)—this shortcoming is then taken advantage of and developed by combining with other materials, such as liquid lipids.[17]

The Distinctions between NLCs and SLNs:

NLCs are an extension of SLNs, but they have disadvantages: the low diffusion rate necessitates a longer release time; the system's high-water content can lead to crystallisation, which reduces the solubility of bioactive compounds, causing them to be released abruptly or burst upon release. In order to improve the efficacy of increasing the loading of active compounds, prevent leakage in the lipid matrix, increase the loading of active components in the lipid matrix, and modulate the release of active compounds, formulation in the form of NLCs was carried out. By combining solid lipids with liquid lipids or oils, this development or change is accomplished.[18]

As seen in **Figure 2**, three models can be used to explain how active substances or medications are incorporated into SLNs and NLCs.

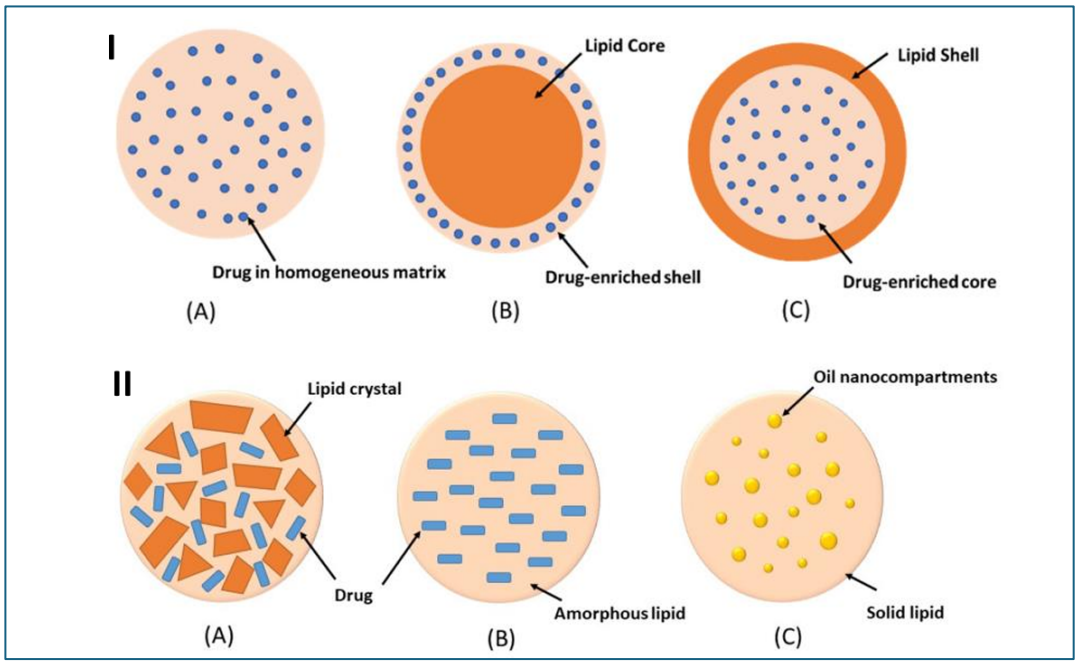

Figure 2: The active ingredients or drug incorporation models of NLCs (II) are imperfect crystal type (A), amorphous type (B), and multiple-oil-in-fat-in-water type (C); those of SLNs (I) are homogeneous matrix (A), drug-enriched shell (B), and drug-enriched core (C).[54]

Solid lipids, liquid lipids, surfactants, and cosurfactants are typically used in the formulation of NLCs. Stearic acid, cetyl alcohol, glyceryl monostearate, and glyceryl behenate are examples of common solid lipids. Oleic acid and isopropyl myristate are examples of liquid lipids that can be utilised. Polysorbate 80 and Poloxamer 188 are two common surfactants. The cosurfactants ethanol, propylene glycol, glycerine, and sucrose stearate are frequently utilised.

In order to create NLCs, a solid lipid matrix is formed at both room temperature and body temperature. However, the solid lipid matrix contains sections that are filled with liquid lipids. When creating stable NLCs, the ratio of solid lipids to oils can range from 70:30 to 99.9:0.1. The loading capacity of NLCs is greater than that of SLNs due to the larger gaps in the NLC structure caused by the different composition of NLCs that use liquid lipids. Nevertheless, compared to SLNs, the nanoparticles in NLCs have a less compact form. This results from liquid lipids in NLCs inhibiting crystallisation.[19]

As seen in **Figure 3**, a scanning electron microscope (SEM) and a transmission electron microscope (TEM) can be used to determine the morphological structure of the nanoparticles in SLNs and NLCs.

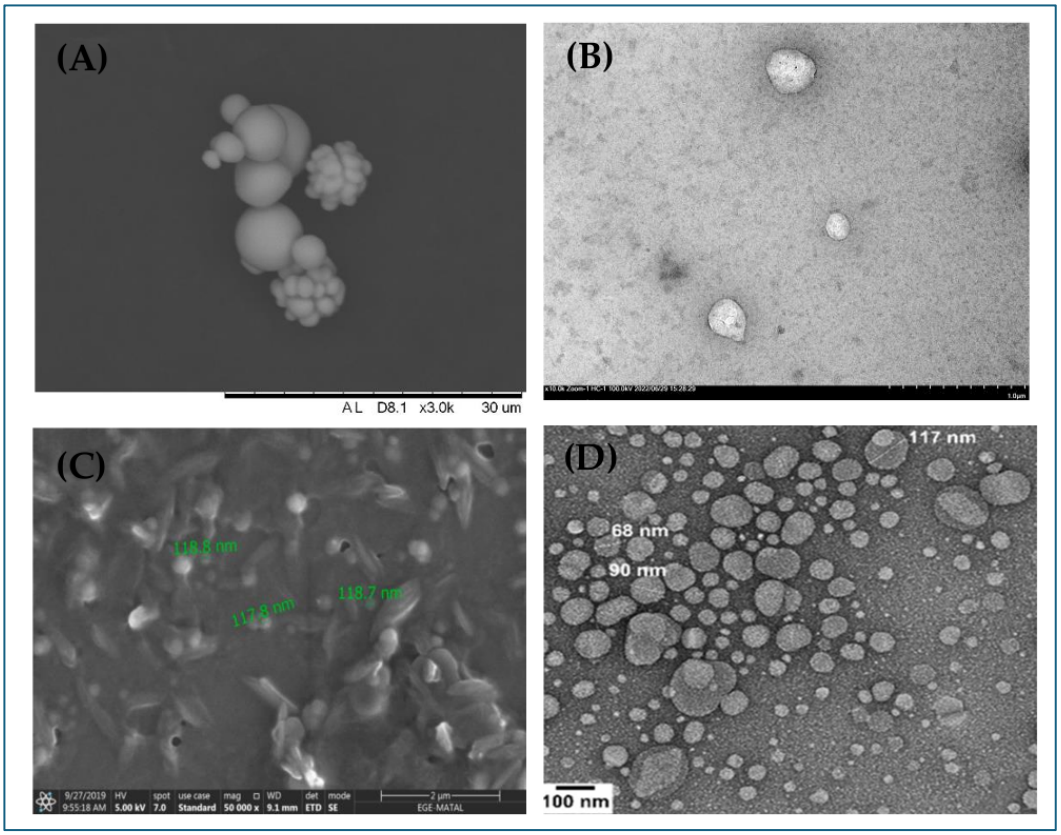

Figure 3: SLN characterisation using TEM (B) and SEM (A). The morphological analysis of NLCs using TEM (D) and SEM (C)[54]

Because of their capacity to regulate the precise release of medications or active compounds on the target, as well as the fact that their nanoparticle size results in the bioactive components being well-encapsulated, NLCs of active substances are commonly used in the pharmaceutical industry in drug delivery systems. Because it relates to the food safety requirements of the substances utilised, the development of suitable NLCs in the food industry has not been extensively pursued. Food-grade materials that fall under the GRAS (Generally Recognised as Safe) category are required to make NLCs. **Table 1** shows the distinctions between SLNs and NLCs.[20]

Table 1: SLNs and NLCs differ from one another

Qualities	**SLNs**	**NLCs**
Components	Solid lipids, active substances, cosurfactants (optional), and surfactants	Solid and liquid lipids, active substances, surfactants, and optional cosurfactants
Active substances	Compounds that are hydrophilic and hydrophobic	Ideal for substances that are hydrophobic
structure of crystals	Consistent and flawless	Lots of open space, irregularities, and imperfections
The capacity of the lipid matrix to attach to active substances	Minimal or slight	More than SLNs

Utilisation	Strengthening	Additional
Expense	Cheap	Expensive
Difficulty of fabrication	Simple	Difficult

Compared to SLNs, NLCs have the benefit of being able to hold more drug molecules or active chemicals while preventing particle coalescence and minimising harm to active compounds during storage. Nevertheless, some chemicals in NLC preparations are improperly formed, which is a drawback of these NLCs. NLCs are more successfully used for supplements than for food product fortification because of their strong capacity to bind to active ingredients, which makes them suited for use in medicine delivery in high doses. Because of their identical polarity features, the release mechanism of NLCs added to cream preparations can speed up the diffusion process through the stratum corneum. This is made possible by a matrix of NLCs that include a lot of lipids.[21]

In contrast to SLNs, where the crystal structure is more regular and there are typically fewer drug molecules in the lipid matrix, NLCs' lipid matrix preparation results in numerous crystal imperfections that provide plenty of room for the placement of drug molecules and active compound molecules.

Fabrication Techniques of SLN:

High-speed homogenisation and ultrasonication, high-pressure homogenisation at high or low temperatures, solvent evaporation, supercritical fluid extraction of emulsions (SFEE), multiple emulsions, and spray-drying are some of the techniques that can be used to synthesise or fabricate SLNs.[22]

Ultrasonication and High-Shear/High-Speed Homogenisation:

One widely used and rather simple SLN fabrication technique is high-shear homogenization/high-speed homogenisation with ultrasonication. When solid lipid nanodispersions were first created using the high-shear homogenisation technique, the resulting particle size was still micro-sized. Increased stirring speed improves the polydispersity index marginally but does not necessarily result in a significant change in particle size. However, by using cavitation energy at high frequencies, this technique can be paired with ultrasonication to assist reduce dispersion particles to nanoscale. The high-shear homogenisation method has a number of benefits, including increased product stability and medication or active chemical loading, the ability to be employed for large-scale production, and the absence of organic solvents.[23]

The hot homogenisation technique is another name for the high-shear homogenisation procedure, which is often performed at high temperatures. **Figure 4** shows a schematic illustration of the high-speed homogenisation and ultrasonication process.

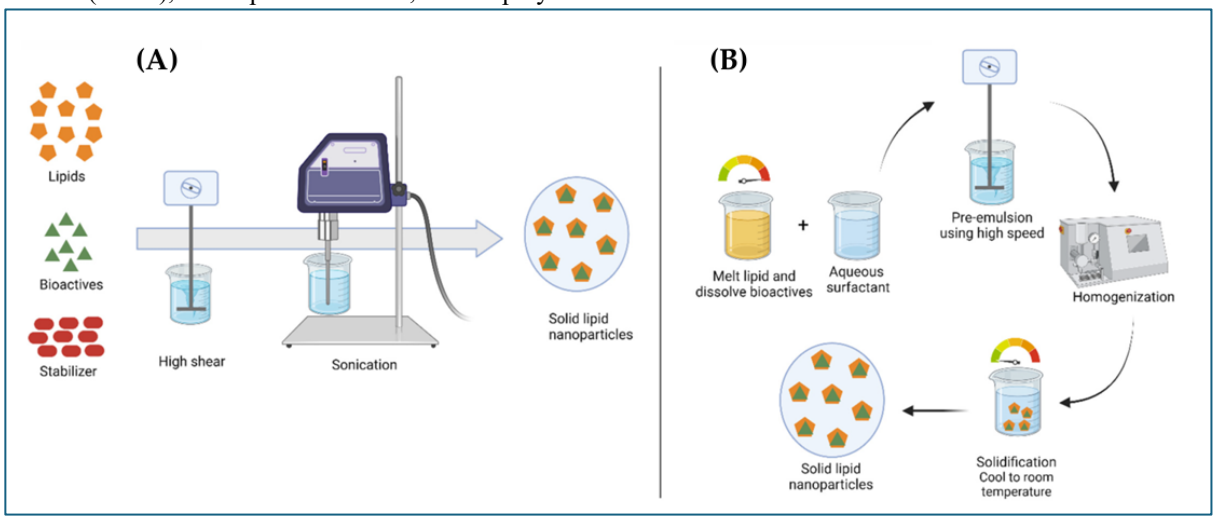

Figure 4: Diagrammatic representation of the ultrasonication method (A), and homogenization technique (B)[54]

SLNs can be successfully fabricated using the ultrasonication process and high-speed homogenisation. The first step often involves combining the components of the active chemicals that are added to the melted lipid. The liquid phase, which has been heated to the same temperature, is then added to the mixture and emulsified using a high-speed stirrer or ultrasonication. An ultrasonicated pre-emulsion can be produced by pouring the water phase over the lipid phase while vigorously swirling.[24]

To avoid recrystallisation during the fabrication process, the production temperature is maintained at least 5 °C above the lipid's melting point. The resultant SLNs are stored at 4 °C after the nanoemulsion (o/w) is filtered through a membrane to exclude contaminants transported during ultrasonication. The lyophilization method, which yields SLN powder through freeze-drying, can be used to improve formulation stability. At a later stage, cryoprotectants, such as trehalose or mannitol (5%), can be added to the SLNs to provide protection.

This method's fabrication of SLNs is comparatively easy and doesn't require high surfactant concentrations; the necessary equipment is readily available in the lab. Because of this, SLNs are frequently applied as coatings and delivery systems for a variety of medications and active substances. Nevertheless, there is a flaw in this process: occasionally, the resulting particle size distribution is not uniform, which affects its stability during storage. Additionally, because of the ultrasonication process, this approach may result in metal contamination.[25]

The production of SLNs using the ultrasonication technique was then refined to create a stable formulation. By lowering the surface tension on the nanoparticles, the combination of the ultrasonication technique with high-speed homogenisation at a high temperature can create smaller SLN particles. When paired with other techniques, such high-shear homogenisation, the ultrasonication approach for SLN synthesis yields more optimal nanoparticles. Therefore, it is possible to overcome the ultrasonication method's shortcoming.[26] Glyceryl behenate and tri-behenate (Compritol), glycerol monostearate (GMS), tris-tearin glyceride, and stearic acid are among the lipids utilised in the ultrasonication and high-speed homogenisation techniques. Lecithin, Tween, and Poloxamer 188 are surfactants that can be utilised together. The active substance to be encapsulated in melted lipid is dissolved before the mixture is heated to 10 °C above the lipid melting point in order to create SLNs using the ultrasonication process. Next, a liquid phase comprising preheated surfactants and cosurfactants is combined with the mixture of lipids and active chemicals. The mixture is heated to the same temperature and gently agitated until a pre-emulsion is created.[27]

After that, the pre-emulsion is emulsified using an ultrasonicator for three to five minutes at a stress efficiency of 35 to 40%. According to Woo et al., the homogenisation process using a homogeniser on a mixture of lipids and surfactants can be completed prior to the ultrasonication process. High-shear homogenisation or high-speed homogenisation are two possible homogenisation methods. A high-shear homogenisation treatment for pre-emulsion can be performed at 13,000 rpm for 4 minutes or with a high-speed homogeniser at 10,000 rpm.[28]

In order to crystallise the SLNs and create a nanoparticle suspension, the emulsion created by the ultrasonication procedure must be placed into cold water (1–4 °C) and agitated with a magnetic stirrer for three minutes. Centrifugation at 12,000 rpm for 60 minutes at 4 °C is used to gather the crystallised SLNs. After being lyophilised using a freeze-dryer, SLNs were refrigerated. Because it is simple to prepare and produces good results, high-shear homogenisation in conjunction with ultrasonication is the recommended approach and has been used extensively. **Table 2** shows several applications of high-shear homogenisation techniques and ultrasonication in the production of SLNs.[29]

Table 2. SLNs of different active chemicals are made using a variety of high-shear homogenisation techniques and ultrasonication.

Approach/Treatment	Materials	Features of the Product	References
Ultrasonography	Stearic acid is a lipid. Tween 80 is a surfactant; cosurfactant: NaDC Ciprofloxacin is the active ingredient	SLNs have a particle size of roughly 163–369 nm with an EE of 51.25–90.08%, depending on the surfactant and lipid makeup.	[30]
Ultrasonication	Stearic acid is a lipid; enrofloxacin is an active ingredient.	Formulated Solid Lipid Nanoparticle has a diameter of 217.3 nm and an entrapment efficiency (EE) of 70.56%.	[31]
Ultrasonication and hot homogenisation	Stearic acid is a lipid; Tween 60 is a surfactant. Salicylic	SLNs have particle sizes between 194 and 255 nm, and their EE values fall between 49 and 69%.	[32]

	acid is the active component.		
Ultrasonication and hot homogenisation	Lipid: monolaurin-rich fat and stearic acid; Tween 80 is a surfactant. Ferrous sulphate is the active ingredient.	SLNs have Z-averages between 278.7 and 540.4 nm, polydispersity indices between 0.88 and 1.24, and EE values between 99.7 and 99.9%.	[30]
Ultrasonication and high-shear homogenisation	Stearic acid is a lipid; surfactant Imatinib mesylate is the active ingredient in quillaja saponin.	SLNs range in size from 143.5 to 641.9 nm, with an EE of 41–66.2%, a polydispersity index (PI) of 0.127–0.237, and a zeta potential (ZP) of −2.43–0.95 mV.	[31]
Ultrasonication and high-shear homogenisation	Stearic acid is a lipid; surfactant Voriconazole is the active ingredient in Tween80.	SLNs have a ZP of −15 mV to −11 mV with a particle size range of 286.6 to 313.1 nm.	[32]
High-speed ultrasonication and homogenisation	Stearic acid is a lipid, and surfactant Candesartan clexetil (CDC) is the active ingredient in Poloxamer 188.	ZP is around −21.3 mV, and the ideal SLN particle size is 197.9 nm.	[30]
High-speed ultrasonication and homogenisation	Lipids: Apifil®, glycerol monostearate, and stearic acid; surfactants: The active components of Tego Care and Planta Care are: Ceramide	Planta Care 1% had a polydispersity index (PI) of 0.263, a particle diameter of 113.5 nm, and a ceramide content of 92.26% after two months of storage. Stable SLN ceramide has a loading capacity of 4% with Apifil® capacity of 4%.	[31]

Homogenisation at High Pressure:

Among the techniques that have been developed, high-pressure homogenisation (HPH) is one of the most widely used. Industry can employ this technique to produce SLNs on a wide scale. This procedure uses a pressure range of 100 to 2000 bar, with up to 40% of the formula being fat. The HPH method can be used in two ways to fabricate SLNs: hot procedures and cold processes. The temperature settings for the hot homogenization procedure are set at 5–10 °C above the fat's melting point. Using an Ultra-Turrax mixer, the active chemicals or micronutrient components are dissolved in the melted lipid and disseminated in the aqueous surfactant phase to create a pre-emulsion. When heat is used, the viscosity decreases because the temperature rises, leading to smaller and more consistent particle sizes.[33]

The final result of nanoparticles in this technique is influenced by the quality of the pre-emulsion. Therefore, in order to prevent the active components from degrading, temperature and pressure must be controlled. The micronutrient components or active compounds are dissolved in melted lipids and quickly chilled using dry ice or liquid nitrogen in the cold homogenisation process. Ball milling is used to crush the cooled fat into microparticles (50–100 μm) that can be distributed in the cold surfactant phase to create pre-suspensions. To create a dispersion system, the pre-suspension is homogenised in a cold, high-pressure reactor. Until nanoparticles are created, the HPH process is repeated. The issue with the hot homogenisation approach has been resolved by extending the cold homogenisation technique, particularly to avoid damaging the active chemicals by using high temperatures.[34]

Evaporation of Solvents:

By adding fat that has been combined with the o/w emulsion system, this technique of SLN production uses emulsification. Next, a solution of water and a non-polar organic solvent (cyclohexane) is used to dissolve the lipophilic components. Fat microparticles are produced by evaporating the organic solvent under mechanical stirring or pressure-reducing treatment. Nanoparticles

are created by precipitating the fat microparticles once again. Sjostrom used an emulsifier, lecithin/sodium glycocholate, to create cholesterol acetate nanoparticles with diameters ranging from 25 to 100 nm. Westesen and Siekmann have demonstrated these findings by creating phospholipid-stabilized solid lipid nanoparticles and successfully forming lipid o/w emulsions.[35]
Both the concentration of fat used in the recipe and the combination of fat with surfactants or emulsifiers have a significant impact on the SLNs produced by this approach. Because the production process is conducted at low temperatures, this technology can be applied to active components with thermosensitive qualities. It can also be utilised to combine hydrophilic components with o/w/o emulsions. Finding non-toxic solvents is crucial because this method's disadvantage is that using organic solvents might be hazardous.[36]

Alternative Techniques:
The double-emulsion method, spray-drying technique, and supercritical fluid technique are further fabrication techniques that have been developed. One benefit of adopting the supercritical fluid methodology for SLN production is that it doesn't require solvents, making the process quicker and safer than alternative solvent-based processes. Supercritical carbon dioxide solutions (RESS) procedures allow for the rapid production of SLNs, one of several advances in nanoparticle synthesis. The best SLNs can be produced by using carbon dioxide (99.99%) as a solvent substitute in this process.

The evaporation of the emulsification of the solvent used to insert the hydrophilic chemical into the SLNs is the basis for the double-emulsion method of SLN preparation. It is possible to create the double emulsion w/o/w in two steps. Initially, a mixture of melted lipid and surfactant/cosurfactant is combined with a solution containing the active component at a temperature just above the lipid's melting point to create a homogenous w/o microemulsion.[37]
monoglycerides. The resulting w/o microemulsion is then combined with a solution of water, surfactant, and cosurfactant to create a w/o/w double emulsion. Tween 80 is typically used to create w/o/w emulsions. **Figure 5** shows how SLNs are prepared using the double-emulsion approach. To avoid partitioning into the aqueous phase during the solvent evaporation process, hydrophilic chemicals added to SLNs must be shielded or stabilised using a stabiliser. SLNs are then centrifuged at a low temperature (± 4 °C) for 30 minutes at 12,000× g. As an alternative to the lyophilization process, which transforms SLNs from liquid to solid (powder) form, spray-dryer techniques are used. For spray drying, Freitas and Müller advise using lipids with a melting point greater than 70 °C. 1% SLNs in an aqueous trehalose solution or 20% trehalose in an ethanol–water mixture (10/90 v/v) produced the greatest results. Although spray-drying is less expensive than lyophilization, the high temperatures, shear strength, and partial melting of the particles lead to particle agglomeration.[38]

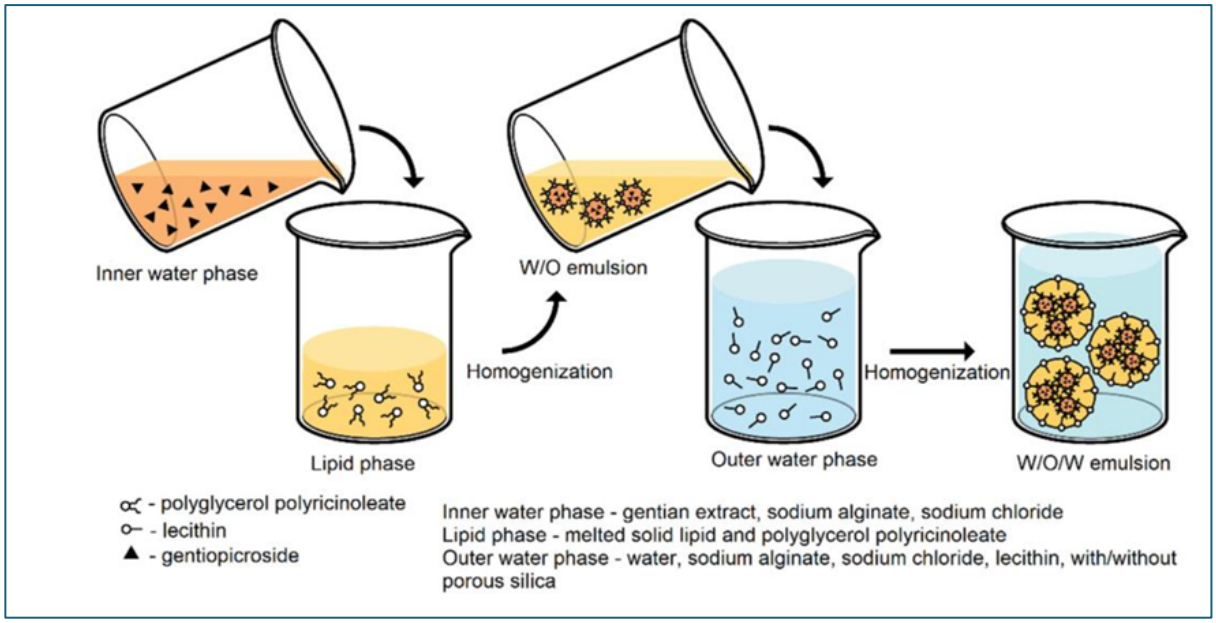

Figure 5: SLN preparation using the double-emulsion technique [54]

As a result, trehalose must be added or lipids with a high melting point must be used. The nature of the active substances employed, the availability of tools and materials, and the associated prices must all be adjusted because each approach for creating SLNs has pros and cons. **Table 3** provides an overall evaluation of the benefits and drawbacks of various SLN production techniques.

Table 3. A comparison of the benefits and drawbacks of several SLN fabrication techniques

Approach	Benefits	Drawbacks	References

Homogenisation at High Pressure	Low cost, capable of large-scale or small-scale production (laboratory)	It can harm biomolecules and necessitates a lot of energy and pressure on a huge scale.	[39]
High-Speed Homogenisation and Ultrasonication	decreases surface tension effectively, is simple, sustainable, and commercially viable.	The tool's high rotational speed increases the risk of metal contamination, and large-scale production necessitates a significant financial outlay.	[40]
High-shear uniformity	The procedure is simple and doesn't require the use of solvents.	The particles are less homogeneous and have a comparatively big size.	[41]
Method of Solvent Evaporation	The generated SLNs can be commercialised since they are uniform and stable.	uses a lot of energy, biomolecule damage is possible, and hazardous solvents could be present.	[42]
Supercritical Fluid Method	doesn't need a solvent; powdery particles are produced.	The price is exorbitant.	[43]
The Double-Emulsion Approach	Able to include hydrophilic elements	At the end of the manufacturing process, large particles	[44]
Method of Spray-Drying	less expensive than lyophilization	Particle aggregation potential as a result of high temperatures	[45]

Applications of SLN in Different Domains:

Topical, pulmonary, cutaneous, and parenteral drug delivery are just a few of the many uses for solid lipid nanoparticles (SLNs). These SLN application solutions have also been created to improve treatment efficacy and reduce the harmful side effects of extremely powerful medications. Additionally, they have demonstrated strong potential in the food, cosmetics, and gene transfer industries.[46]

Role of SLN as Biologics:

In spite of obstacles like limited drug loading and scale-up challenges, solid lipid nanoparticles (SLNs) are a promising platform for enhancing the efficacy and safety of biologic therapies because they function as biocompatible and biodegradable carriers that protect sensitive therapeutic molecules like proteins, peptides, and nucleic acids from enzymatic degradation, improve their solubility and bioavailability, and enable controlled and targeted delivery to specific tissues.[47]

SLNs in Cosmetics and Different Medical Specialities:

In the medical field, SLNs are typically used for oral drug administration to boost the bioavailability of medications that initially have low bioavailability because of their limited water solubility. Furthermore, the use of SLNs can enhance the body's release of pharmaceuticals, prolong their residence duration and lymphatic absorption, and possibly boost the bioavailability of medications that are poorly soluble in water, particularly lipophilic medications.

Because the SLN formulation is comparable to the structure of the skin, SLNs can also be used in the dermatological and cosmetic industries. When administered topically, SLNs do not exhibit any harmful effects or interference. SLNs are typically used in this industry for sunscreen, acne treatment, and anti-aging skin care. In addition to increasing skin moisture content and shielding delicate molecules from chemical deterioration, SLNs can penetrate active substances in the skin, block UV rays, and hydrate the skin.

When topical treatments are applied, SLNs can form an occlusive layer on the skin's surface, which is influenced by their size, which is less than 400 nm. This is one of the processes for releasing SLNs in the field of drug delivery. When SLNs are applied to the skin's surface, the water in the preparation evaporates and leaves behind an adhesive layer that covers the skin. This reduces trans epidermal water loss, which may allow the medication to enter the skin's deepest layers, decreasing corneocyte density and increasing the gap between corneocytes.[48]

SLNs in a Range of Food Products and as a Drug or Active Compound Delivery System:

Another application of SLNs is in the food sector, because they can be excellent potential carriers for sensitive compounds in the food industry to improve food quality and nutrition. SLNs have also been applied for the fortification with nutrients that are easily

damaged by environmental influences or nutrients that have an unfavourable taste and aftertaste that need to be protected or encapsulated in the form of SLNs. In addition to carrying nutrients, SLNs have also been widely used as a drug delivery agent or as a carrier for other active compounds that are beneficial to health, such as medicinal compounds and antioxidants SLNs have been widely applied for delivery of drugs for neurological diseases and cancer, and for preventing antibiotic resistance, because this carrier can contain many antimicrobial drugs, increase drug absorption, and reduce bacterial efflux. SLNs are a good alternative in terms of functionality and biocompatibility, because they can directly reach the site of infection, increase drug bioavailability, and reduce toxicity or side effects.[49]

SLNs are lipid-based drug delivery systems that have distinctive properties, such as large surface area, high drug loading, and protection of the drug or active compounds from the environment. In addition, SLNs can increase the absorption efficiency or bioavailability of drug delivery systems. SLNs can have two advantages in drug delivery systems, namely in the effective protection of drugs and active compounds during the formulation process due to increased encapsulation efficiency; the effect of this system is preferred because of the increased release of drugs and active compounds due to the homogenization process in the production of SLNs.[47]

The use of SLNs as an active compound delivery system is included in the solid fat material model, and the enriched nuclei are the desired active compounds. In drug delivery systems, molecular dispersion occurs in a solid lipid matrix when the particles are formed by surfactants or cosurfactants using cold homogenization techniques. Drug delivery with SLNs has a very strong interaction, especially in its lipid components. In a drug delivery system with SLNs, the solid lipid core is formed after the lipid recrystallization temperature is reached, and the concentration of the SLN output will melt due to dispersion when the temperature decreases. The essence of the drug delivery system with SLNs is the cooling of the nano- or microemulsion, which results in supersaturation of the drug delivery dissolved by the melting lipid approaching its saturation solubility, and precipitation will occur before lipid recrystallization. The extra cooling eventually leads to recrystallization of the lipid that surrounds the drug delivery system as a thin, membrane like layer.[46]

The primary goals of developing the SLN system for different active chemicals are to improve the loading capacity, stability, and solubility. The use or application of SLNs in relation to the absorption and release of their active chemical core constituents has been the subject of numerous investigations. According to Pople and Singh, vitamin A-containing SLNs have better release penetration than traditional preparations; specifically, the concentration is doubled when compared to traditional gels, and they also have superior stability when applied to drug use. Another study by Kim et al. shown that cyclosporin produced as SLNs had strong penetration and enhanced release that was twice as high as that of traditional preparations in vitro.

SLNs and other lipid nanoparticles have also been widely employed in mRNA delivery, particularly in mRNA vaccines that have undergone clinical testing and been shown to be both safe and efficacious. The distribution of the COVID-19 vaccine, which was previously a pandemic in several nations, has also benefited from this breakthrough. The constituent lipid matrix, the surfactant employed, and the encapsulated mRNA or active ingredient were the first steps in the development of several lipid nanoparticle formulae for mRNA vaccines. Francis and associates. used SLNs to deliver non-viral DNA vaccines to DNA vaccine candidates that use monophosphorylate lipid A to encode urease alpha (UreA). SLNs were discovered to be taken up by cells in the endosome compartment in less than three hours. In THP-1 cells, SLNs were able to increase the expression of the pro-inflammatory cytokine TNF-α. Using cationic lipids, Lou et al. encapsulated mRNA vaccine encoding the rabies virus glycoprotein (RVG) in the form of lipid nanoparticles. They discovered that at a dose of 1.5 μg, lipid nanoparticles elicited strong humoral and cellular immune responses and have the potential to become an effective form of mRNA vaccine delivery. Table 4 shows how solid lipid nanoparticles are used in different industries.[50]

Table 4: Uses of Solid Lipid Nanoparticles in different industries

Product Type or Field	Conditions of Fabrication	Features of the Product	References

Skincare products for excessive pigmentation	The active component N-acetyl-d-glucosamine (NAG)High-shear homogenisation is the method. Phosphatidylcholine, cetyl palmitate, Peg-25, and hydrogenated castor oil make up the lipid phase. Phase of water: cleaned water Resveratrol, vitamin E, and epigallocatechin gallate (EGCG) are the active components.	NAG has the ability to stabilise emulsions. The process of NAG penetration and release into the skin, which can aid in skin regeneration, can be impacted by variations in concentration.	[51]
Skincare	High-pressure homogenisation is the method. Cetyl palmitate, phospholipon 80, and compritol are examples of solid lipids. Sesame oil is a liquid lipid. Tween 80 is a surfactant.	EGCG does not exhibit the same effects as resveratrol and vitamin E, which protect against UV-induced components to avoid deterioration.	[52]
Photodynamic treatment	DH-I-180-3 is the active component. Solvent evaporation and heat homogenisation are the methods used Lipids: Capmul1 MCM C8 and stearic acid Poloxamer 188 is the surfactant. Lecithin is a cosurfactant.	DH-I-180-3 is added to SLNs to improve photocytotoxicity and targeting effectiveness.	[53]
Drug administration	Oxyresveratrol (OXY) is the active component. High-shear homogenisation is the method. Phase of lipid: C888 Water phase: soy lecithin and Tween 80	increases OXY's bioavailability by up to 125% when compared to OXY that isn't SLN-coated.	[54]
Drug administration	Hydrochlorothiazide (HCT) is the active component. Method: Ultrasonication and high-shear homogenisation Precirol®ATO5 is a surfactant that has Tween 80 and Pluronic F68 are two distinct surfactants.	Tween 80 does not provide continuous release; instead, it causes full drug release at 150 minutes. Using pluronic F68 guarantees a 1.8-fold increase over simple drug suspensions and a sustained release of over 75% at the conclusion of the test.	[55]
Drug administration	Clarithromycin is the active component. High-speed homogenisation is the method. Stearic acid, tripalmitin, and glyceryl behenate are in the lipid phase. Tween 80 is a surfactant.	The Clarithromycin-SLNs demonstrated prolonged release for up to 48 hours, and the optimal particle size was 318.0 nm with a polydispersity index of 0.228–0.472.	[50]
Drug administration	Gliclazide is the active component. High-shear homogenisation is the method. Stearic acid is the lipid phase. Tween 80 and PEG 400 are surfactants.	spherical particles with an optimal size of 745.8 nm, an absorption efficiency of 75.29%, and a polydispersity index of 0.776.	[52]

Conclusion:

In the realm of biologics, solid lipid nanoparticles (SLNs) have become a game-changing platform that bridges the gap between conventional drug delivery methods and the intricate requirements of contemporary therapeutic compounds. Sensitive biologics including proteins, peptides, and nucleic acids are protected from enzymatic destruction and early clearance by their special architecture, which consists of a solid lipid core stabilized by surfactants. For biologics, which frequently have poor pharmacokinetic characteristics, this structural advantage translates into increased stability,

higher bioavailability, and the potential for regulated release. SLNs are suitable for oral, parenteral, and even topical administration routes because they combine biocompatibility, biodegradability, and adaptability, in contrast to conventional carriers.

Decades of research have led us to the conclusion that SLNs are active facilitators of biologic therapy rather than just passive carriers. Through surface alterations like PEGylation or ligand attachment, they enable site-specific targeting, which lowers systemic toxicity and improves therapeutic accuracy. This is especially important in fields like immunology, neurology, and oncology, where biologics need to enter particular cellular compartments or tissues in order to work. Additionally, SLNs provide the possibility of sustained release, which lowers the frequency of doses and enhances patient compliance—a crucial but frequently disregarded component of therapeutic success. Additionally, its lipid-based makeup guarantees safety by reducing the dangers of polymeric or synthetic carriers.

However, there are still difficulties. Drug loading capacity constraints, lipid polymorphism transitions that might change release patterns, and challenges with large-scale production are among issues that SLNs must deal with. These obstacles highlight the necessity of ongoing innovation in lipid chemistry, nanotechnology, and formulation science. However, the direction of SLN research indicates that these challenges can be overcome. The scalability and reproducibility of SLN manufacturing are continuously being improved by developments in high-pressure homogenization, microemulsion methods, and new lipid excipients. Additionally, the incorporation of SLNs with state-of-the-art biologics including gene-editing tools, RNA therapies, and monoclonal antibodies suggests that SLNs will eventually form the foundation of next-generation biologic delivery systems.

To sum up, SLNs represent the fusion of biotechnology and nanotechnology, providing a flexible, secure, and efficient way to administer biologics. They signify a paradigm shift in our understanding of drug delivery, from straightforward transport vehicles to sophisticated systems that can safeguard, target, and release intricate therapeutic compounds. SLNs have the potential to turn biologic medicines into workable, patient-friendly solutions, despite ongoing difficulties. SLNs are positioned to be crucial to the advancement of precision medicines, customized medicine, and international healthcare innovation as long as research keeps improving their design and overcoming present constraints. SLNs are among the most promising instruments in the toolbox of contemporary medicine because of their path from laboratory curiosity to clinical reality, which highlights the significant impact that nanotechnology can have on the biologics landscape.

References:

1. Babazadeh, A.; Ghanbarzadeh, B.; Hamishehkar, H. Formulation of Food Grade Nanostructured Lipid Carrier (NLC) for Potential Applications in Medicinal-Functional Foods. J. Drug Deliv. Sci. Technol. 2017, 39, 50–58.
2. Nguyen, V.H.; Thuy, V.N.; Van, T.V.; Dao, A.H.; Lee, B.-J. Nanostructured Lipid Carriers and Their Potential Applications for Versatile Drug Delivery via Oral Administration. OpenNano 2022, 8, 100064.
3. Gaba, B.; Fazil, M.; Ali, A.; Baboota, S.; Sahni, J.K.; Ali, J. Nanostructured Lipid (NLCs) Carriers as a Bioavailability Enhancement Tool for Oral Administration. Drug Deliv. 2015, 22, 691–700.
4. Esposito, E.; Sguizzato, M.; Drechsler, M.; Mariani, P.; Carducci, F.; Nastruzzi, C.; Valacchi, G.; Cortesi, R. Lipid Nanostructures for Antioxidant Delivery: A Comparative Preformulation Study. Beilstein J. Nanotechnol. 2019, 10, 1789–1801.
5. Souto, E.B.; Doktorovova, S.; Zielinska, A.; Silva, A.M. Key Production Parameters for the Development of Solid Lipid Nanoparti cles by High Shear Homogenization. Pharm. Dev. Technol. 2019, 24, 1181–1185.
6. Mahajan, A.; Kaur, S. Design, Formulation, and Characterization of Stearic Acid-Based Solid Lipid Nanoparticles of Candesartan Cilexetil to Augment Its Oral Bioavailability. Asian J. Pharm. Clin. Res. 2018, 11, 344–350.
7. Subramanian, P. Lipid-Based Nanocarrier System for the Effective Delivery of Nutraceuticals. Molecules 2021, 26, 5510.
8. Sastri, K.T.; Radha, G.V.; Pidikiti, S.; Vajjhala, P. Solid Lipid Nanoparticles: Preparation Techniques, Their Characterization, and an Update on Recent Studies. J. Appl. Pharm. Sci. 2020, 10, 126–141.
9. Ganesan, P.; Narayanasamy, D. Lipid Nanoparticles: Different Preparation Techniques, Characterization, Hurdles, and Strategies for the Production of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Oral Drug Delivery. Sustain. Chem. Pharm. 2017, 6, 37–56.
10. Yukuyama, M.N.; Ghisleni, D.D.M.; Pinto, T.J.A.; Bou-Chacra, N.A. Nanoemulsion: Process Selection and Application in Cosmetics–A Review. Int. J. Cosmet. Sci. 2016, 38, 13–24.
11. Dolatabadi, J.E.N.; Valizadeh, H.; Hamishehkar, H. Solid Lipid Nanoparticles as Efficient Drug and Gene Delivery Systems: Recent Breakthroughs. Adv. Pharm. Bull. 2015, 5, 151–159.
12. Sinha, V.R.; Srivastava, S.; Goel, H.; Jindal, V. Solid Lipid Nanoparticles (SLN'S)-Trends and Implications in Drug Targeting. Int. J. Adv. Pharm. Sci. 2010, 1, 212–238.
13. Khairnar, S.V.; Pagare, P.; Thakre, A.; Nambiar, A.R.; Junnuthula, V.; Abraham, M.C.; Kolimi, P.; Nyavanandi, D.; Dyawanapelly, S. Review on the Scale-Up Methods for the Preparation of Solid Lipid Nanoparticles. Pharmaceutics 2022, 14, 1886.

14. Alarifi, S.; Massadeh, S.; Al-Agamy, M.; Al Aamery, M.; Al Bekairy, A.; Yassin, A.E. Enhancement of Ciprofloxacin Activity by Incorporating It in Solid Lipid Nanoparticles. Trop. J. Pharm. Res. 2020, 19, 909–918.
15. Xie, S.; Zhu, L.; Dong, Z.; Wang, X.; Wang, Y.; Li, X.; Zhou, W.Z. Preparation, Characterization and Pharmacokinetics of Enrofloxacin-Loaded Solid Lipid Nanoparticles: Influences of Fatty Acids. Colloids Surf. B Biointerfaces 2011, 83, 382–387.
16. Woo, J.O.; Misran, M.; Lee, P.F.; Tan, L.P. Development of a Controlled Release of Salicylic Acid Loaded Stearic Acid-Oleic Acid Nanoparticles in Cream for Topical Delivery. Sci. World J. 2014, 2014, 205703.
17. Karthik, S.; Raghavan, C.V.; Marslin, G.; Rahman, H.; Selvaraj, D.; Balakumar, K.; Franklin, G. Quillaja Saponin: A Prospective Emulsifier for the Preparation of Solid Lipid Nanoparticles. Colloids Surf. B Biointerfaces 2016, 147, 274–280.
18. Kelidari, H.R.; Babaei, R.; Nabili, M.; Shokohi, T.; Saeedi, M.; Gholami, S.; Moazeni, M.; Nokhodchi, A. Improved Delivery of Voriconazole to Aspergillus Fumigatus through Solid Lipid Nanoparticles as an Effective Carrier. Colloids Surf. A Physicochem. Eng. Asp. 2018, 558, 338–342.
19. Mehnert, W.; Mäder, K. Solid Lipid Nanoparticles: Production, Characterization and Applications. Adv. Drug Deliv. Rev. 2001, 47, 165–196.
20. Mesa, J.; Hinestroza-Córdoba, L.I.; Barrera, C.; Seguí, L.; Betoret, E.; Betoret, N. High Homogenization Pressures to Improve Food Quality, Functionality and Sustainability. Molecules 2020, 25, 3305.
21. Rahmi, D. LemakPadat Nanopartikel; Sintesis Dan Aplikasi. J. Kim. dan Kemasan 2010, 32, 27.
22. Garg, U.; Jain, K. Dermal and Transdermal Drug Delivery through Vesicles and Particles: Preparation and Applications. Adv. Pharm. Bull. 2022, 12, 45–57.
23. Sjöström, B.; Bergenståhl, B. Preparation of Submicron Drug Particles in Lecithin-Stabilized o/w Emulsions I. Model Studies of the Precipitation of Cholesteryl Acetate. Int. J. Pharm. 1992, 88, 53–62.
24. Westesen, K.; Siekmann, B. Investigation of the Gel Formation of Phospholipid-Stabilized Solid Lipid Nanoparticles. Int. J. Pharm. 1997, 151, 35–45.
25. Xu,L.; Wang, X.; Liu, Y.; Yang, G.; Falconer, R.J.; Zhao, C.-X. Lipid Nanoparticles for Drug Delivery. Adv. NanoBiomed Res. 2022, 2, 2100109.
26. Pooja, D.; Tunki, L.; Kulhari, H.; Reddy, B.B.; Sistla, R. Optimization of Solid Lipid Nanoparticles Prepared by a Single Emulsification-Solvent Evaporation Method. Data Br. 2016, 6, 15–19.
27. Chattopadhyay, P.; Shekunov, B.Y.; Yim, D.; Cipolla, D.; Boyd, B.; Farr, S. Production of Solid Lipid Nanoparticle Suspensions Using Supercritical Fluid Extraction of Emulsions (SFEE) for Pulmonary Delivery Using the AERx System. Adv. Drug Deliv. Rev. 2007, 59, 444–453.
28. Campardelli, R.; Cherain, M.; Perfetti, C.; Iorio, C.; Scognamiglio, M.; Reverchon, E.; Porta, G.D. Lipid Nanoparticles Production by Supercritical Fluid Assisted Emulsion–Diffusion. J. Supercrit. Fluids 2013, 82, 34–40.
29. Iqbal, M.; Zafar, N.; Fessi, H.; Elaissari, A. Double Emulsion Solvent Evaporation Techniques Used for Drug Encapsulation. Int. J. Pharm. 2015, 496, 173–190.
30. Nabi-Meibodi, M.; Navidi, B.; Navidi, N.; Vatanara, A.; Reza Rouini, M.; Ramezani, V. Optimized Double Emulsion-Solvent Evaporation Process for Production of Solid Lipid Nanoparticles Containing Baclofene as a Lipid Insoluble Drug. J. Drug Deliv. Sci. Technol. 2013, 23, 225–230.
31. Mudri´c, J.; Šavikin, K.; Đeki´c, L.; Pavlovi´c, S.; Kur´cubi´c, I.; Ibri´c, S.; Đuriš, J. Development of Lipid-Based Gastroretentive Delivery System for Gentian Extract by Double Emulsion–Melt Dispersion Technique. Pharmaceutics 2021, 13, 2095. 105. Freitas, C.; Müller, R.H. Spray-Drying of Solid Lipid Nanoparticles (SLNTM). Eur. J. Pharm. Biopharm. 1998, 46, 145–151.
32. Ristroph, K.D.; Feng, J.; McManus, S.A.; Zhang, Y.; Gong, K.; Ramachandruni, H.; White, C.E.; Prud'homme, R.K. Spray Drying OZ439 Nanoparticles to Form Stable, Water-Dispersible Powders for Oral Malaria Therapy. J. Transl. Med. 2019, 17, 97.
33. James, O.; Oloo, F.; Ng'etich, J.; Kivunzya, M.; Omwoyo, W.; Gathirwa, J. Comparison of Freeze and Spray Drying to Obtain Primaquine-Loaded Solid Lipid Nanoparticles. J. Nanotoxicol. Nanomed. 2017, 2, 31–50.
34. Silva, A.C.; Kumar, A.; Wild, W.; Ferreira, D.; Santos, D.; Forbes, B. Long-Term Stability, Biocompatibility and Oral Delivery Potential of Risperidone-Loaded Solid Lipid Nanoparticles. Int. J. Pharm. 2012, 436, 798–805.
35. Jacob, S.; Nair, A.B.; Shah, J.; Gupta, S.; Boddu, S.H.S.; Sreeharsha, N.; Joseph, A.; Shinu, P.; Morsy, M.A. Lipid Nanoparticles as a Promising Drug Delivery Carrier for Topical Ocular Therapy–An Overview on Recent Advances. Pharmaceutics 2022, 14, 533.
36. Nugraha, M.W.; Iswandana, R.; Jufri, M. Preparation, Characterization, and Formulation of Solid Lipid Nanoparticles Lotion from Mulberry Roots (Morus Alba L.). Int. J. Appl. Pharm. 2020, 12, 182–186.
37. Lai, F.; Wissing, S.A.; Müller, R.H.; Fadda, A.M. Artemisia arborescens L. Essential Oil-Loaded Solid Lipid Nanoparticles for Potential Agricultural Application: Preparation and Characterization. AAPS PharmSciTech 2006, 7, 2.

38. Cirri, M.; Mennini, N.; Maestrelli, F.; Mura, P.; Ghelardini, C.; di Cesare Mannelli, L. Development and in Vivo Evaluation of an Innovative "Hydrochlorothiazide-in Cyclodextrins-in Solid Lipid Nanoparticles" Formulation with Sustained Release and Enhanced Oral Bioavailability for Potential Hypertension Treatment in Pediatrics. Int. J. Pharm. 2017, 521, 73–83.
39. Jain, A.; Sharma, G.; Thakur, K.; Raza, K.; Shivhare, U.S.; Ghoshal, G.; Katare, O.P. Beta-Carotene-Encapsulated Solid Lipid Nanoparticles (BC-SLNs) as Promising Vehicle for Cancer: An Investigative Assessment. AAPS PharmSciTech 2019, 20, 100.
40. Oehlke, K.; Behsnilian, D.; Mayer-Miebach, E.; Weidler, P.G.; Greiner, R. Edible Solid Lipid Nanoparticles (SLN) as Carrier System for Antioxidants of Different Lipophilicity. PLoS ONE 2017, 12, e0171662.
41. Mendoza-Muñoz, N.; Urbán-Morlán, Z.; Leyva-Gómez, G.; De La Luz Zambrano-Zaragoza, M.; Piñón-Segundo, E.; Quintanar Guerrero, D. Solid Lipid Nanoparticles: An Approach to Improve Oral Drug Delivery. J. Pharm. Pharm. Sci. 2021, 24, 509–532.
42. Lu, H.; Zhang, S.; Wang, J.; Chen, Q. A Review on Polymer and Lipid-Based Nanocarriers and Its Application to Nano Pharmaceutical and Food-Based Systems. Front. Nutr. 2021, 8, 783831.
43. Satapathy, M.K.; Yen, T.-L.; Jan, J.-S.; Tang, R.-D.; Wang, J.-Y.; Taliyan, R.; Yang, C.-H. Solid Lipid Nanoparticles (SLNs): An Advanced Drug Delivery System Targeting Brain through BBB. Pharmaceutics 2021, 13, 1183.
44. Adepu, S.; Ramakrishna, S. Controlled Drug Delivery Systems: Current Status and Future Directions. Molecules 2021, 26, 5905.
45. Ana, R.D.; Fonseca, J.; Karczewski, J.; Silva, A.M.; Zieli´nska, A.; Souto, E.B. Lipid-Based Nanoparticulate Systems for the Ocular Delivery of Bioactives with Anti-Inflammatory Properties. Int. J. Mol. Sci. 2022, 23, 12102.
46. Montoto, S.S.; Muraca, G.; Ruiz, M.E. Solid Lipid Nanoparticles for Drug Delivery: Pharmacological and Biopharmaceutical Aspects. Front. Mol. Biosci. 2020, 7, 587997.
47. Sakellari, G.I.; Zafeiri, I.; Batchelor, H.; Spyropoulos, F. Formulation Design, Production and Characterisation of Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) for the Encapsulation of a Model Hydrophobic Active. Food Hydrocoll. Health 2021, 1, 100024.
48. Molet-Rodríguez, A.; Martín-Belloso, O.; Salvia-Trujillo, L. Formation and Stabilization of W1/O/W2 Emulsions with Gelled Lipid Phases. Molecules 2021, 26, 312.
49. Campos,D.A.; Madureira, A.R.; Sarmento, B.; Pintado, M.M.; Gomes, A.M. Technological Stability of Solid Lipid Nanoparticles Loaded with Phenolic Compounds: Drying Process and Stability along Storage. J. Food Eng. 2017, 196, 1–10.
50. Sridhar, K.; Inbaraj, B.S.; Chen, B.-H. Recent Advances on Nanoparticle Based Strategies for Improving Carotenoid Stability and Biological Activity. Antioxidants 2021, 10, 713.
51. Tang, C.-H.; Chen, H.-L.; Dong, J.-R. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) as Food-Grade Nanovehicles for Hydrophobic Nutraceuticals or Bioactives. Appl. Sci. 2023, 13, 1726.
52. Ghasemiyeh, P.; Mohammadi-Samani, S. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers as Novel Drug Delivery Systems: Applications, Advantages and Disadvantages. Res. Pharm. Sci. 2018, 13, 288–303.
53. Shinde, P.B.; Gunvantrao, D.S.; Vivekanand, S.M. Lipid Based Nanoparticles: SLN/NLCs-Formulation Techniques, Its Evaluation and Applications. Int. J. Creat. Innov. Res. All Stud. 2019, 1, 20–31.
54. Subroto, E.; Andoyo, R.; Indiarto, R.; Solid Lipid Nanoparticles: Review of the Current Research on Encapsulation and Delivery Systems for Active and Antioxidant Compounds. Antioxidants. 2023, 12, 633, https://doi.org/10.3390/antiox12030633
55. UdDin, F.; Zeb, A.; Shah, K.U. Zia-ur-Rehman Development, in-Vitro and in-Vivo Evaluation of Ezetimibe-Loaded Solid Lipid Nanoparticles and Their Comparison with Marketed Product. J. Drug Deliv. Sci. Technol. 2019, 51, 583–590.