Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers

Subjects: Others

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Solid–lipid nanoparticles and nanostructured lipid carriers are delivery systems for the delivery of drugs and other bioactives used in diagnosis, therapy, and treatment procedures. These nanocarriers may enhance the solubility and permeability of drugs, increase their bioavailability, and extend the residence time in the body, combining low toxicity with a targeted delivery. Nanostructured lipid carriers are the second generation of lipid nanoparticles differing from solid lipid nanoparticles in their composition matrix. The use of a liquid lipid together with a solid lipid in nanostructured lipid carrier allows it to load a higher amount of drug, enhance drug release properties, and increase its stability. Therefore, a direct comparison between solid lipid nanoparticles and nanostructured lipid carriers is needed.

lipid nanoparticle NLC nanocarrier nanoparticle characterization

1. Introduction

Nanomedicine aims to provide accurate diagnoses and treatments for diseases more effectively, with minimal adverse effects. Nanomedicine has gained popularity because of its efficiency in delivering drugs and other bioactives to target tissues more accurately in a controlled manner by encapsulating or attaching them to nanostructures [1][2]. These drug delivery systems involve nanocarriers that are colloidal drug carrier systems having submicron particle sizes, typically below 1000 nm. Due to their high surface area to volume ratio, nanocarriers can modify the basic properties and bioactivity of drugs. They also allow drug protection (e.g., from humidity, pH changes, and enzymes); improved pharmacokinetics and biodistribution of the drugs; either by passive or active targeting, resulting in reduced toxicities and improved therapeutic benefits [3][4][5]; enhanced bioavailability; controlled drug releasing profiles; prolonged blood circulation times; enhanced intracellular penetration; and site- and organ-specific targeted delivery.

Different types of materials have been used to produce nanoparticles, mainly polymeric, lipid, and inorganic materials. Among these, lipid nanocarriers have considerable advantages due to their biocompatibility, biodegradability, low toxicity, scale-up capacity, and delivery of both hydrophilic and lipophilic drugs in a controlled or targeted manner [6][7]. These carriers may also permeate physiological barriers, such as the blood–brain barrier and the intestinal epithelium [8]. Further, to combine the advantages of different materials, hybrid nanoparticles may also be obtained to improve the features of lipid-based nanoparticles. For example, a new approach can be

developed based on the physical modification of the lipid matrix with polymers, producing a lipid–polymeric matrix to entrap the drugs [9][10][11].

Intralipid® was the first safe lipid parental emulsion developed in the 60s [12]. In the same decade, liposomes were first described by Bangham et al., and since then, liposomes have become the traditional models for lipid-based formulations [13][14]. A spherical vesicle with an aqueous nucleus enclosed by a lipidic bilayer membrane is what defines a liposome. Since then, liposomes have been extensively studied from pharmaceutical to cosmetic applications, due to their advantages as a carrier system with the additional benefit of protection from enzymatic activity. However, further development of liposomal formulations has been hindered by its major obstacles. Some of those are the limited physical stability of the liposomal suspension, drug leakage, low targeting ability, non-specific clearance by monocytes and macrophages, and up-scaling difficulties [3][15][16][17]. Several other carrier systems of a lipidic nature were developed, such as nanopellets for perioral administration, described by Speiser and colleagues (lipidic microparticles), nanosuspensions produced by ball milling or high-pressure homogenization (HPH), lipospheres [18][19][20], and many others.

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

Lipid particles with sizes on a nanoscale possess unique physical, mechanical, chemical, and biological features, which may differ greatly from their core components in SLNs and NLCs (**Figure 1**). These nanostructures are essentially composed of lipids and surfactants and can be used to deliver therapeutic agents (by encapsulation, incorporation, or/and surface attachment) and deliver them to target tissues [2][21]. **Table 1** describes the compounds mostly used in their production. The structural key feature differences between SLNs and NLCs are represented in the following sections.

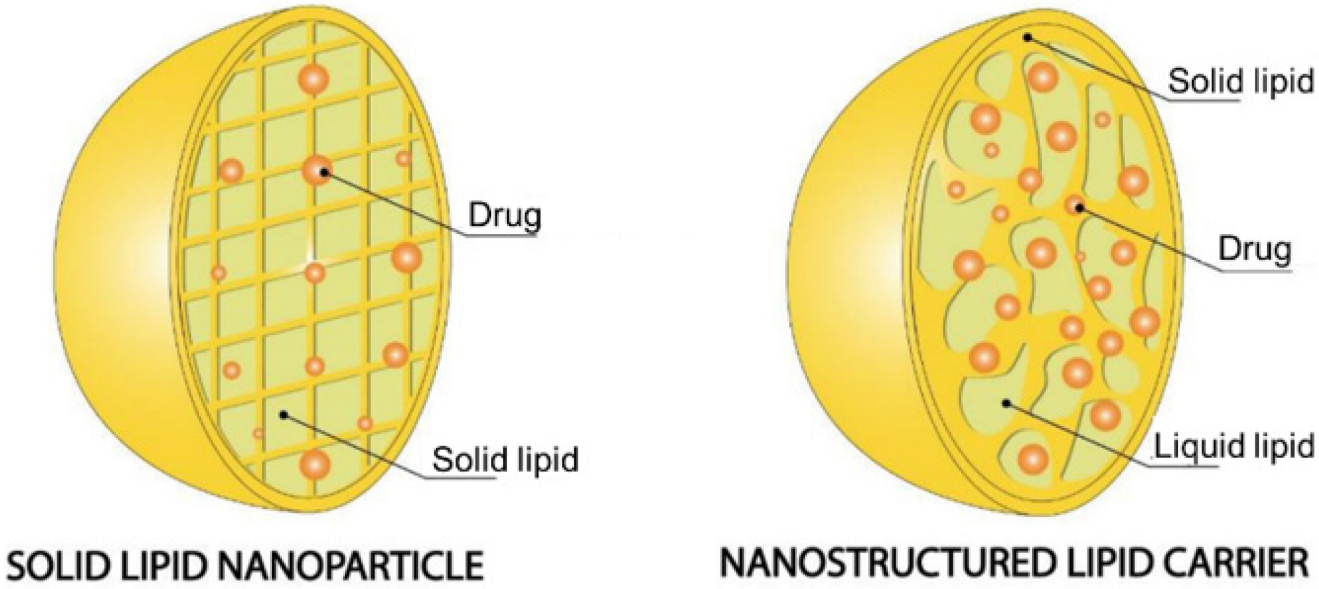

Figure 1. Structural matrix of SLN and NLC. Adapted with permission from [22].

Table 1. Chemical classification, source, and function of the compounds used to produce SLNs and NLCs.

Compound	Classification	Source	Function
1-Tetradecanol (myristyl alcohol)	Straight chain saturated fatty alcohol	*Myristica fragrans*	Solid lipid
Beeswax	Wax ester	Honey bees (*Apis mellifera*)	Solid lipid
Caprylic/capric triglyceride	Triglyceride	Coconut oil	Liquid lipid
Castor oil	Fatty acid composed	Castor beans	Liquid lipid
Cetyl palmitate	Wax ester	Stony corals, *Psidium guajava*	Solid lipid
Cholesteryl myristate	Cholesterol ester	*Trachyrhamphus serratus*	Solid lipid
Cholesterol	Modified steroid	Animal, vegetable fat	Solid lipid
Compritol® 888 ATO	Mixture of mono-, di- and triglycerides of behenic acid (C22)	-	Surfactant
1,2-dioleoyl-3-dimethylammonium propane (DODAP)	Ionizable cationic lipid	-	Solid lipid
Dipalmitoylphosphatidylcholine (DPPC)	Phospholipid	Pulmonary surfactant	Solid lipid
1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)	Amine phospholipid	*Escherichia coli*	Solid lipid
Gelucire® 50/13	Mixture of fatty acids (C16 and C18), esters of glycerol, PEG esters and free PEG	-	Surfactant
Glyceryl monostearate	Glycerol ester of a saturated fatty acid	*Aristolochia cucurbitifolia, Lobelia longisepala*	Surfactant
Labrafac™ CC	Mixture of medium chain triglycerides, mainly from caprylic (C8) and capric (C10) acids	-	Liquid lipid
Lecithin	Mixture of phospholipids in oil	Soybean, egg	Surfactant

Compound	Classification	Source	Function
Miglyol® 812 N	Glycerol triester of caprylic and capric acid (triglyceride esters)	Coconut, palm kernel oil	Liquid lipid
Myristylmyristate	Tetradecanoate ester	Coconut, palm kernel oil	Solid lipid
Oleic acid	Middle chain triglyceride	Olive oil	Liquid lipid
Palmitic acid	Saturated fatty acid	Palm oil	Solid lipid
Phosphatidylcholine	Phospholipid	Soybeans, eggs	Solid lipid
Poloxamer 407/Pluronic® F-127	Triblock copolymer	-	Surfactant
Precirol® ATO-5	Mixtures of diesters of glycerin and stearic acid	-	Solid lipid
Polyvinylalcohol (PVA)	Synthetic polymer of vinyl alcohol	-	Surfactant
Sodium lauryl sulfate (SLS)	Ethoxylated lauryl alcohol	Coconut, palm kernel oil	Surfactant
Squalene	Triterpenoid	Olive, wheat germ, and rice bran oils	Liquid lipid
Steric acid	Saturated fatty acid	Animal, vegetable fat	Solid lipid
Tricaprin	Triglyceride	Milkfat, palm kernel oil, and coconut oil	Solid lipid
Tripalmitin	Triglyceride	*Lysiphlebia japonica, Tagetes erecta*	Solid lipid
Tristearin	Triglyceride	*Lysiphlebia japonica, Sciadopitys verticillata*	Solid lipid
Tween®	Mixture of sorbitol, ethylene oxide, and oleic acid	-	Surfactant

l used for production in a patent application [23]. However, the term SLN was only used a few years later by the same group, when describing a method for loading magnetite into nanoparticles [18]. SLNs are composed of a physiological lipid that is solid at room and body temperature, a surfactant, and water [15][17][24]. The SLN lipidic phase is usually produced from steroids, di- or triglycerides, glyceride mixtures, or even waxes, typically used at 0.1 and 30% (*w*/*v*) and remaining in the solid state at room and body temperature. On the other hand, the surfactant concentration is in a range of 0.5 to 5% (*w*/*v*), in the generally recognized as a safe (GRAS) category [17][24][25][26]. A combination of surfactants can be also used to improve the stability of the SLN [27].

The structure of SLNs depends on various factors, such as the components of the formulation, the solubility of the compounds including the drug, and the production method. Three different structures of SLN are reported [15][28]. In the SLN homogeneous matrix model (Type I) (**Figure 2**), the particles are produced by a cold or hot

homogenization technique for very lipophilic drugs. In the first method, the drug is dissolved in a lipid matrix, and, due to high-pressure homogenization, mechanical breakings cause nanoparticle formation. In the second method, the lipid is dissolved in a lipid matrix while increasing the temperature and the nanoparticles are formed similarly. In the SLN drug-enriched shell model (Type II) (**Figure 2**), the particles may be produced by the hot homogenization technique. During the cooling of the system, the lipid molecules precipitate first, forming a lipid core. Meanwhile, the concentration of the drug increases in the rest of the melted lipid until its solubility limit is reached. When this point is reached, the mix of drug and melted lipid crystalizes, forming an outer shell. This model is not the best for prolonged release of the drug but can be very interesting to increase drug penetration with topical application, especially when associated with the occlusive effect of SLNs. Lastly, the SLN drug-enriched core model (Type III) (**Figure 2**) forms nanoparticles when the drug concentration is close to its solubility limit in the melted lipid. This type is the opposite of type II since the first compound to precipitate is the drug, which forms the core, and the shell is composed of the lipid and a low concentration of the drug [15][26][28][29][30][31]. **Table 2** describes several examples of studies about the development, applications, and characterization of SLNs.

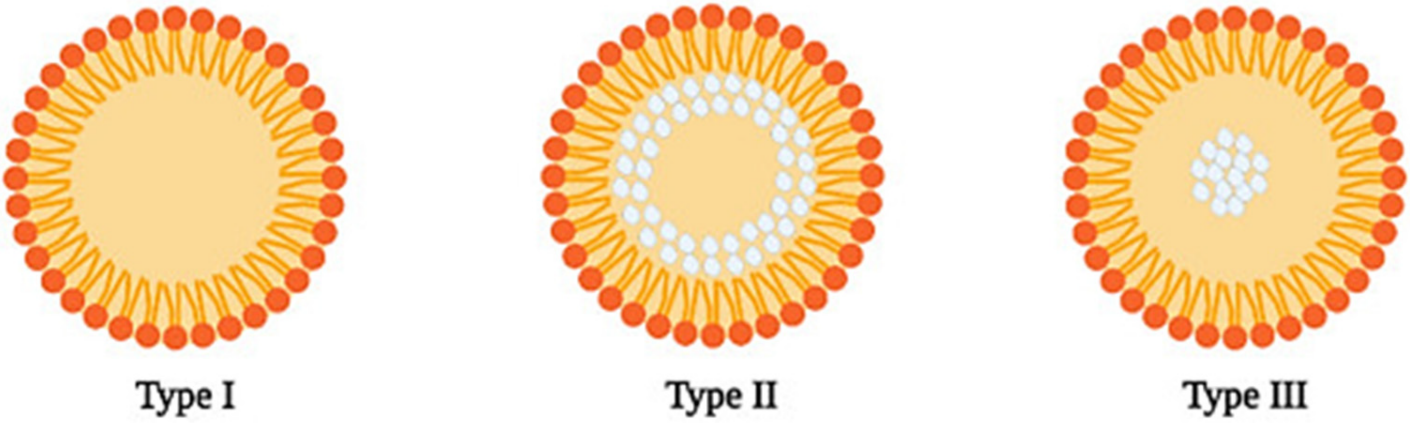

Figure 2. Structure of the 3 different types of SLN: homogenous matrix model (Type I), drug-enriched shell model (Type II), and drug-enriched core model (Type III). The drug is represented in white color. Reprinted with permission from [32].

Table 2. Examples of studies performed using SLN. The nanoparticles components and features, loaded drug, production method, and therapeutic purpose are debriefed.

Solid–Lipid	Surfactant	Drug	Production Method	Therapeutic Purpose	Delivery Route	Characteristics	Ref
Gelucire® 50/13	Tween® 85	Grapeseed-derived proanthocyanidins	Melt Emulsification Technique	Chronic Respiratory Diseases	Spray Instillation	Size: 243 ± 24 nm PdI: 0.41 Zeta: −14.5 ± 1.0 mV EE: NA	[33]
Palmitic Acid/Cholesteryl Myristate (68,5/31,5%)	Sodium Lauryl Sulfate (SLS)	Rifampicin	Melt Emulsification	Tuberculosis	NA	Size: 400 ± 20 nm	[34]

Solid–Lipid	Surfactant	Drug	Production Method	Therapeutic Purpose	Delivery Route	Characteristics	Ref
(*w*/*w*)			Technique			PdI: 0.43 ± 0.09 Zeta: −35.3 ± 0.29 mV EE: 56.48% (*w*/*w*)	
Compritol 888 ATO, cholesterol, and Tf-PEG-OA	1% Polyvinylalcohol (PVA)	Paclitaxel (PTX)	Solvent Evaporation Method	Leukemia	NA	Size: 176 nm PdI: NA Zeta: −22.5 ± 1.56 mV EE: 92.5 ± 1.35%	[35]
Tripalmitin/Hydrogenated soybean phosphatidylcholine (HSPC) (80/20%) (*w*/*w*)	Polyethylene glycol monostearate (PGM)	Apomorphine	NA	Parkinson's Disease	Oral	Size: 63.20 ± 0.98 nm PdI: 0.31 ± 0.02 Zeta: 7.3 ± 0.25 mV EE: NA	[36]
Compritol® 888 ATO	Tween® 80	Quercetin	NA	Alzheimer's Disease	Oral	Size: 0.42 to 4.62 µm PdI: NA Zeta: −23.6 to −5.13 mV EE: 85.7%	[37]
Beeswax	Tween® 80 Poloxamer 407	NA	Hot melt microemulsion	Skin Hydration	Topical	Size: 95.72 ± 9.63 nm PdI: 0.323 ± 0.03 Zeta: −9.85 ± 0.57 mV EE: NA	[38]
Stearic Acid	Poloxamer 407 Soybean Phosphatidylcholine	Resveratrol	Sonication	Anti-tumoral	Topical	Size:155.50 ± 0.26 nm PdI: 0.140 ± 0.02 Zeta: −2.60 ± 1.27 mV EE: NA	[39]
Poly Lactic-co-Glycolic Acid (PLGA)	1% polyoxyethylenepolyoxypropylene	Apigenin	Nanoprecipitation	Cosmetic	Topical	Size: 102.19 ± 0.002 nm PdI: 0.258 Zeta: 12.1 ± 0.0 mV	[40]

In addition to the advantages, SLNs also have relevant disadvantages such as possible aggregation, instability during storage, and low drug loading for some drugs [7]. For these reasons, and to overcome them, NLCs have been developed.

2.2. Nanostructured Lipid Carriers

NLCs are the second generation of lipid nanocarriers and were created in the late 90s to solve the disadvantages of SLN [15][28]. NLCs are composed of a mixture of solid and liquid lipids, in a ratio of up to 70:30, respectively, and an aqueous phase composed of a surfactant [42][43]. The lipids used in these formulations are biologically compatible, which is important to reduce toxicity [44].

Solid–Lipid	Surfactant	Drug	Production Method	Therapeutic Purpose	Delivery Route	Characteristics	Ref
		[45]				EE: 87.2 ± 0.005	
Tricaprin	Cetyl Palmitate, Tween® 60 Tego Care 450 Amphisol K, 1-Tetradecanol	Resveratrol	Hot melt homogenization	Cosmetic	Topical	Size: 102.190 ± 0.002 nm PdI: 0.258 Zeta: 12.1 ± 0.0 mV EE: 52.45%	[41]

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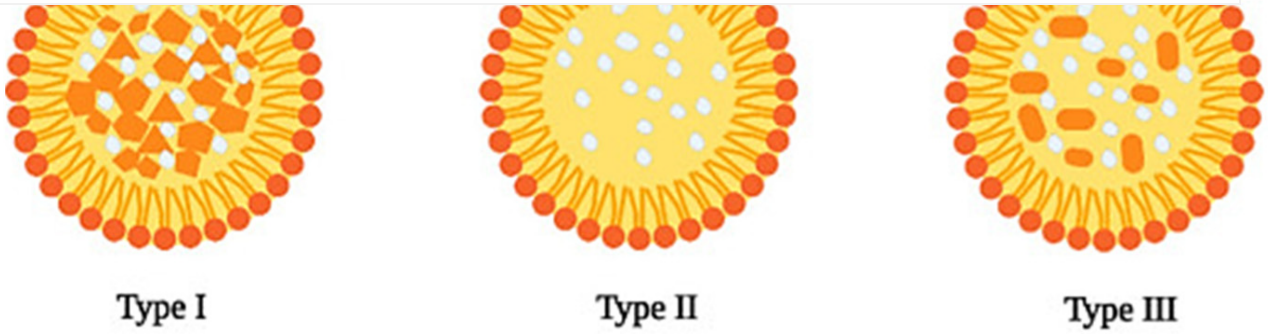

Figure 3. Structures of different types of NLC: imperfect crystal (Type I), amorphous (Type II), and multiple type (Type III). The drug is represented in white. Reprinted with permission from [32].

The imperfect crystal type (Type I) results from mixing lipids with different chain lengths or by using either mono-, di- or triglycerides. By doing so, a matrix comprising several voids and imperfections provides a more suitable environment for drug incorporation. The amorphous type (Type II) is obtained by using medium chain length triglycerides along with solid lipids. The solid lipids do not undergo recrystallization after NLC cooling, thus resulting in solid particles with an amorphous structure. By not recrystallizing during the cooling phase, and even during storage, the unwanted release of the drug is reduced, thus improving its shelf life. Multiple type NLCs (Type III) are obtained by mixing solid lipids with an oil such as an oleic acid and/or medium and long-chain triacylglycerols. To achieve a multiple type NLC, the oil must be mixed in a ratio above its solubility in the solid lipid, resulting in the formation of very small oil compartments (nanocompartments) in the NLC matrix during the cooling phase of the nanoemulsion [28][29][45]. **Table 3** summarizes several examples of studies about the development and application as well nanoparticle characterization of NLC.

Table 3. Examples of studies performed with NLC. The nanoparticles' components and features, drug loading, production method and therapeutic purpose are debriefed.

Solid Lipid	Liquid Lipid	Surfactant	Drug	Production Method	Therapeutic Purpose	Delivery Route	Characteristics	Ref
Stearic acid	Oleic acid	Soya Lecithin Glyceryl Monostearate	Docetaxel (DTX)	Modified film ultrasonication–dispersion method	Murine Malignant Melanoma	Parenteral	Size: 203.67 ± 4.15 nm PdI: NA Zeta: −31.17 ± 2.20 mV EE: 89.39 ± 0.99%	[46]

Solid Lipid	Liquid Lipid	Surfactant	Drug	Production Method	Therapeutic Purpose	Delivery Route	Characteristics	Ref
Precirol® ATO-5	Squalene	Myverol	Lovastatin	Hot melt homogenization	Cholesterol	Oral	Size: 278.8 ± 0.6 nm PdI: ≤0.25 Zeta: −32.4 ± 0.4 mV EE: 83.8 ± 2.5	[47]
Comprito® 888 ATO	Miglyol 812N	Lecithin	Vinpocetin (VIN)	High-pressure homogenization	Brain Disorders	Oral	Size: 177 ± 5.4 nm PdI: NA Zeta: −24.7 ± 1.4 mV EE: 95.3 ± 1.4	[48]
Precirol® ATO-5	Oleic Acid	Tween® 80	1-carbaldehyde-3,4-dimethoxyxanthone (LEM2)	Ultrasonication	Melanoma	Topical	Size: 219.67 ± 5.26 nm PdI: ≤0.3 Zeta: −24.88 ± 1.78 mV EE: 72%	[49]
Cetyl Palmitate	Miglyol 812N	Tween® 60	Curcumin	Modified hot homogenization	Brain Disorders	Oral/Intravenous	Size: 183 ± 12 nm PdI: 0.13 ± 0.01 Zeta: −21 ± 2 mV EE: 82 ± 15%	[50]
Glyceryl Tribehenate	Oleic acid	P 407	Raloxifene hydrochloride (RLX)	Hot homogenization	Osteoporosis	Oral	Size: 120 ± 3 nm PdI: 0.293 Zeta: 14.4 ± 0.5 mV EE: 91.71	[51]
Precirol ATO-5	Miglyol 812N	Tween® 80	Rifapentine (RPT)	Hot ultra-sonication	Tuberculosis	Oral/Pulmonary	Size: 242 ± 9 nm PdI: 0.17 ± 0.01 Zeta: −22 ± 2 mV EE:	[52]
Glycerol monostearate (GMS)	Medium chain triglyceride (MCT)	Poloxamer 188 Soybean lecithin	Amoitone B	Emulsion-evaporation and low temperature-solidification	Tumor Therapy	NA	Size: 241.2 ± 4.4 nm PDI: NA Zeta: 18.4 ± 0.2 mV	[53]

2.3. Comparison between Solid Lipid Nanoparticles and Nanostructured Lipid Carrier

SLNs have been widely studied as systems for drug delivery for several delivery routes, such as oral, parenteral, and topical delivery. Due to their structure, which can be finely tuned depending on the chemical profile of its active ingredients and excipients, one expects several advantages. However, the modified release property is dependent

Solid Lipid	Liquid Lipid	Surfactant	Drug	Production Method	Therapeutic Purpose	Delivery Route	Characteristics	Ref
							EE: 71.5 ± 1.1%	
Myristyl Myristate	Crodamolt GTCC-LQ	Pluronic F128	Metvan	Sonication	Bone Cancer	NA	Size: 230.8 ± 3.1 nm PdI: 0.235 ± 0.010 Zeta: −7.9 ± 0.8 mV EE: 77.6 ± 4.8%	[54]
Stearic acid or beeswax	Carvacrol	Kolliphor188®	Carvacrol	Warm microemulsion oil in water (*o*/*w*)	Leishmaniasis	Parenteral	Size: 98 ± 0.80 nm PdI: 0.166 ± 0.04 Zeta: −25 ± 5 mV	[55]

pressed undergo a more ation for gs to be N matrix [3][7][9][29][56]. To the use 1, which remain in the solid state at both body and room temperature, and by controlling the content of liquid lipids in the formulation, improved incorporation and immobilization of drug molecules is achieved. Whereas in SLNs, the drug molecules are dispersed in their molecular form, in NLCs the imperfections in the matrix formed by the differences between solid and liquid lipids leads to more spaces available for drugs, which improves the incorporation of drug molecules in both molecular form and amorphous clusters, also avoiding the potential expulsion of the active compound during storage [3][9][29][56][57][58]. In **Table 4** their classification by properties is shown, which highlights the comparison between SLNs and NLCs.

Table 4. Comparison between SLN and NLC. Advantages and disadvantages.

SLN	NLC	
Lipids	Use of physiological lipids; however, there is a lower stability comparatively with other materials	
Solvents	Absence of organic solvents	
Application	Application in different industries (food, cosmetic, pharmaceutical)	
Bioavailability	Improved bioavailability of drugs	
Drugs loaded	Loads both lipophilic and hydrophilic drugs; however, has difficulty in loading therapeutic proteins	
Drug delivery	Targeted drug delivery and enhanced drug permeation	
Scale-up	Cheaper and easier to scale up than polymeric nanoparticles	
Protection	Protection of drug molecules from enzymatic activity, harsh pH, and moisture	
Cytotoxicity	Cytotoxicity concerns due to the nature and concentration of matrix lipids	
Drug loading capacity	Limited drug loading capacity	Improved drug loading capacity
Controlled drug release	Difficulty in adjusting the drug release profile	Better controlled drug release

SLN	NLC	
profile		profile
Polymorphic transitions	Prone to polymorphic transitions	No polymorphic transition takes place
Release during storage	Unwanted drug release during storage	Minimal drug release during storage
Physical stability	Possible particle aggregation or fusion during storage	Better physical stability during storage
Water content	High water content	Low water content

3. Production Methods of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

There are several methodologies to produce lipid nanoparticles such as SLNs and NLCs. The most common methods are high-pressure homogenization (hot and cold), microemulsification, solvent emulsification (evaporation or diffusion), solvent injection, double emulsion, ultra-sonication or high-speed homogenization, spray drying, and microfluidics. These methods are schematized in **Figure 4** and **Figure 5** and are briefly described in the following sections.

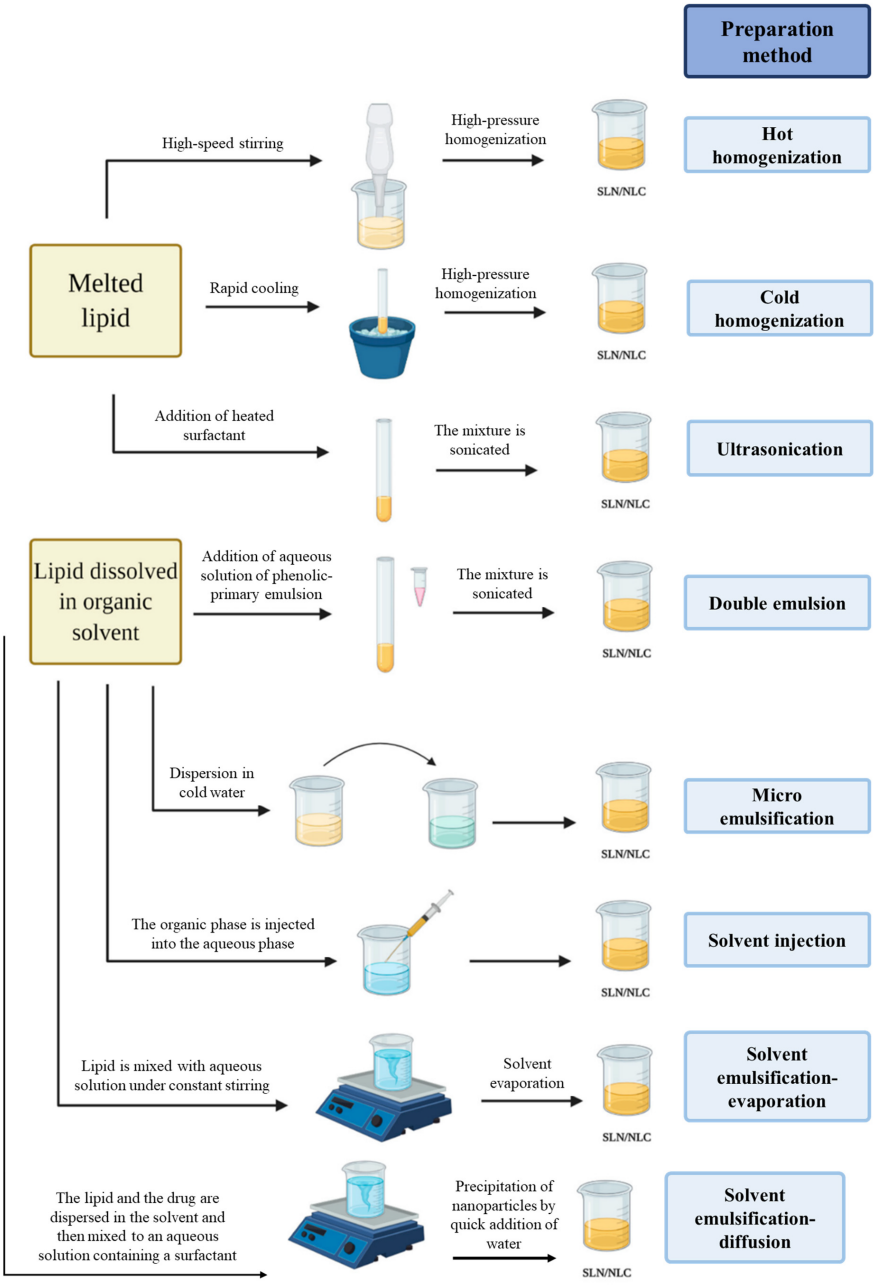

Figure 4. Production methods to obtain SLNs and NLCs. Adapted from [32].

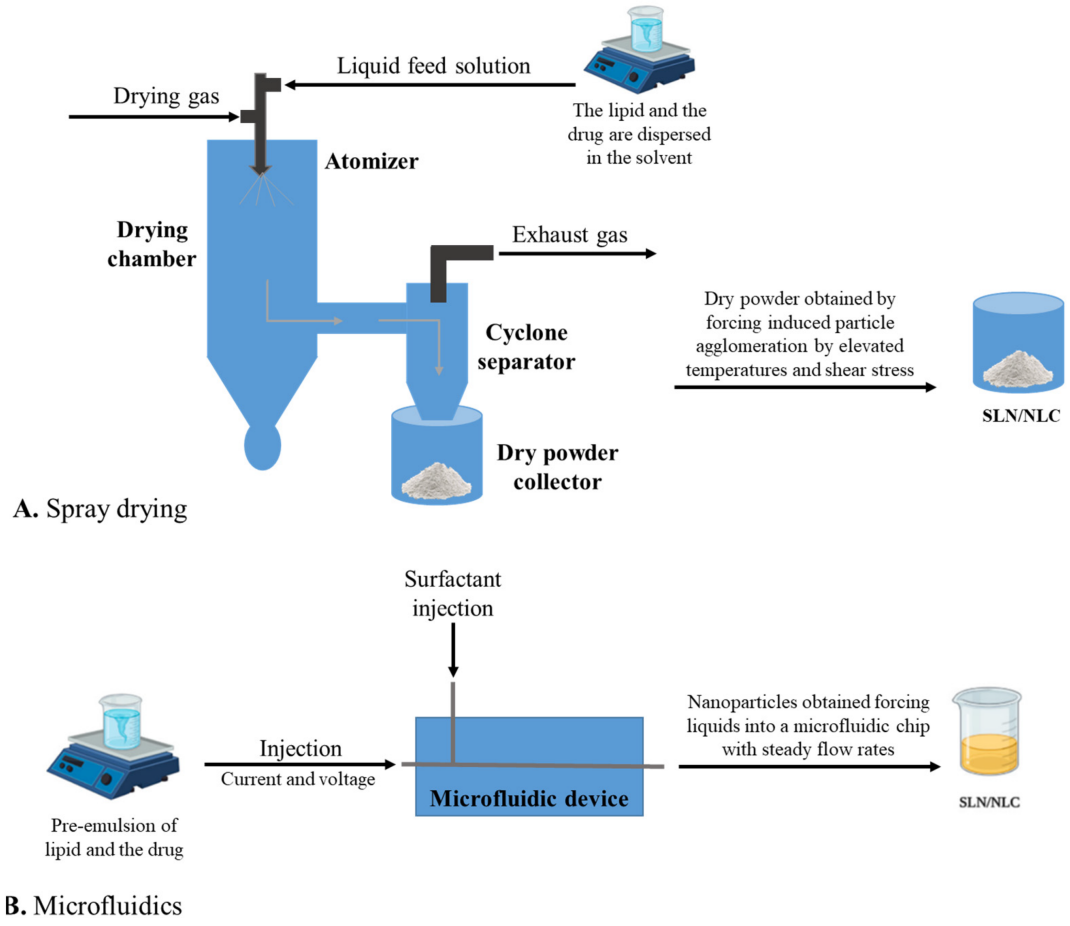

Figure 5. Spray drying (**A**) and microfluidics (**B**) methods to obtain SLN and NLC.

3.1. High-Pressure Homogenization

HPH is the most common method and consists of a potent and trustworthy technique for the preparation of SLNs and NLCs [59]. There are two types of high-pressure homogenization, hot HPH, and cold HPH. In both, the first step is to dissolve the drug in a solid lipid melted at approximately 5–10 °C above its melting point [24][60].

Hot HPH consists of adding an aqueous surfactant solution at the same temperature as the melted lipid to the drug–lipid melt. After this step, the substances are homogeneously dispersed by high-shear mixing, forming the pre-emulsion. The hot pre-emulsion is then submitted, at the same temperature, to high-pressure homogenization to reduce particle size to the nanoscale. Generally, three cycles at 500 bars are appropriate. The last step is cooling down the oil-in-water (*o*/*w*) nanoemulsion to room temperature, which leads to lipid re-crystallization, thus forming the solid matrix of the lipid nanoparticle [24][61].

The cold HPH method consists of rapidly cooling the drug–lipid melt, using either dry ice or liquid nitrogen. The rapid cooling forces the drug to be homogenously mixed within the lipid matrix. Afterward, the obtained solid is pulverized into particles within the micron range (with either a ball mill or mortar), followed by its dispersion in an aqueous surfactant solution which is already cooled down (pre-emulsion). The pre-emulsion is then subjected to

high-pressure homogenization at room or below room temperature, breaking the microparticles into nanoparticles [24][59][61].

3.2. Ultra-Sonication or High-Speed Homogenization

Ultra-sonication and high-speed homogenization are used to mix the lipid phase and the containing surfactant aqueous phase [62][63]. Nanoparticles obtained by this method usually have high polydispersity, which can be dealt with by using probe-based sonicators. Despite obtaining a less dispersed distribution, there is a risk of cross-contamination from the probe metal [64]. Even if this method has its drawbacks, high-speed homogenization, for example, becomes much more efficient, simpler, cheaper, and easier to reproduce if multiple cycles of homogenization at high velocities and high pressure (100–200 MPa) conditions are implemented.

3.3. Double Emulsion

The double emulsion method involves the preparation of a primary emulsion (*w*/*o*), which consists of dissolving a drug molecule (usually hydrophilic) in an aqueous solvent (inner aqueous phase) that is dispersed in a lipid phase containing an emulsifier, known as the oil phase. Afterward, an aqueous solution containing a hydrophilic emulsifier is added to the primary emulsion, which forms a double emulsion (*w*/*o*/*w*) after stirring. Since this method generates nanoparticles with high polydispersity, it is not recommended for delivery in some administration routes [24][65][66].

3.4. Microemulsion Method

The microemulsion method was developed by Gasco et al., and similarly to HPH, it starts by melting the solid lipid(s) at a temperature higher than its/their melting points (by 5 to 10 °C) and dissolving the drug in melted lipid(s) [67]. In the following step, an aqueous surfactant solution with a temperature above the temperature of the melted lipid is added to the drug–lipid melt with continuous stirring until a transparent microemulsion is obtained. The microemulsion formed is dispersed in cold water by gentle stirring and the microparticles are broken into nanoparticles which crystallize to form the SLN or NLC. Nanoparticles produced by this method are diluted, so at the end of the process, the preparation needs to be concentrated by ultrafiltration or lyophilization. The main disadvantage is the need for a high concentration of surfactants [61][68].

3.5. Solvent Injection

This novel approach consists of lipids being dissolved in water-miscible organic solvents pharmacologically accepted, such as ethanol, acetone, or isopropanol, followed by injection in an aqueous phase with constant mixing, causing the lipid precipitation. The dispersion is then filtered to remove excess lipid content. By adding an emulsifier to the aqueous phase, lipid droplets form at the injection site and stabilize the particle until solvent diffusion occurs [69].

3.6. Solvent Emulsification-Evaporation

In this method, the solid lipid is dissolved in an organic solvent and afterward emulsified in an aqueous solution while stirring. The organic solvent evaporates during stirring, forming nanoparticles by precipitation of the lipid in the aqueous phase. The concentration of the lipid will directly impact the size of the particles. This method is suitable for thermolabile drugs due to the absence of thermal stress. However, this method is not suitable for drugs capable of interacting with the organic solvent [61][70].

3.7. Solvent Emulsification-Diffusion

The solvent emulsification-diffusion technique uses a partially water-miscible organic solvent containing saturated water to achieve thermodynamic equilibrium, avoiding the diffusion of the solvent from the droplets into the aqueous phase. The lipid and the drug are dispersed in the solvent and then added to an aqueous solution containing a surfactant, forming an *o*/*w* emulsion. The particles are formed by adding more water, which facilitates solvent diffusion into the continuous phase and incites precipitation of the nanoparticles [71][72].

3.8. Spray Drying

Spray drying is a common method for high melting point lipids. It is also used as an alternative method to lyophilization in SLN and NLC formulations [73]. The principle behind spray drying consists of inducing particle agglomeration through elevated temperatures and shear stress, resulting in partial melting and increased kinetic energy. This leads to multiple particle collisions. Despite being more efficient than other methods, it is rarely used due to the risk of inducing particle aggregation and structural changes in the lipid core and surfactant films or even particle degradation by high temperatures [74][75][76][77][78].

3.9. Microfluidics

Microfluidics is a more recent method, which has been introduced as a novel methodology to produce nanoparticles with optimized uniformity [79][80]. By forcing liquids into a microfluidic chip at steady flow rates, the nanoliter amount of these reagents collides and rapidly mixes under precise pressure [81]. Submitting a pre-emulsion to high-pressure microfluidics and cooling it down to room temperature can minimize the particles' polydispersity, reduce production times, and avoid organic solvents. Overall, it could be a promising approach for the large-scale production of drug-loaded SLNs and NLCs [82][83].

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