Journal of *Nanotheranostics*

MDPI

Review

Characteristics and Preparation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Marjorie de Carvalho Vieira Queiroz and Luís Alexandre Muehlmann *

Faculty of Ceilandia, University of Brasilia, Brasilia 72220-900, DF, Brazil; marjoriecvq94@gmail.com
* Correspondence: luisalex@unb.br

Abstract: Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have emerged as promising systems for delivering active ingredients. They are derived from physiological, biodegradable, and biocompatible lipids, offering benefits such as sustained release promotion and increased drug stability. These systems are apt for the efficient transport of therapeutic drugs to target tissues while also providing advantages such as facilitating large-scale industrial production, bioavailability, and protection against degradation. The preparation of these nanoparticles involves utilizing diverse types of lipids, surfactants, and solvents. Common lipid varieties encompass triglycerides, steroids, and fatty acids, selected based on the active ingredient for stabilization within the lipid matrix. Preparation methods can be categorized into high-energy and low-energy approaches. This study investigated the differences between the main methodologies used, comparing SLN and NLC systems, and scrutinizing their respective advantages, disadvantages, and applications.

Keywords: bioactive molecules; formulation techniques; lipid dispersion; nanostructures; nanotechnology

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Citation: Queiroz, M.d.C.V.; Muehlmann, L.A. Characteristics and Preparation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers. *J. Nanotheranostics* **2024**, *5*, 188–211. https://doi.org/10.3390/jnt5040012

Academic Editor: Dmitri Simberg

Received: 28 August 2024
Revised: 8 November 2024
Accepted: 18 November 2024
Published: 25 November 2024

1. Introduction

Nanotechnology holds significant potential for enhancing the performance and safety of formulations containing bioactive compounds, making it a valuable asset across multiple industrial sectors. Its applications are not limited to therapeutic purposes but can also extend to the food industry, for example, using nanostructures in food packaging, such as silver nanoparticles, which exhibit antimicrobial activity, thus being able to prevent early food spoilage [1,2]. Among the nanostructures already used for active ingredient encapsulation, those based on lipids present some interesting features. Usually, these nanostructures are prepared with biomolecules that can be fully processed by human metabolism, reducing concerns about their biocompatibility [3]. Furthermore, the lipid nanomatrix can delay the degradation of the bioactive molecules and thus increase their stability while also controlling the release of lipophilic substances and protecting the load against enzymatically catalyzed reactions [4,5]. Nanostructures formulated with lipids include liposomes, microemulsions, nanoemulsions, and lipid nanoparticles. The latter combine some benefits of polymeric nanoparticles, liposomes, and microemulsions, with superior biocompatibility, reducing the likelihood of toxicity, and the ability to simultaneously accommodate hydrophilic and lipophilic substances without the use of organic solvents [6,7]. To enhance the performance of the delivered active substances, lipid–drug conjugates (LDCs) can also be encapsulated in these nanostructures. LDCs are drug molecules that have been covalently modified with lipids. The conjugation of lipids to drug molecules increases lipophilicity and also alters other drug properties, providing improved bioavailability, enhanced targeting to the lymphatic system and tumors, and reduced toxicity [8].

Among nanoparticles with a lipid core, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are notable for their capacity to enable the controlled release of the encapsulated active ingredient and its targeted delivery to specific tissues [9–11]. These lipid nanostructures consist of a lipid matrix stabilized by surfactants and can be synthesized using various preparation methods involving lipids, solvents, and surfactants. The

selection and ratio of surfactants and the lipid matrix significantly affect the encapsulation efficiency of the nanoformulation, as indicated by several studies [12].

Due to their lipophilic properties, lipid nanoparticles can overcome certain physiological barriers, such as the epidermis and the blood–brain barrier, without requiring surface modification [13–15]. Moreover, the versatility of commonly used lipid excipients allows for the creation of a wide range of formulations that can modify the drug's pharmacokinetics, enhancing its characteristics [16–18]. When selecting components for the formulation, it is crucial to consider the melting point of the lipid mixture—which should be above body temperature for yielding nanoparticles—loading capacity, drug solubility, and physical structure to ensure they align with the intended application [19–21]. Similarly, the type and ratio of surfactants are critical factors in formulation development, as they create an interfacial barrier between the dispersed matrix and the dispersant, preventing nanoparticle aggregation and coalescence [22]. Therefore, this review will discuss the main characteristics and applications of SLNs and NLCs, as well as their primary preparation methods, highlighting their advantages, disadvantages, and limitations. Of the articles studied and selected for this review, 55 are from before 2020.

2. General Features of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

The first generation of lipid nanoparticles includes the different SLNs, while the second generation consists of NLCs. Both are colloidal particles with diameters ranging from 10 to 1000 nm, mostly used to encapsulate bioactive ingredients [23].

The advantages of using these structures include their scalability for industrial batches, their protection of unstable compounds from degradation, their increased bioavailability, their biocompatibility, their ability to form an occlusive film, their potential for formulation without the use of volatile organic solvents, their protection against moisture and physiological pH, and their compatibility with all administration routes, adapting to specific therapeutic needs [24,25]. Due to their hydrophobic nature, lipid nanostructures in aqueous environments are scarcely hydrated and therefore cannot spontaneously dissolve or disperse in water. Thus, preparing these dispersions requires energy transfer to the system or the addition of specific chemicals, such as surfactants, able to generate very small particles.

The drug release from these nanostructures can occur in different ways. In SLNs, the solid lipid matrix slows down the release of the drug by hindering its diffusion to the external environment, promoting a sustained and controlled release. In NLCs, due to greater flexibility in the composition of the matrix, a more adjustable release can be achieved. Both SLNs and NLCs can respond to variations in pH and temperature to adjust their release profiles; however, NLCs can be more easily adapted for this type of responsive release. By altering the ratio of solid to liquid lipids, the release profile can be tuned. Additionally, due to the presence of liquid lipids, the drug may be more dispersed in the NLC matrix, showing a higher tendency for initial rapid release. SLNs may exhibit this initial rapid release (burst release) if the drug is located on the surface or at the interface between the lipid matrix and the surfactant [26].

The morphology and stability of lipid nanoparticles depend on their composition, including the type of lipid used, the active ingredient, and surfactant, as well as the production method, loading capacity, encapsulation efficiency, and nanoparticle size. These factors directly affect the application efficiency [27,28]. The types of lipids most used for formulating these structures are triacylglycerides, steroids, and fatty acids. The choice of lipid is crucial because the active ingredient must be well-stabilized within the lipid matrix to ensure the efficacy of the delivery system. The solid lipids used are lipids that remain solid at room and body temperature and are crucial for providing a stable structure to the nanoparticles. These include long-chain fatty acids, waxes, and long-chain triglycerides, such as stearic acid, palmitic acid, glyceryl stearate, and vegetable butters. These lipids form the basis of the lipid matrix that encapsulates the active ingredient, offering physical stability to the system and contributing to the control of sustained drug release. Due to their higher melting point, they delay the release of the encapsulated active ingredient,

promoting prolonged release, which can improve the drug's bioavailability and allow for longer intervals between doses. These lipids also help protect the encapsulated drug from manipulation, whether by hydrolysis, oxidation, or enzymatic action, enhancing its stability during storage and application [3,16]. The liquid lipids used are unsaturated oils or medium-chain triglycerides, which remain liquid at room temperature, providing greater fluidity and flexibility to the nanoparticle matrix. They are derived from plant sources, seed oils, and fruits, such as canola oil and ethyl oleate. The increased fluidity of the matrix prevents the nanoparticle structure from becoming too rigid, allowing for a higher degree of the incorporation of bioactive molecules. This enhances the load capacity of the nanostructure, especially for lipophilic molecules. The presence of a liquid phase in the matrix facilitates the solubilization of the drug, resulting in greater encapsulation efficiency [16,19,29].

There is also the possibility of using PEGylated lipids, also known as lipids conjugated with polyethylene glycol (PEG). These are lipid molecules that have one or more PEG chains attached to their structure, a modification that imparts special properties to the lipids, making them particularly useful in creating stealth nanocarriers for medical and pharmaceutical applications [30]. The PEGylated lipid Distearoylphosphatidylethanolamine–polyethylene glycol (DSPE-PEG) is often used to stabilize liposomes and nanoparticles, helping to prolong their circulation time in the blood and reduce early uptake by the reticuloendothelial system [31], and Dipalmitoylphosphatidylcholine–polyethylene glycol (DPPC-PEG) is used in some liposome formulations to increase stability and blood circulation. DPPC is a common component of lipid bilayers, and its PEGylated version helps to reduce interaction with plasma proteins [32,33].

Some of the lipids and surfactants used to prepare SLNs and NLCs are exemplified in Table 1.

Table 1. Examples of solid lipids, liquid lipids, and surfactants used to prepare SLNs and NLCs.

Liquid Lipids	Solid Lipids	Surfactant
Oleic acid Alpha-tocopheryl acetate Squalene Medium chain triglycerides (MCT) Caprylic and capric triglycerides PEG-8 caprylic/capric glycerides Propylene glycol dicaprylocaprate Olive oil	Glyceryl monostearate Glyceryl tridecanoate Glyceryl tripalmitate Glyceryl behenate Stearic acid Glyceryl distearate	Brij™ O10 Soybean phosphatidylcholine Lecithin Solutol® HS 15 Soy lecithin Poloxamer 188 Poloxamer 407 Tween® 80 PEG-40 hydrogenated castor oil

SLNs possess a solid lipid core at room temperature, which forms a well-organized lipid matrix. This matrix efficiently protects the active ingredient and regulates its release with enhanced quality [34]. SLNs are stabilized by an outer layer of a surfactant, and the active ingredient can be accommodated within the lipid core, in the surfactant interface, or distributed throughout the entire nanostructure. SLNs were developed in the 1990s to address the rapid degradation and drug stability in liposomes and the toxicity associated with polymeric nanoparticles due to the use of volatile organic solvents. The sustained release of the active ingredient over a prolonged period in SLNs occurs through a combination of different factors, such as the degradation rate of the lipid matrix, the diffusion of the encapsulated or adsorbed drug in the nanostructure to the external medium, and the crystalline organization of the lipid matrix [35]. Furthermore, the lipids used in SLN formulations are biocompatible and biodegradable, which minimizes toxicity [9]. In a study by Akel et al. [36], the efficiency of SLNs and polymeric nanoparticles for the nasal administration of meloxicam was compared. The findings demonstrated that SLNs had smaller particle sizes, better drug release profiles, and superior mucoadhesive properties

compared to polymeric nanoparticles. This underscores the superior application potential of lipid nanostructures over other nanostructures in drug delivery systems.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have significant differences in their lipid phase structures, which are adapted to improve the encapsulation, protection, and controlled release of drugs. The structure of SLNs can follow the homogeneous matrix model, the drug-enriched shell model, and the drug-enriched core model [25].

In the homogeneous matrix model, the drug is uniformly distributed throughout the lipid matrix, resulting in a controlled release of the drug. However, this model is only applicable if the drug and the lipid are completely miscible. Additionally, high concentrations of the drug can make it difficult to form a truly homogeneous matrix, leading to the crystallization or segregation of the drug. The drug-enriched shell model is designed to maximize the drug load within the nanoparticles, improving encapsulation efficiency and potentially increasing the therapeutic efficacy of the drug. In this model, a drug-free lipid core is formed along with an external layer of lipids and drugs. Compared to the homogeneous matrix model, the drug-enriched shell model can offer a faster release of the drug. One of the challenges with this model is ensuring the long-term stability of the nanoparticles, as the drug on the surface may be more susceptible to environmental degradation compared to drugs that are fully encapsulated within a solid matrix. The drug-enriched core model forms when the amount of drug is nearly saturated, making it suitable for the need for prolonged drug release and for increasing the drug's bioavailability [25,37].

The lipid structure of NLCs also presents itself in three distinct ways. The imperfect crystal model occurs when there is a mixture of sufficient quantities of liquid lipids and solid lipids, creating a matrix with a large number of voids and imperfections where the drug can be accommodated. In the amorphous model, the lipid matrix is formed by a random arrangement of lipid molecules. There are no regular packing patterns or crystalline alignment, resulting in a highly disorganized structure, creating an amorphous lipid matrix that minimizes drug expulsion. The multiple model consists of a solid lipid matrix that encapsulates small droplets of liquid lipids. The presence of oil droplets in the solid matrix allows for a larger amount of drug to be incorporated. Drugs that are more soluble in liquid lipids can concentrate in the oil droplets, while the solid matrix provides structural support. This feature is especially useful for lipophilic drugs that have difficulty dissolving in rigid lipid matrices [25,37,38].

However, due to the characteristics of their matrices, particularly the crystallization of the solid lipids, SLNs may exhibit low drug loading capacity and expulse the drug to the dispersing phase during storage. Lipid polymorphism in nanoparticles refers to the ability of lipids to crystallize into different structural forms. As the solidification process begins, the viscosity of the molten lipid gradually increases, hindering the accommodation of lipid molecules. As a result, lipid crystals form with varying degrees of three-dimensional organization with different polymorphic forms. The type of structure acquired by the lipid during cooling and storage directly influences the drug accommodation efficiency, as the more thermodynamically stable the structure, the more organized it will be, and the spaces for incorporating active compounds will be smaller. The crystalline structure model acquired by the lipid matrix can be of the α (hexagonal), β′ (orthorhombic), and β (triclinic) types, with the hexagonal being the most thermodynamically unstable and the triclinic the most stable. Generally, a lipid matrix composed of a single type of fatty acid or of solid lipids at room temperature crystallizes at the most stable β point, while matrices with different lipids crystallize in the α conformation, the latter providing a greater capacity for accommodating active ingredients [39]. If drugs are not adequately incorporated into the lipid matrix, they may migrate to the surface of the SLNs or become separated from the nanostructure matrix.

The primary distinction between SLNs and NLCs lies in the composition of their lipid matrices. NLCs were specifically developed in the early 2000s to address and overcome the limitations associated with SLNs. While SLNs consist solely of solid lipids, NLCs are formulated with a combination of solid and liquid lipids. This unique composition prevents the formation of an overly organized lipid matrix, thereby allowing more space within the nanostructure for drug accommodation (Figure 1). This structural characteristic enhances the stability of the formulation by preventing solid lipid recrystallization, which helps maintain particle size during storage [40].

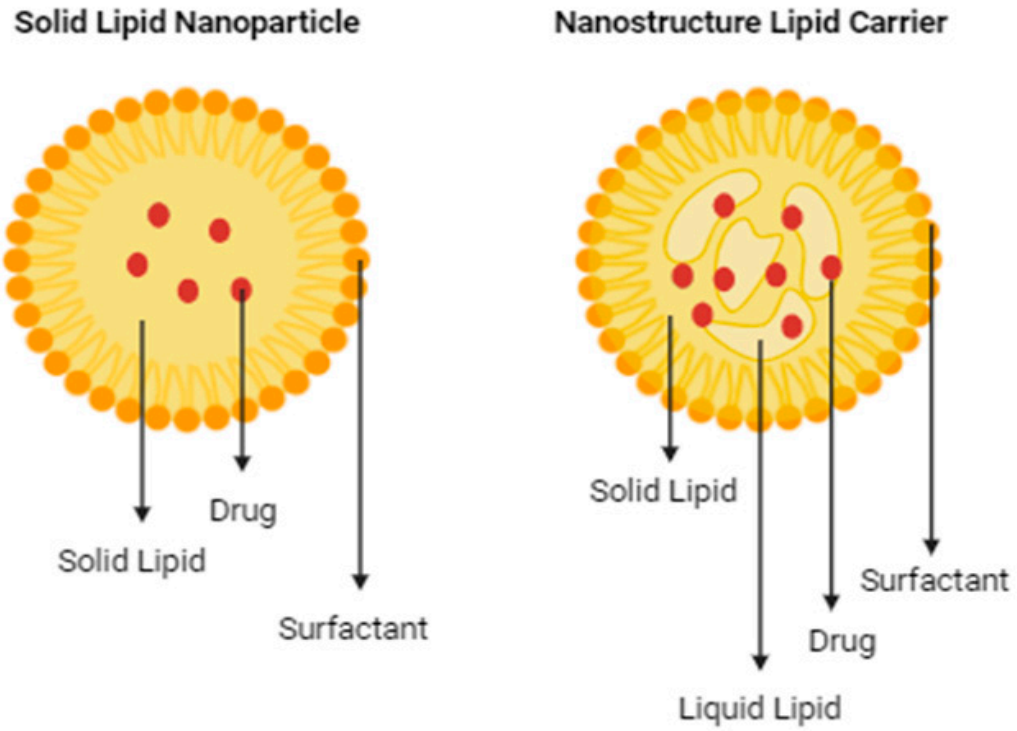

Figure 1. The structural matrix of solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs), with a demonstration of the lipid core composition, surfactant, and drug accommodation capacity. SLNs are represented with solid lipids, surfactants, and the active ingredient, while NLCs present with solid and liquid lipids, surfactants, and the drug.

Furthermore, the presence of liquid lipids in NLCs improves the solubility of certain drugs, allowing for the encapsulation of higher concentrations of the active ingredient [41]. In the work of Chen et al. [42], NLCs made of 10% (w/v) Precirol and squalene and SLNs made of Precirol were prepared by hot homogenization, both containing 1% lovastatin in the lipid phase and 0.2% myverol or hydrogenated soy phosphatidylcholine as lipophilic emulsifiers. The lovastatin loading capacity in these nanostructures was investigated, and the lovastatin encapsulation efficiency of the NLCs was higher than that of the SLNs in all formulations, with a maximum efficiency of 87.6% compared to 72.8% for the SLNs. Depending on the lipid matrix used, NLCs can exhibit three distinct structural types, namely the imperfect crystal type, the amorphous type, and the multiple type [43]. The imperfect crystal type arises from the combination of lipids with varying chain lengths, resulting in a matrix with voids, ideal for drug accommodation. The amorphous type is formed when medium-chain triacylglycerides are used together with solid lipids, preventing full recrystallization and creating an amorphous structure that mitigates drug expulsion. The multiple type incorporates solid lipids along with oils and/or medium and long triacylglycerides, offering additional structural variations. Despite potentially offering greater stability compared to SLNs, NLCs suffer from the possible loss of excess liquid lipids, which may cause instability of their lipid matrix [44,45]. Moreover, the fluid

and dynamic structure of the NLC matrix may result in a faster and less controllable drug release compared to SLNs. Eventually, NLCs typically involve a mixture of solid and liquid lipids, which can complicate the manufacturing process compared to SLNs that use only solid lipids. This complexity can affect reproducibility and the production scale [12].

In a study conducted by Dudhipala et al. [46], the performances of SLNs and NLCs loaded with nisoldipine for oral administration were evaluated, as nisoldipine has low oral bioavailability, around 5%, due to first-pass metabolism. The NLCs were produced using oleic acid and trimyristin as the liquid and solid lipids, respectively, and poloxamer-188 and egg lecithin as surfactants. For the SLNs, only trimyristin was used as the lipid, with the same surfactants. The choice of lipids aimed to enhance the drug's solubility in the composition. Poloxamer-188 is a nonionic amphiphilic copolymer, and egg lecithin is an unsaturated phospholipid with a phosphoric acid group as the hydrophilic phase and two saturated fatty acids. Both nanostructures were prepared by hot homogenization followed by the ultrasonication method. The results revealed that both formulations significantly increased the bioavailability of the drug. A slightly higher plasma concentration of the drug was observed for NLCs, at 12.27 μg/mL compared to the SLN formulation, which showed 11.94 μg/mL. However, both nanostructures significantly increased the bioavailability of nisoldipine in comparison to the isolated drug, which was 7.01 μg/mL. The time to reach the peak concentration of the drug loaded into nanostructures, however, was similar to that of nisoldipine alone. The mean residence time and half-life of NLCs and SLNs were almost double compared to nisoldipine, indicating a prolonged release and the avoidance of first-pass metabolism through lipid nanoparticles. The bioavailability of nisoldipine in the NLC and SLN formulations increased by 2.46 and 2.24 times when compared to the administration of the free drug. Additionally, there was an improvement of approximately 1.09-fold in the increase in oral bioavailability of NLCs compared to the SLN formulation. However, NLCs demonstrated a greater capacity to increase nisoldipine bioavailability compared to SLNs, underscoring their superior efficacy in drug delivery applications.

Lipid nanoparticles can be absorbed by the lymphatic system after oral administration, avoiding first-pass metabolism. In this way, the drug is distributed without being metabolized by the liver immediately after absorption [20]. Lipophilic molecules associate with lymphatic lipoproteins in the enterocytes of the small intestine, leading to transport to the systemic circulation via intestinal lymphatic system. After absorption in the enterocyte, the impermeability of blood capillaries to large colloidal particles, along with the more open intercellular junctions of lymphatic vessels compared to those of blood vessels, preferentially direct the lipoproteins to uptake by the intestinal lymphatic system instead of the blood capillaries. The colloidal structures formed during the digestion of lipids in the gastrointestinal tract provide structures that preserve drugs, thus preventing precipitation and increasing drug absorption [47]. Therefore, by utilizing this property of the lymphatic system, the absorption of lipidic molecules can be facilitated, thereby bypassing the portal circulation [48]. The fat molecules resulting after absorption by the enterocytes (chylomicrons) are moved into the systemic circulation through the lymphatic system. It has been observed that nanoparticles, once located in the cytosol of the enterocyte, share these chylomicron transport pathways within the enterocyte and in the lymphatic vessels [49].

In the work of Mura et al. [50], SLNs and NLCs were compared for the vectorization of hydrochlorothiazide for pediatric oral administration. Glyceryl distearate/palmitostearate and diethyl glycol monoethyl ether of higher purity were used as solid and liquid lipids, respectively, and lauroyl polyoxyl-32 glyceride as the surfactant. The choice of lipids considered the solubilization of the drug, and the surfactant was chosen for its amphiphilic nature. They were prepared by hot homogenization followed by ultrasonication with a drug concentration of 0.2% *w/v* in both formulations. The NLCs showed better performance than the SLNs, achieving 90% drug entrapment against 80%, and more than 90% drug release after 300 min compared to 65% for the SLNs. Both formulations showed good physical stability during 6 months of storage at 4 °C, similar PDI and zeta potential values,

and no toxic effects. However, a greater loss of encapsulated drug due to drug expulsion was observed after 6 months of storage in SLNs, at 15% compared to NLCs, which was less than 5%.

The comparison between these two nanostructures was also addressed in the work of Aditya et al. [51], where SLNs and NLCs were loaded with quercetin for oral bioavailability evaluations. The solid lipid used was Imwitor 900 K, medium-chain triglycerides (MCTs) were used as the liquid lipid, and Tween 80 (a hydrophilic nonionic surfactant), Span 20 (a lipophilic nonionic surfactant), and soy lecithin were used as surfactants, and they were prepared by high-pressure homogenization. In the SLNs, the encapsulation efficiency was 93%, while in the NLCs, it was 91%. However, the loading capacity was higher in the NLCs than in the SLNs, with values of 0.9% and 0.6%, respectively. In terms of quercetin bioaccessibility, after 2 h of administration, the NLCs showed 52.7% and the SLNs 39.7%, and the quercetin release rate was approximately 53% for SLNs and 79% for NLCs. This may occur due to the lipid mixture present in the NLCs, which can better stabilize the drug.

For topical application, the two lipid structures were compared regarding occlusive effect and skin permeation in the work of López-García et al. [52]. SLNs and NLCs were prepared by high-shear homogenization, glyceryl dibehenate was chosen as the solid lipid, and caprylic/capric triglycerides as the liquid lipid for this formulation, along with poloxamer-188 as the surfactant. The occlusive effect was evaluated by in vitro testing and measuring TEWL, which is the transepidermal water loss, using pig skin, and the skin penetration test was performed using Nile red as a marker. As results, the SLNs had a size of 200 nm and the NLCs of 192 nm. For the occlusion factor, the results were 36%–39% for both, while a reduction in TEWL of 34.3% and 26.2% was observed after treatment with SLNs and NLCs, respectively. Although the results found are similar for the two nanostructures, the NLCs allowed for the penetration of a larger amount of Nile red than the SLNs, which was 4.7 µg compared to 1.7 µg. The author suggests that this fact could be explained by the lipid composition of NLCs, which affects the ability to enhance the penetration of molecules through the skin tissue due to differences in the interaction of lipids with skin components.

These lipid-based systems are extensively studied due to their adjustable structure based on the active ingredients and excipients used; therefore, various advantages are expected with their use, as illustrated in Table 1. In the food industry, their application aims to protect active ingredients against oxidation and pH variation. In the pharmaceutical field, these structures promote the accumulation of the drug at the target site and are already used in different administration routes to improve the therapeutic response of the treatment [53,54].

In another study, NLCs were shown to increase the permeability of ceftriaxone through the meninges when administered intravenously [55]. The lipid matrix was prepared with glyceryl monostearate and Capriol 90 in a 70:30 ratio, with Tween 80 as the surfactant. As the meninges are highly lipophilic in nature and the drug is hydrophilic, NLCs are efficient choices to improve drug penetration through the blood–brain barrier. The NLCs were prepared by the hot homogenization method with 90 mg of ceftriaxone. The formulation was lyophilized, and the particle size was 130.58 nm, the zeta potential was 29.05 mV, entrapment efficiency was 44.32%, and drug loading was 8.10%. The lyophilized NLC formulation exhibited a prolonged release pattern, showing approximately 91% of the total drug amount released over 24 h. In vitro permeability studies using an artificial membrane with porcine polar brain lipids showed that NLC permeability was 28 times higher compared to the aqueous solution of ceftriaxone. It was also found that the permeability of NLCs loaded with ceftriaxone, even with 44.32% drug entrapment in the NLCs, was able to increase the biodistribution of ceftriaxone 7.9 times compared to the biodistribution of the drug after the administration of ceftriaxone solution in a rat model.

Other studies highlight the potential application of SLNs and NLCs for drug delivery to the brain. In Chen et al.'s study [56], the plasma concentration of curcumin was increased by 6.4 times compared to isolated curcumin when it was associated with NLCs made of tripalmitin and oleic acid (50/50%) in mice via intraperitoneal administration for brain cancer treatment. This association also enhanced the targeting of curcumin to the brain and tumor, increasing the drug's inhibition efficiency from 19.5% to 82.3%.

Drug accumulation in the brain was also observed in the study by Alam et al. [57], where NLCs with lamotrigine administered intranasally were evaluated for brain targeting efficiency compared to intranasal lamotrigine and lamotrigine oral solution in a rat model. The NLCs had a size of 151.6 $\pm$ 7.6 nm and encapsulation efficiency of 96.64 $\pm$ 4.27%. The estimated brain concentrations of lamotrigine after treatment were 1746,443, 1261,756, and 342,365 ng for the intranasal nanoformulation, intranasal solution, and oral solution, respectively.

In formulations containing chemotherapeutic agents, both SLNs and NLCs have demonstrated efficacy in enhancing drug permeability and retention [58–62]. In the work by Amasya et al. [58], for cutaneous applications, NLCs loaded with 5-fluorouracil were formulated by high-pressure homogenization and presented an average particle size of 205.8 nm and a zeta potential of -30.20. The cytotoxicity profile of the NLCs was evaluated using epidermoid carcinoma cells and human keratinocyte cells, showing a significantly higher anticancer effect on carcinoma cells compared to free 5-fluorouracil, and also less cytotoxicity towards human keratinocyte cells. It also presented a cumulative amount of 5-fluorouracil in rat skin dermal tissues higher than that of the 5-fluorouracil hydrogel. These lipid nanoparticles exhibit a high affinity for the lipid-rich stratum corneum, making them ideal for topical formulations, although they also show significant benefits for other administration routes. In the work by Rudhrabatla et al. [59], SLNs with melphalan, tristearin, soy lecithin, and poloxamer-188 were developed for intravenous administration using the hot homogenization technique to overcome the side effects of the chemotherapeutic agent and improve systemic circulation time. Pharmacokinetic studies were conducted in rats, and the circulation half-life increased by approximately four times with SLNs compared to the melphalan solution, in addition to having an encapsulation efficiency of 92%. The time to maximum drug plasma concentration was 0.25 h for melphalan and 6.0 h for the SLNs, demonstrating that the nanoformulation promoted controlled drug release, which helps reduce toxicity.

In a study by Vital et al. [63], the intravenous administration of NLCs containing paclitaxel resulted in reduced pain and reduced toxicity in patients with bone metastasis. Patients with advanced-stage cancer may be too debilitated to withstand the toxicity of other chemotherapy regimens. Thus, the association of drugs with nanostructures would reduce toxicity. Additionally, the intravenous administration of drugs has a rapid onset of action and high elimination rates from the body, necessitating frequent dosing. NLCs enable controlled drug release, maintaining drug concentration within the therapeutic window and reducing the frequency of administration. The NLCs were formulated using high-pressure homogenization, with a lipid matrix containing stearic acid and cholesteryl oleate with the surfactants poloxamer-188 and octadecylamine. All patients were treated with 175 mg of the nanoformulation per square meter of body surface area, diluted in 200 mL of saline solution, administered intravenously over 90 min, every 3 weeks. None of the patients exhibited clinical or laboratory toxicity that could be attributed to NLC treatment, with adverse events or hepatic and renal toxicity, commonly associated with paclitaxel treatment, being grade zero, demonstrating the efficacy of this method in reducing toxicity. It was also observed that pain relief was achieved in 13 out of 18 study participants with NLC administration, resulting in reduced doses of analgesics or a switch to weaker analgesics.

Lipid nanoparticles have been shown to adhere to the pulmonary mucosa, resulting in a more effective and prolonged therapeutic response [64]. The efficacy of the nasal administration of SLNs loaded with paclitaxel in reducing the number and size of lung

metastases was evaluated in comparison to the intravenous administration of the same drug using the conventional formulation. A decrease in the number and volume of lung metastases after the inhalation of SLNs during the first 15 days was observed compared to the group treated with free paclitaxel. In the study, mice were treated with paclitaxel-loaded SLNs via inhalation (1.0 mg/kg per dose) twice a week, following this protocol for four weeks. This effect may be attributed to the disorganized structure of vessels resulting from cancer cell angiogenesis, which increases the permeability of colloidal particles, leading to their accumulation in regional lymph nodes and subsequent presence in the extrapulmonary space. Additionally, the lipid nanoparticles adhere to the mucus on the pulmonary surface, enhancing drug selectivity and limiting systemic circulation. The mechanical deposition of aerosol particles also contributes to this effect and reduces the drug's systemic toxicity. This allows the SLNs to interact with the bronchoalveolar epithelium, alveolar cells, and interstitial space, thus reaching the lung-associated lymphatic system. In this way, the selectivity provided by pulmonary administration, combined with the capacity for endocytosis, can increase the drug's antineoplastic effect. Thanks to the size of the nanoparticles, along with their lipophilic characteristics, greater cellular internalization can be anticipated, likely mediated by intracellular endocytic pathways. This would facilitate the release of the drug within the intracellular space, promoting a more selective delivery to cells, increasing the drug concentration inside the cells after specific degradation of the glycerides in endocytic vesicles, which would also enhance antineoplastic activity.

Their use as delivery systems for antibiotics promotes a sustained drug release, maintains therapeutic plasma levels, and helps prevent the selection of resistant bacterial strains, as observed by Ghaderkhani et al. [65]. In this study, SLNs loaded with rifampicin were produced to evaluate antibacterial activity. The formulation contained stearic acid as the lipid matrix and poloxamer 407 and Lipoid S-100 as surfactants. An improvement in antibacterial effect was demonstrated when the drug was associated with nanostructures, which is attributed to increased solubility, sustained release, and protection of the drug from inactivation. In the evaluation of the minimum inhibitory concentration, it was found that free rifampicin is active for a maximum of 2 days, after which the antibacterial activity of free rifampicin diminishes, confirmed by a higher number of colony counts in the culture medium. The SLNs with rifampicin prevent the drug from being inactivated and together with its controlled release over time, act more efficiently against bacteria than free rifampicin, resulting in a significantly lower number of colonies. For orally administered drugs, nanoencapsulation offers protection against enzymatic degradation and improves adhesion to the gastrointestinal epithelium [66,67]. Additionally, due to their small size, both SLNs and NLCs present high surface area-to-volume ratios, increasing the interaction of active molecules with the gastrointestinal epithelia and accelerating the action of orally administered drugs [19].

The use of these nanostructures as drug delivery systems, while efficient, presents limitations in overcoming vascular barriers, requiring a long circulation time to increase the likelihood of crossing these barriers and escaping the reticuloendothelial system. The reticuloendothelial system (RES), is a network of cells and tissues that plays a crucial role in defending the body against pathogens, removing dead cells, and regulating the immune system [68]. The RES includes some cells that act as scavenger cells, such as Kupffer cells, macrophages, and dendritic cells. These cells play an important role in the immune response and are essential in the interaction with nanoparticles, as they identify nanoparticles through specific receptors on their membranes. They register, engulf, and degrade foreign particles to the body, including nanoparticles, through phagocytosis [69,70]. Other important cells are the scavenger endothelial cells, such as the liver sinusoidal endothelial cells (LSECs) [71]. A notable functional characteristic of LSECs is their high endocytic capacity compared to other endothelial cells, playing a key role in the elimination of macromolecules and residual nanoparticles carried by the blood. LSECs have a structure with small pores that facilitate the passage of molecules between the blood and hepatocytes

but also allows for the capture of larger particles. This helps filter substances present in the blood that circulate through the hepatic sinusoids. They express several types of pattern recognition receptors (PRRs), including scavenger receptors, which are particularly important for capturing modified lipoproteins, immune complexes, fragments of dead cells, and molecular debris. These receptors allow LSECs to identify and internalize substances that need to be eliminated from the bloodstream, capturing macromolecules, cellular debris, and nanoparticles. These cells recognize nanoparticles as foreign particles and phagocytize them before they reach the target tissue. This can reduce the amount of nanoparticles that reach the desired location, decreasing the effectiveness of the treatment. They can also reduce the circulation time of nanoparticles in the blood by capturing them quickly, especially if the nanoparticles do not have coatings that protect them from this capture. This is particularly problematic for treatments that require prolonged distribution or accumulation in specific target tissues [68,71].

To avoid early capture by scavenger cells, nanoparticles can be modified with coatings that reduce recognition by these cells. Stealth nanocarriers are drug delivery systems designed to evade detection by the immune system, prolonging their circulation in the body and enhancing the efficiency of transporting active substances to target sites, such as specific tissues or cells [72]. These nanocarriers have the ability to escape elimination by the reticuloendothelial system, especially by phagocytic cells in the liver and spleen, which normally detect and remove foreign particles from the blood. This ability to avoid immune recognition is called the stealth effect and plays a central role in enabling nanomaterials for drug delivery applications by having a longer half-life in the bloodstream, allowing them to remain in the body longer and increase the chances of reaching the desired location. By circulating longer in the body and being able to preferentially accumulate in the target tissue, stealth nanocarriers minimize systemic side effects. This is particularly important in treatments like chemotherapy, where drugs can be highly toxic to healthy cells. The hydrophilic coating also provides greater stability in biological environments, preventing particle aggregation and protecting the encapsulated drug from premature degradation. Stealth nanocarriers, especially in cases of tumor treatment, can benefit from the EPR effect (enhanced permeability and retention). Due to the dysfunctional architecture of blood vessels in tumors, nanoparticles tend to accumulate in these locations, helping to deliver more drugs directly to cancer cells [73].

To achieve this, stealth nanocarriers are often modified with substances that make it difficult for scavenger cells to detect them, ensuring that the nanoparticles reach the desired location before being captured and degraded. These substances can be polymers, such as polyethylene glycol (PEG) and poly(lactic-co-glycolic acid) (PLGA), proteins like albumin, and lipids such as phospholipids [69]. Regarding the use of SLNs (solid lipid nanoparticles) and NLCs (nanostructured lipid carriers) for drug delivery, the use of PEG as a coating agent for these nanoparticles can lead to even more interesting effects. The use of PEG, a hydrophilic polymer, is already well-described in the literature as a tool to camouflage nanoparticles, as it forms a layer that prevents the adherence of plasma proteins and the subsequent elimination by the reticuloendothelial system. This process is called "PEGylation" and can improve the biodistribution of the nanoparticles, prevent aggregation, and can be used in combination with other agents that allow the nanoparticles to target specific sites, such as receptors on tumor cells or inflamed areas [74,75].

In Jin et al.'s [74] study, cationic solid lipid nanoparticles (SLNs) made of cholesteryl oleate and glycerol trioleate were conjugated with PEGylated small interfering RNAs (siRNAs) targeting human c-Met for the treatment of glioblastoma. The use of siRNAs can silence oncogenes that control the proliferation, apoptosis, angiogenesis, or migration of tumor cells, but siRNAs exhibit low stability in biological fluids and non-specific cellular uptake. PEG conjugation can overcome these issues. c-Met is a tyrosine kinase receptor that when mutated is involved in the angiogenesis and proliferation of various cancers, including glioblastoma. The size of the SLNs was 117.4 $\pm$ 11.7 nm, and in the proliferation assay, treatment with SLNs reduced tumor cell proliferation by 23.4% compared to the un-

treated control group and c-Met expression was reduced by 32.5%. In the tumor xenograft model in mice, the treatment inhibited tumor growth in a dose-dependent manner, with the 0.125 mg/kg, 0.5 mg/kg, and 2 mg/kg groups showing tumor volume reductions of 50%, 62%, and 91%, respectively, compared to the control. In the blood–brain barrier permeability evaluation, the treatment showed higher fluorescence intensity in the brain compared to the control, indicating that the formulated SLNs can reach the brain, and no apparent systemic toxicity was observed.

The use of SLNs and NLCs for mRNA delivery therapy is another widely explored area, as these nanostructures can prevent mRNA degradation by ribonucleases and allow it to pass through cell membranes to reach the target [12]. mRNA can be used to encode tumor-associated antigens for cancer immunotherapy, antigens for vaccination against infectious diseases, and therapeutic proteins that are missing or dysfunctional in individuals with certain diseases. Additionally, mRNA does not need to enter the cell nucleus and thus it does not alter the cell's genetic material, eliminating concerns related to gene editing or permanent mutations [76].

SLNs containing mRNA were prepared as a strategy for the production of interleukin-10 (IL-10) in corneal cells to combat inflammation in this region and were compared to SLNs containing pDNA [77]. The topical administration of IL-10 is an effective treatment for corneal inflammation, but it has a short half-life and low ocular bioavailability. The SLNs were prepared using three different methods, namely solvent evaporation/emulsification (SLNEE), hot melt emulsification (SLNHM), and coacervation (SLNC). SLNEE was formulated with Precirol® ATO 5 and the cationic lipid DOTAP, with Tween 80 as the surfactant and dichloromethane. SLNHM was produced with the same lipids and surfactant but used water as a solvent. SLNC was composed of behenic acid, PVA 9000, DEAE-dextran, and water. To prepare the vectors, protamine was added to the mRNA or pDNA. Dextran or hyaluronic acid dissolved in water was then added. The nanoparticle sizes ranged from 93.3 to 307.8 nm. In the quantification study of interleukin-10 secreted in HCE-2 cells, the mRNA vectors induced greater secretion than the pDNA-based vectors. Among the mRNA-based vectors, SLNEE formulations were the most effective, while SLNC vectors showed the lowest levels. For the same type of SLNs, those containing dextran were more effective than those containing hyaluronic acid. In the mouse evaluation, mRNA vectors were administered as eye drops, and transfection efficacy was analyzed 24 h after the last administration. IL-10 was continuously observed throughout the corneal epithelium in all sections analyzed, being higher when the corneas were treated with nanosystems than in the case of mRNA not associated with nanostructures.

In general, the use of SLNs and NLCs for therapeutic applications offers significant improvements. For anticancer drug delivery, these structures enable prolonged drug release and selective accumulation in tumor tissues through the EPR effect, increasing drug concentration at the tumor site while minimizing damage to healthy cells [78–80]. In anti-inflammatory and anti-infective therapies, they enhance the bioavailability of drugs that are usually poorly soluble in water, boosting therapeutic efficacy and reducing the need for high doses, thus minimizing side effects [81–83]. In neurodegenerative diseases like Alzheimer's and Parkinson's, SLNs and NLCs improve drug delivery to the central nervous system, utilizing their ability to cross the blood–brain barrier. The formulation of neuroprotective and antioxidant drugs in nanoparticles ensures that a significant amount of the medication reaches the brain, enhancing treatment outcomes [84–86]. NLCs and SLNs can also serve as adjuvants or carriers of antigens in vaccines, increasing immune response and vaccine efficacy by protecting antigens from degradation before reaching immune cells and providing controlled release for a more efficient and lasting immune response [87,88]. For topical products, these nanoparticles improve drug penetration through the skin barrier, increasing the effectiveness of active substances that are difficult to absorb when used in conventional formulations [89,90]. In the treatment of metabolic diseases, they can be used to encapsulate insulin and other diabetes medications, facilitating a prolonged release and enhancing the stability of these drugs. This reduces the need

for frequent injections, making treatment more convenient for patients and improving glycemic control [91,92]. They also improve the solubility of drugs in ophthalmic solutions and extend the release of medications in the eyes or lungs, enhancing treatment efficacy and patient comfort [93,94].

Overall, the main advantage of using these lipid nanostructures over other nanoformulations is the possibility of using biocompatible and eco-friendly materials, as well as scalable preparation methods [75,95–97]. Additionally, other reported benefits include increased drug stability by protecting it against chemical and enzymatic degradation, enabling application in all administration routes and allowing for the selection of the best therapy; versatility in carrying drugs from different pharmacological groups, as it is efficient in entrapping both lipophilic and hydrophilic drugs; possibility of application in combination therapy, as it can carry more than one drug; reduced diameter improving drug delivery; and the biocompatibility of the lipids used, which reduces the possibility of intoxication [16]. The disadvantages of applying these systems are mainly related to stability issues during storage. Drug expulsion can occur during the polymorphic transition of lipids, nanoparticle agglomeration, coalescence, and polydispersity. Additionally, they are less effective for protein transport. The main benefits of SLN and NLC applications are represented in Table 2.

Table 2. Advantages and disadvantages of solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs) as drug carriers.

Characteristics	SLN	NLC
Composition	Made of solid lipids only	Combination of solid and liquid lipids
Physical State	Solid at room temperature	Solid with fluid internal structure
Stability	Generally more stable due to solid matrix	Can be less stable due to presence of liquid lipids
Drug Loading Capacity	Limited by solid matrix's capacity	Higher due to possibility of accommodating more drug in defects
Control Over Drug Release	More controlled and predictable release	Can be less controlled due to dynamic nature of matrix
Manufacturing Complexity	Relatively simpler due to single-phase lipids	More complex due to handling of two different lipid phases

3. Preparation Methods

There are numerous techniques for the preparation of SLNs and NLCs described in the scientific literature. Selecting the most appropriate method requires careful consideration of the physicochemical properties of active ingredients, lipid matrices, and surfactants to ensure the production of stable nanostructures. The preparation methods are broadly categorized into two types, which are high-energy methods and low-energy methods.

Low-energy methods involve the formation of nanodroplets without the use of devices that actively transfer energy into the system. Instead, these methods rely on physicochemical processes that generate energy through alternating heating and cooling cycles or by simply mixing the components. In these cases, the intrinsic properties of the surfactants and solvents are adequate for nanoparticle formation [97,98]. Examples of low-energy methods include emulsification, microemulsification, and the phase inversion temperature (PIT) methods.

High-energy methods, in contrast, require specialized equipment capable of imparting significant energy into the system to form nanoparticles. The equipment generates high shear forces or induces high-pressure variations that provide energy greater than the interfacial tension between water and oil. Techniques such as high-pressure homogenization, solvent injection, and ultrasonification fall into this category. Shear stress refers to the force per unit area resulting from lateral interactions between fluid layers, causing

material deformation due to friction among fluid particles moving at different velocities within the system [99,100]. The particle size reduction achieved with high-energy methods depends on the type of equipment used and its operational parameters, including energy input, processing time, number of cycles, formulation specifics, and system properties. While high-energy methods are highly effective for large-scale production, they tend to increase production costs due to the sophisticated machinery required and may inactivate thermolabile drugs. The primary methods for producing SLNs and NLCs are illustrated in Figure 2 and elaborated upon below, and Table 3 shows examples of SLNs and NLCs prepared by different methods, with lipid compositions and surfactants used.

Table 3. Examples of solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs) prepared by different methods.

Lipid Nanoparticle	Incorporated Molecule	Lipids	Surfactants	Method	Solvent	Size	Application
SLN	Aluminum phthalocyanine	Murumuru butter	Brij™ O10	PIT	Water	40 nm	Photodynamic therapy against melanoma [101]
NLC	Ondansetron hydrochloride	Tristearin Phosal® 53MCT	Polysorbate 80	Cold high-pressure homogenization	Ethanol	206–280 nm	Nausea and vomiting [102]
SLN	Cholesteryl-9-carboxynonanoate	Stearic acid Cholesteryl oleate	Poloxamer 188 Octadecylamine	Microemulsion	Water	150–250 nm	Target antagomiR oligonucleotides to macrophages [103]
SLN	Rifabutin	Glyceryl dibehenate Glyceryl tristearate	Tween 80	Hot high-pressure homogenization	Water	99–186 nm	Antitubercular therapy [104]
NLC	Pentapeptide Dexamethasone	Glycerol trilaurate Medium-chain triglycerides	Solutol® Myrj 52	Solvent evaporation	Anhydrous ethanol Anhydrous acetone	190–203 nm	Anti-inflammatory effect [105]
NLC	Rivastigmine	Precirol® ATO5 Vitamin E	Polysorbate 80 Phosphatidylcholine hydrogenate	Ultrasound method	Water	80–220 nm	Alzheimer's disease [106]
SNL	Coumarin 6	Lipoid S100	Polysorbate 80	Solvent-injection	Methanol PBS—phosphate-buffered saline	100–180 nm	Mucoadhesive film formulation [107]

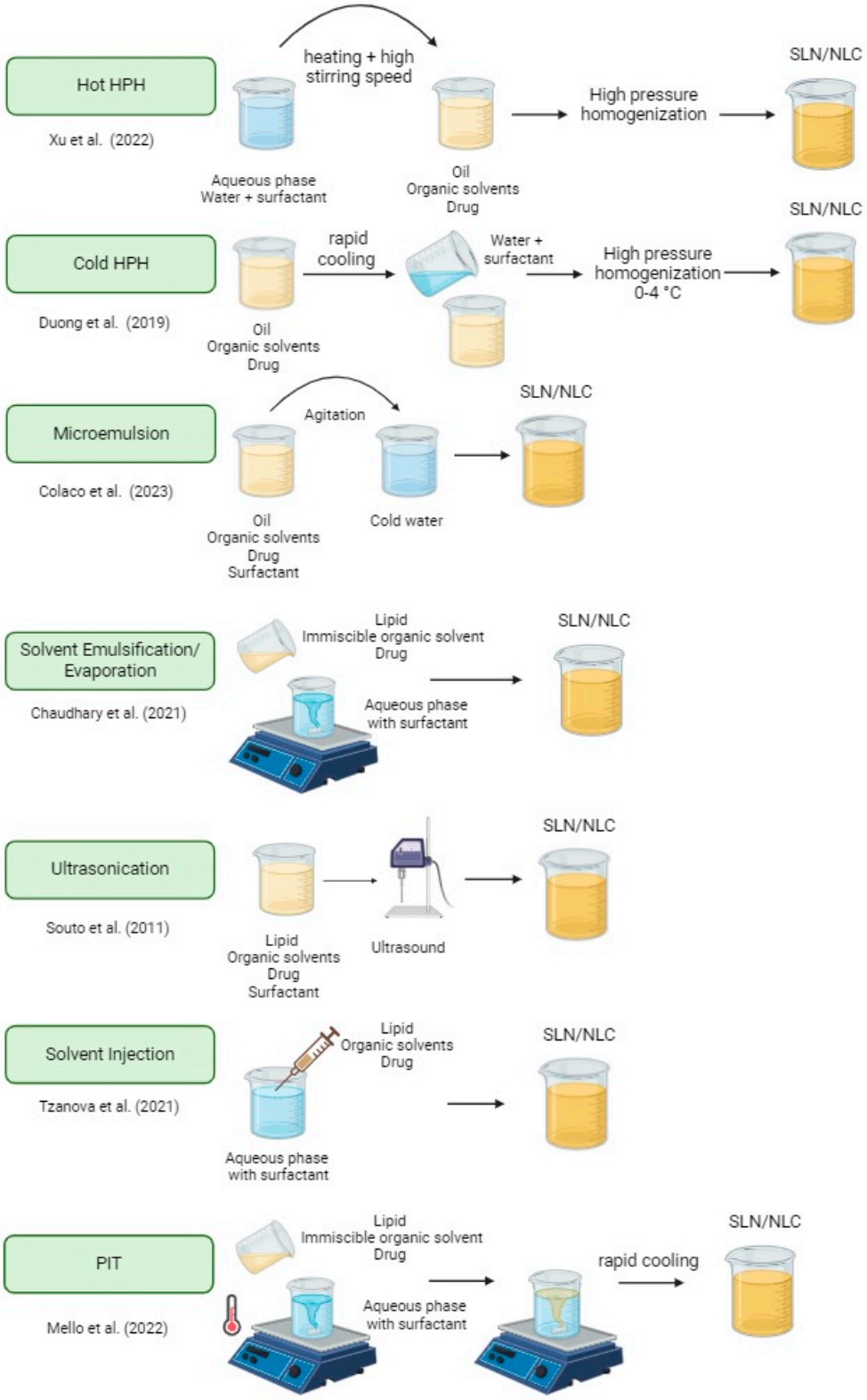

Figure 2. Main preparation methods of solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs). Hot HPH (hot high-pressure homogenization) [108], Cold HPH (cold high-pressure homogenization) [102], microemulsion [109], solvent emulsification/evaporation [110], ultrasonication [111], solvent injection [107] and PIT (phase inversion temperature) [101].

3.1. High-Pressure Homogenization

This technique is based on particle size reduction under high pressure. Homogenizers drive the liquid at high pressure, between 100–2000 bar, through narrow tubes. This high pressure accelerates the liquid and generates high shear stress and turbulence, breaking the particles into nanoscale sizes [102]. The process is performed in cycles until the particles reach the desired size. This method can be conducted in two ways, hot HPH or cold HPH. In hot HPH, the active ingredients are dissolved or dispersed in lipids by heating the mixture to a temperature 5–10 °C above the melting point of the chosen lipids. Another mixture containing an aqueous phase with a surfactant is heated separately to the same temperature and then added to the lipid mixture under constant stirring. This pre-emulsion is then added to the homogenizer [108].

This method was used to prepare inhalable SLNs with rifabutin for antitubercular therapy [104]. In this study, it was demonstrated that the hot HPH preparation method was efficient for drug retention, with concentrations close to those presented in the molten lipid. Despite being an effective method for large-scale SLN and NLC preparation, the number of cycles used can increase particle size due to coalescence and transfer the drug to the aqueous phase due to high pressures [112]. Drug degradation can also occur if very high temperatures are used; therefore, this method is not suitable if the drug is water-soluble or has a low melting point [100].

This issue with temperature and active migration can be resolved with the cold HPH method. In this method, after dissolving the active ingredient in the heated lipid, the mixture is quickly cooled using liquid nitrogen or dry ice. After cooling, the mixture is ground and added to the surfactant solution and homogenized at a temperature between 0–4 °C [102]. This cold preparation provides better homogenization of the active ingredient within the lipid matrix, preventing its migration, and can be used for hydrophilic drugs, but it presents a higher variability in particle size. In the work of Kaur et al. [113]), it was demonstrated that with cold HPH, the incorporation rate of streptomycin sulfate increased to 30% compared to the microemulsion preparation method, which was 10%.

3.2. Microemulsion Method

A microemulsion is formed by combining the drug dissolved in molten lipids with an aqueous phase of water and surfactants heated to the same temperature. This microemulsion is then added to cold water between 2–10 °C with stirring, forming a dispersion of lipid nanostructures with lipid crystallization [108]. This technique was used to formulate NLCs with lipid cholesterol-9-carboxynonanoate (9CCN) as a phagocytic signal to target antagomiR oligonucleotides to atherosclerotic plaque macrophages at the level of the aortic valves, proving to be an efficient and highly selective formulation for the treatment of atherosclerosis [103]. This is a reproducible method and does not use solvents, making it suitable for thermolabile drugs. However, it requires the use of a large amount of surfactant and necessitates evaporating excess water at the end of the preparation [109].

3.3. Emulsification/Solvent Evaporation Method

An organic phase containing lipids and immiscible organic solvent is prepared, with incorporation of the active ingredient by dissolution or dispersion. This phase is then incorporated, under stirring, into an aqueous phase containing the surfactant, forming a nanoemulsion. The solvent is removed from the system by mechanical evaporation, for example, and SLNs or NLCs are formed by lipid precipitation. This method can be beneficial when using active ingredients that cannot be subjected to high temperatures or pressure. However, it has the disadvantage of requiring a process to remove the toxic organic solvent at the end of the formulation. Additionally, the suspensions are diluted, requiring evaporation or ultrafiltration to remove excess water [109]. For hydrophilic drugs, this method is not ideal because the active ingredient can migrate to the continuous phase due to low encapsulation capacity [110].

3.4. Ultrasound Method

In this method, high-intensity sound waves propagate through the liquid, generating alternating pressure. This process creates vacuum bubbles through cavitation that absorb energy from the system and implode upon reaching their energy limit, forming nanoparticles. This method is typically used in conjunction with high-speed stirring because ultrasound alone does not transfer energy uniformly throughout the system, resulting in nanoparticles of varying sizes [111]. Although this method is easy to execute, the lipid concentration is low and the surfactant concentration is high, making this procedure less appealing compared to other methods that have higher lipid content and thus higher drug concentration. In the work by Eroglu et al. [114], this technique was used to prepare solid lipid nanoparticles with silymarin for use as a diagnostic marker in nuclear medicine.

3.5. Solvent Injection Method

In this method, a miscible solvent is used to dissolve the lipid and drug, while the aqueous phase consists of water or a buffer solution combined with a surfactant. The lipid phase is injected into the aqueous phase with stirring through a needle. As the solvent diffuses through the aqueous phase, it forms smaller droplets, increasing the lipid concentration in these droplets, which are stabilized by emulsifiers in the aqueous phase. These emulsifiers reduce the interfacial tension between the water and solvent, leading to the formation of small solvent droplets containing lipids. The rapid injection speed of the solvent causes these droplets to break into even smaller droplets with uniform lipid concentrations. The energy released during the redistribution of the solvent provides the necessary energy for droplet division and lipid precipitation [115].

An example of SLNs produced by this method is seen in the work of Tzanova et al. [107], where the SLNs produced with soybean phosphatidylcholine were incorporated into a mucoadhesive film composed by hydroxypropyl methylcellulose and glycerol, designed to increase retention time on the oral mucosa. Coumarin 6 (C6) solubilized in the particles was used as a marker to simulate a lipophilic drug. There was little variation in particle size, ranging from 100 to 200 nm. The incorporation of the nanoparticles increased the thickness and flexibility of the film. To evaluate the permeation rate of C6, mucus-producing HT29-MTX cells were used. When the SLNs were incorporated into the mucoadhesive film, the results showed that the inclusion of SLNs in the mucoadhesive film achieved a higher rate and degree of permeability, at 0.8 $ng/cm^2 \times h$ compared to free C6 (0.3 $ng/cm^2 \times h$) and SLNs not associated with the film (<0.2 $ng/cm^2 \times h$).

3.6. Phase Inversion Temperature (PIT) Method

This method is based on the ability of nonionic surfactants to change their affinity for water and oil according to temperature changes. In this method, the oil and surfactant mixture is melted and then added to water under constant stirring. The system remains heated until it reaches the cloud point and is then quickly cooled. During heating, the oil/water emulsion changes to water/oil, and during cooling, an oil/water emulsion forms again [116]. With each phase inversion, the particle size decreases, allowing for the formation of nanoparticles at the end of the procedure. It is a method easily scalable for industrial use, does not involve volatile organic solvents, and has a good cost–benefit ratio [117]. However, it can only be performed with drugs that are not temperature-sensitive and with high-concentration surfactants that are affected by temperature in their physicochemical properties [118]. In the work by Carbone et al. [96], SLNs were produced by this method for the dual administration of clotrimazole and alpha-lipoic acid for the treatment of candidiasis. The study showed that the method was effective for SLN production, accommodating both active ingredients, presenting controlled release and preserving microbial activity. In the work by Mello et al. [101], SLNs were produced by the PIT method with murumuru butter and surfactant Brij™ O10, loaded with aluminum phthalocyanine chloride for application in photodynamic therapy against melanoma cells in vitro. The produced nanostructure had a diameter of 40 nm and encapsulation efficiency

of 66.4%. For the skin permeability evaluation, murine melanoma cells (B16-F10) were used. This test demonstrated that aluminum phthalocyanine chloride in solution did not permeate the skin, possibly because it was retained in the stratum corneum. However, when encapsulated in SLNs, it was found that nearly 100% permeation occurred within 8 h of contact, proving to be efficient for transporting this photosensitizer. According to the authors, this may be due to the low hydrodynamic diameter of the formulation, which was approximately 17 nm, and the ability of SLNs to allow for greater penetration of the encapsulated active ingredient by adhering to the stratum corneum of the skin. The 50% cytotoxic concentration (IC50) of the formulation was 19.62 nM in B16-F10 cell monolayers, with apoptosis being the observed type of cell death, demonstrating high photodynamic activity against this type of cell.

4. Future Perspective

NLCs and SLNs offer numerous advantages over other colloidal systems, such as increased drug bioavailability, reduced cytotoxic effects, enhanced stability, and drug protection. In this regard, various studies have been conducted with SLNs and NLCs to deliver various active ingredients, as it has been found that these systems significantly improve the delivery and efficacy of these products. The selection of SLNs and NLCs is primarily due to their easy modifiability and scalability. Another promising aspect is the ability to modify the surface of SLNs and NLCs with different types of molecules, which can enhance therapeutic performance. The vectorization of mRNA through lipid nanoparticles is a pathway that should be further explored, as it may represent an advancement in the treatment of comorbidities that currently have no cure or effective therapy. There are already commercially available products with these nanostructures, primarily in cosmetics, and others are in clinical trials. However, more studies are needed on the toxicity of these nanoparticles, especially for formulations that do not exclusively use biocompatible and biodegradable materials. It is crucial to thoroughly understand the mechanisms by which SLNs and NLCs interact with the body, their biodistribution, degradation, and excretion processes to accurately assess exposure and potential risks. This would enable more reliable results and greater success in clinical therapy, whether for reformulating existing products or introducing new ones to the market.

Regarding the medical use of these nanostructures, research is advanced yet continues across multiple domains. SLNs and NLCs are under investigation for their drug delivery capabilities, especially in targeting specific tissues or organs and ensuring controlled pharmaceutical release [119,120]. They are utilized in transporting a diverse array of therapeutic agents, including anticancer drugs, anti-inflammatory medications, vaccines, and genetic materials. Various clinical trials and studies have been carried out to evaluate their effectiveness and safety for different medical purposes. These investigations address issues such as bio-distribution, biocompatibility, and the capacity to overcome biological barriers, such as the blood–brain barrier.

SLNs and NLCs have indeed found commercial applications, especially in the cosmetics industry, due to their ability to encapsulate and deliver active ingredients effectively while providing stability and controlled release. These nanostructures are used in various cosmetics products such as anti-aging creams, sunscreens, and moisturizers. They enhance the penetration of active ingredients, improve hydration, and offer prolonged release, making them popular in skincare formulations. Some products marketed with this technology include Eucerin Sunscreen [121] and Sebamed Anti-Aging Q10 Lifting Eye Cream [122].

No toxicity data are currently available for SLNs and NLCs. The main components of these nanocarriers are physiological lipids and excipients generally recognized as safe. The literature shows that these lipid nanoparticles do not cause toxicity after administration, whether oral, parenteral, dermal, or ocular. However, since these nanocarriers are designed to deliver bioactive molecules to the human body, it is necessary to clarify how they are distributed in tissues and how they interact with biological systems. Metabolism and excretion issues also need to be analyzed, as it is not yet known whether they may cause

adverse effects in the future due to tissue accumulation. Although sufficient data on the efficiency and quality of SLNs and NLCs are available, limited information is available on the safety of these lipid nanoparticles, especially regarding surfactants, which can activate the immune system. The use of these structures in medicine holds potential for the formulation of personalized therapies, adjusting treatments to the individual characteristics of each patient, as well as for use in combined therapies within a single delivery system or for diagnostic technologies. The food industry can explore these carriers to increase product shelf life and reduce food waste, especially for perishable items. The large-scale production of these nanostructures depends on delivering results related to their safety. Large-scale production requires nanoparticles to be manufactured consistently, as variations in manufacturing conditions can affect the efficacy and safety of the products. Monitoring particle size, drug distribution, and encapsulation efficiency in large quantities is complex but necessary to ensure quality control. Surface modifications of NLCs and SLNs, such as PEGylation, are difficult to perform effectively on a large scale. Additionally, protocols and standard operating procedures must standardize nanostructure development for large-scale production. The use of lipids in the manufacturing of these nanoparticles can vary in quality and characteristics depending on the source and batch. This variability can affect the consistency and quality of the final product, requiring rigorous quality control of the lipids [123]. In formulations that require sterilization, exposure to radiation and high temperatures can also trigger lipid polymorphism [124]. Selecting an appropriate sterilization method remains critical to ensuring the stability and efficacy of SLNs and NLCs during industrial production. The stability of lipids during storage and the production process is also crucial. Lipids may undergo oxidation or hydrolysis, which compromises the integrity and efficacy of the final products. Lipid oxidation during storage can affect the surface charge of the particles, the drug release properties, and stability, which may compromise therapeutic efficacy [125]. The production of NLCs and SLNs requires precise process conditions such as temperature, pressure, and agitation. Scaling these conditions industrially for mass production can be challenging, as minor variations can significantly impact the stability and characteristics of the nanoparticles [126]. For example, in a study conducted to scale up nanoparticles, it was observed that an increase in the speed and duration of agitation decreased the particle size, although the entrapment efficiency was not altered [127]. The costs associated with the upscale of lipid nanoparticles are significant. The equipment required for high-pressure homogenization or ultrasonication, which are common techniques for the production of SLNs and NLCs, is expensive. Moreover, complying with pharmaceutical industry regulations for the production of lipid nanoparticles, such as documentation, process validation, and conformity testing, requires significant investments in time and resources [113]. Once these challenges are addressed, the future of NLCs and SLNs is promising, with the potential to offer new solutions to the market.

5. Conclusions

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) present significant advantages over other nanostructures, which include low toxicity, high drug loading capacity, biodegradability, scalability for industrial production, and versatility in formulations, thanks to the numerous preparation techniques and the diversity of lipids that can be employed. Additionally, they offer targeted delivery of the active ingredient, enhanced permeation to target tissues, and efficiency in carrying both hydrophilic and lipophilic drugs. This versatility allows for their application across multiple administration routes, including topical, oral, parenteral, ocular, pulmonary, and cerebral routes. This flexibility has attracted considerable interest from both researchers and the industry, extending their use to other sectors such as food and cosmetics. SLNs and NLCs are excellent options for improving the pharmacokinetic profile of encapsulated drugs, thereby enhancing therapeutic outcomes. While SLNs and NLCs share structural similarities, NLCs are generally more advantageous due to their higher drug loading capacity and better stability. The selection of the appropriate preparation method for these nanoparticles depends on the

intended application and the specific drug being used. Furthermore, these nanoparticles can be formulated using eco-friendly and biocompatible methods that avoid the use of volatile organic solvents.

High-pressure homogenization is an effective method for large-scale production, but it is not suitable for thermolabile drugs and may result in high variability in nanoparticle size. Moreover, this method necessitates sophisticated equipment. Techniques such as microemulsion, solvent evaporation, and solvent injection can address the limitations of high-pressure homogenization; however, they require the removal of excess water used in microemulsion and volatile organic solvents in other techniques at the end of the preparation process. Although the ultrasound method can produce smaller nanoparticles, it is the least advantageous due to its low lipid concentration, which directly affects the drug concentration, and the high amount of surfactant required. Conversely, the phase inversion temperature (PIT) technique allows for a high drug concentration and is simpler and more cost-effective to execute, making it suitable for industrial production. The selection of the optimal technique depends on its reproducibility, which is influenced by the physicochemical properties and intended application of the materials used in the formulation.

Funding: This work was funded by the Brazilian agencies FAP-DF/Brazil (00193.00001053/2021-24), CNPq (403536/2021-9), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001.

Conflicts of Interest: The authors declare no conflicts of interest.

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