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PREPARATION OF SOLID LIPID NANOPARTICLES (SLN) AND NANOSTRUCTURATED LIPID CARRIERS (NLC)

Rabia Taj[1*], Waseem Khan[2], Abdul Rauf Jamali[3], Aqsa Asim[4], Muhammad Faisal Hassan[5]

[1*]Shaheed Benazir Bhutto Women University of Peshawar, Pakistan,Email: tajrabia7@gmail.com
[2]Assistant Professor, Department of Metallurgical Engineering, NED University of Engineering and Technology, Pakistan, Email: waseemkhan@neduet.edu.pk
[3]Assistant Professor, Department of Materials Engineering, NED University of Engineering and Technology, Pakistan, Email: engrabdulrauf@neduet.edu.pk
[4]Institute of Applied Psychology, University of the Punjab Email: aqsaamin803@gmail.com
[5]Student, Department of Chemistry, Thal University Bhakkar, Pakistan,
Email: faisalhassan6868@gmail.com

***Corresponding Author:** Rabia Taj
*Shaheed Benazir Bhutto Women University of Peshawar, Pakistan,Email: tajrabia7@gmail.com

ABSTRACT:
The dispersion of an oil phase that contains solid and liquid lipids into an aqueous phase that contains high concentrations of surfactants and co-surfactants results in the production of solid lipid nanoparticles (SLN) and nanostructurated lipid carriers (NLC). To produce nanoparticles that are stable, it is necessary to perform a homogenization process that involves a large amount of energy and to create a surfactant shell that provides protection over the surface of the lipid particles. The purpose of this review is to provide an overview of the various production methods for SLN and NLC. There is a discussion of the operation circumstances as well as the effect of the process variables, which takes into account the lyophilization and sterilization procedures. There is also discussion on whether or not these processes are suitable for production on a large scale.

INTRODUCTION:

A number of different approaches have been utilized in order to successfully incorporate lipophilic drugs that have a low solubility in physiological fluids into various pharmaceutical formulations (Müller et al., 2002). These approaches include the reduction of particle size, the dissolution of the active ingredients in water-solvent mixtures and subsequent emulsification at high pressure, the precipitation of the drug with a non-solvent, and the preparation of oil-in-water microemulsions. These microemulsions have been utilized in parenteral nutrition, and they have been administered transdermally, ocularly, and orally (Fang et al., 2008).

In recent years, solid lipid nanoparticles, also known as SLN, have been developed as an alternate method of administering medications that are lipophilic (Andonova & Peneva, 2017). They are colloidal systems that contain a high amount of water (70-95%), are mostly composed of solid physiological lipids that have a tendency to gel and eject the medication while it is being stored, have a limited loading capacity, are biodegradable, and have a good tolerance1. In order to enhance the characteristics and stability of SLNs, liquid lipids, in which the medicine is typically more soluble, have been incorporated into the formulation. This has resulted in the development of new nanoparticle systems that are referred to as nanostructured lipid carriers (NLCs) (Naseri et al.,

2015). With the advantages of liposomes and microemulsions, SLNs and NLCs are more effective for controlled release. They also have the advantages of liposomes (Saupe et al., 2005). Their composition is comprised of matrices that are produced by a solidified lipid that exhibits particular crystalline patterns (Garcês et al., 2018). These matrices may include nanocompartments that contain the liquid lipid. The size of these particles ranges from fifty to one thousand nanometers, and they are stabilized in aqueous suspension by relatively high quantities of hydrophilic polymers or surfactants. Both of these types of lipid nanoparticles (NL) have the physical integrity of solid particles in a certain manner, and they maintain the chemical and physical stability of the components that make them up (Garcês et al., 2018).

The processes for obtaining and scaling SLNs and NLCs have been developed and optimized by a large number of researchers (Müller et al., 2016). These processes combine elements of the various techniques that have been reported, such as high-pressure homogenization, microemulsification with high-speed stirring or ultrasound, emulsification by evaporation or solvent diffusion, double emulsification (w/o/w), and high-speed nanospheronization (Thatipamula et al., 2011). The combination of multiple different mechanisms for partitioning between the lipid phases that make up these lipid carriers, the surfactant, and the aqueous media that surrounds them is what causes the release of a lipophilic chemical from these lipid carriers (Üner et al., 2005). In this study, some of the methods that have been published in recent years for the manufacture of SLN and NLC are described. Additionally, an analysis of the effect that the variables of the manufacturing and scaling process have on the features of the nanoparticles is performed.

In further work, an investigation of the impact of the constituents of the formulation will be carried out (Üner et al., 2005).

CONSIDERATIONS OF A GENERAL NATURE WITH REGARD TO THE MANUFACTURE OF SLN AND NLC

In addition to the nature of the lipid matrix, the mixture of surfactants, the viscosity of the lipid phase and the aqueous phase at the time of emulsification, and the production parameters, primarily the homogenization conditions and temperature, are the primary factors that determine the primary characteristics of SLNs and NLCs. These characteristics include particle size, degree of size dispersion, zeta potential, loading efficiency, and release kinetics (Aditya et al., 2014).

The preparation of the oil phase, which can be accomplished by melting or dissolving the lipids, is the first step in the techniques that are used to prepare SLN and NLC. It is recommended that differential scanning calorimetry (DSC) be used to analyze the selected lipids. This is done with the intention of gaining an understanding of the potential decrease in melting point that the lipids may experience in the mixture, as well as the polymorphic transformations that the lipid matrix may exhibit depending on its capacity charge and the crystalline nature of the active substance that is incorporated (Shidhaye et al., 2008).

When choosing the lipids that will make up the LN matrix, it is important to take into account their capacity to dissolve the drug that makes up the load. This should be done in such a way that the drug has the highest partition coefficient possible (Weber et al., 2014). It is possible that the concentration of the medication in the matrix will have a substantial impact on the size and structure of the particles. This is because the drug will be dispersed or dissolved in the oil phase. In order to achieve the desired increase in loading capacity of the NL, it is necessary to accommodate the drug inside the flaws of the matrix (López-García & Ganem-Rondero, 2015). In order to accomplish this, the lipid must solidify with a poorly ordered crystalline packing and present significant intermolecular distances (Ganesan & Narayanasamy, 2017). Through the use of various kinds of fatty acids or through the incorporation of a different chemical entity, such as an oil5, this circumstance is favored. In the event that the lipid crystallizes prior to the drug during the cooling stage of the process of producing the NL, a phase separation may take place. This would result in the formation of a core that is coated with the drug, which would result in an intense initial release once the LNs have been created (Yoon et al., 2013). The dissolving media contains NL that are suspended in it. This occurrence might be the result of utilizing a high concentration of

surfactants in conjunction with a temperature that is considerably higher than normal. The second stage of the process involves the creation of the aqueous phase, which is typically a solution that contains a high concentration of surfactants and is mixed with co-emulsifiers or polymers that stabilize the mixture (Yoon et al., 2013).

Because they are adsorbed on the surface of fat droplets, surfactants have a significant influence on the quality of NL. This is because they create a steric barrier between the droplets, which in turn gives stability. Out of the several types of surfactants and co-surfactants, there are a few that are capable of being combined with the lipid solution. In every instance, the kind of it and the concentration of it must be determined (Sakellari et al., 2021).

In most cases, surfactant combinations have a synergistic impact, which results in the creation of an interfacial layer that has a high coating capacity and a viscosity that is sufficient to limit the amount of particle aggregation that occurs during production and storage (Tiwari & Pathak, 2011). By increasing the steric effects and rigidity of the exterior layer, as well as by altering the surface charge of the particles, the incorporation of co-emulsifiers, such as sodium glycolate, results in an improvement in the physical stability of the particles.8. The production of a pre-emulsion is the third step in the process of preparing NL (López et al., 2023). This step involves combining both phases in a cold or hot environment with vigorous stirring or ultrasound with equal force. As a result of the need for sufficient energy, high-speed or pressure homogenization must be maintained for a number of cycles in order to facilitate the breakdown of lipid droplets into nanometric particles. The final step involves the concentration of the aqueous dispersion of NL using techniques such as evaporation, centrifugation, ultrafiltration, drying, or lyophilization. This makes the handling and administration of the substance much simpler (HUANG et al., 2008).

METHODOLOGIES FOR THE PREPARATION OF SLNS AND NLCS

The method of homogenization using high pressure As a result of its ability to be carried out at high temperatures or at room temperature, as well as its ability to be quickly scaled up to production level, the high pressure homogenization process is the one that is utilized the most frequently to achieve NL. Through the application of substantial quantities of energy, this technique is able to generate high shear force, turbulence, and cavitation in the oily material. It is also capable of processing dispersions that contain up to forty percent lipids, which results in the formation of nanoparticles that have a low polydispersity index (PI). It is generally accepted that elevating the temperature, increasing the pressure, and/or increasing the number of homogenization cycles will result in the creation of fine particles. It is possible for particles to coalesce when subjected to extremely high pressures.

The cold approach really involves grinding a suspension of solid particles by applying high pressure, whereas the hot high-pressure homogenization method can be thought of as an emulsification for the purpose of homogenization. When heat homogenization is used, the majority of the SLNs that are produced are less than 500 nm and have a low percentage of microparticles. The method of cold homogenization reduces the amount of temperature exposure. However, it does not fully eliminate temperature exposure because lipid fusion is required. Generally speaking, dispersions that are obtained cold yield particles that are larger in size and distribution than those that are obtained hot. This results in less issues during the process of drug encapsulation and crystallization during processing.

The most significant drawback of the hot approach is that it has the potential to accelerate the rate of degradation of the active substances and/or the carrier lipids, in addition to causing conformational changes in the proteins. Because of the substantial size of the particles and the existence of a substantial quantity of surfactants, the lipids may, in certain instances, continue to exist as a supercooled melt for a period of several months. This would have an impact on the release of the medication. The likelihood of this happening is increased when the matrix is constructed using hard fats of complex glycerides that do not recrystallize when the temperature is at room temperature. The typical hot high-pressure homogenization method involves heating the lipid-drug mixture to a

temperature that is 5 to 10 degrees Celsius higher than the melting point of the lipid. After that, the mixture is added to an aqueous solution of surfactant that is kept at the same temperature. This is done using high-speed mechanical stirring or ultrasonic. In most cases, it is advisable to eliminate any crystalline nucleus that may be present in the oily raw material by subjecting it to extended heating prior to the addition of the medicine. This will result in the formation of an entirely distinct solid mass during the cooling process. After being acquired in this manner, the pre-emulsion is next subjected to a high-pressure homogenizer (300-500 bar) for three to five cycles while the temperature is maintained under control. After the nanoemulsion has been allowed to reach room temperature, it will crystallize into either SLN or NLC, depending on the formulation that was administered. the amount of lipid present in the SLN particles that are loaded with tamoxifen citrate High-pressure homogenization is typically accomplished by employing a lipid phase that accounts for ten percent of the total formulation. This lipid phase includes glyceryl behenate that has been melted at 85 degrees Celsius, tri- and monoglycerides of C12-14 fatty acids that have been melted at 65 degrees Celsius, and the addition of up to fifty percent liquid capric–caprylic triglycerides.13. Dispersing the melt with a stirrer at 8,000 revolutions per minute for thirty seconds, the melt is combined with an aqueous solution that contains 2.5% Poloxamer 188, which is kept at the same temperature. Hot homogenization of the premix is performed at a pressure of 500 bar for three cycles, and then the premix is cooled to 22 degrees Celsius. When there is oil present, the particles become smaller and have a somewhat lower internal pressure.

When homogenization is performed, the particle size is determined by the pressure as well as the number of cycles that are performed. It is possible to observe the change in size of the SLN that was generated from various lipids using 3% sodium taurocholate as an emulsifier. This change in size is dependent on the homogenization pressure, with the SLN reaching its smallest size after three cycles at 15,000 psi. More severe conditions lead to an increase in particle size as a result of coalescence, which is brought about by the increased amount of kinetic energy that is utilized. It is possible to observe the impact of the total number of homogenization cycles by looking at Table 1. Because of the manner in which it solidifies within the SLN matrix, the kind of lipid does not usually have a significant impact on the particle size; nevertheless, it does have an impact on the loading efficiency of the drug. Crystallization of glyceryl behenate, which is a mixture of mono- and diglycerides, occurs with an incomplete structure. This structure has the effect of facilitating the solubilization of the active ingredient and enhancing the capacity for encapsulation."14" The cold pressure homogenization technique is an appropriate choice for encapsulating pharmaceuticals that are either thermolabile or hydrophilic. It involves melting the combination of lipid components and dispersing it at a high speed until it forms microparticles. These microparticles are then mixed with a cold aqueous solution of surfactant, and the mixture is homogenized at room temperature (or lower), typically at 500 bar for five cycles.

The use of solutions of inverted solid micelles (SRMS), in which the lipids remain (at least in part) in a solid state as inverted micelles, with a solubilization potential that can reach up to 6.5%, in order to minimize the diffusion that the drug might present towards the aqueous phase during the cold process, is one method that could be utilized. The process is effective in the sustained release of a variety of medications; however, it does have certain limitations when it comes to compounds that are hydrophilic.a 15 The manufacturing procedure of SRMS is comprised of two stages: a) the synthesis of a mixture of lecithin and triglycerides (1:1 w/w) at a temperature of sixty degrees Celsius, stirring without heating, until the micelles in which the medicine dissolves are generated; and b) the grinding of SRMS.

Table 1. Effect of the number of cycles of homogenization and lipid type in SLN size (mm)

Number of cycles	Tristearin	Tripalmitin	Behenato glyceryl
1	1.6	1.8	0.9
2	0.8	0.7	0.5
3	0.2	0.3	0.4
4	0.3	0.4	0.5

in an environment of liquid nitrogen, loading, dispersing the frozen fat in a polysorbate 80 solution at 13,000 revolutions per minute for fifteen to twenty minutes, and homogenizing the thick suspension for two cycles without pressure, followed by twenty to thirty cycles at a pressure of one thousand bar15. The dispersion that was developed has a particle size ranging from 60 to 130 nanometers, an initial particle size (IP) of 0.3, and a loading efficiency that ranges from 37 percent to 99 percent, depending on the lipophilicity of the medication.

Through the use of the cold high-pressure homogenization technique, vaccines have been manufactured by integrating protein antigens into SLN16. One of the factors that contributes to the low loading capacity of proteins in SLNs is their high water partition coefficient. This is a problem that can be resolved by employing surfactants that have the ability to stabilize emulsions. SLNs are able to keep the protein that has not been destroyed, as demonstrated by the inclusion of lysozyme as the type protein. The procedure is carried out by dissolving the protein in an aqueous solution of Poloxamer 182 (at the critical micellar concentration) at room temperature. After that, the protein is incorporated into the mixture of molten lipids that is maintained at a temperature below 50 degrees Celsius on purpose to prevent degradation. After being crushed in the presence of liquid nitrogen, the loaded lipid phase is next dispersed at a high speed in an aqueous solution of surfactant. This process is repeated three times at a temperature of 25 degrees Celsius and a pressure of 1000 bars.16 The diffusion of lipid solutions is accomplished through emulsification, evaporation, and the emulsification method.

The inclusion of thermolabile pharmaceuticals into LNs is made possible through the emulsification of lipids that have been dissolved in organic solvents in the past. This process is carried out in a single stage, without the need for any specialized equipment, and under conditions of mild temperature. This method has a number of drawbacks, the most significant of which are the following: the potential for the retention of solvent residues (up to 100 ppm), the production of very dilute dispersions as a result of the limited solubility of the lipid in the organic material (generally 0.1g/L), and the difficulty in recovering solvents during the scaling process.

When using lipid emulsification techniques from their solutions, it is necessary to guarantee that the initial thermodynamic equilibrium is maintained in both phases. This is accomplished by ensuring that the solvent is saturated with water and that water is saturated with the solvent. The lipid components and the medication are dissolved in a water-immiscible solvent that has been previously saturated (for example, chloroform or toluene), and then the solvent is emulsified at high temperatures with a solution of surfactant that is dissolved in the saturated water. This process is known as the emulsification-evaporation method. After that, the solvent is evaporated under reduced pressure, which causes the lipid to precipitate and results in the creation of practically clear suspensions that include SLN with a thickness of close to 100 nm and a dispersion range that is quite limited. The amount of load and the kind of emulsifier that is utilized will determine whether or not smaller particles (up to 30 nm) are obtained. As a result of the creation of extremely small particles, which present a significant increase in the surface area and/or a decrease in the zeta potential, the flocculation of these particles may be facilitated during the storage process. When using the injection-diffusion method, it is recommended to make use of solvents that have a high miscibility in water. Some examples of such solvents include benzyl alcohol and butyl lactate, which have a miscibility of 3.8% and 7.7%, respectively. Additionally, the use of ethyl formate or methyl-ethyl ketone has been documented. As a result of the amphiphilicity of the solvent that was utilized in the process of preparing NL, the diffusion of the NL is facilitated in a smaller volume of aqueous medium. Additionally, the solubilization capacity of the typically utilized lipids is restricted (Table 2), which results in the rapid precipitation of the droplets and acquisition of suspensions. Something is more focused. In most cases, they also cause changes in the conformation of the chains of the macromolecules that make up the emulsifiers. This influences the way in which the emulsifiers interact with the interface, which in turn modifies the stabilizing layer and the zeta potential of the particles.

In the process of high-pressure homogenization, the rate of nucleation and diffusion of the solvent is increased. On the other hand, the precipitation of larger particles is achieved by the utilization of

magnetic stirring, which is less violent. When the stirring speed is increased, the dispersion rate of the solvent is increased, which may result in a reduction in the particle size. Similarly, when the volume of the solvent is increased, the structure of the droplets may be altered, which may result in an increase in the particle size. The incorporation of an excessive amount of aqueous phase has the effect of accelerating the diffusion of the solvent towards the continuous phase, which in turn favors the precipitation of the NL.

TABLE 2. SOLUBILITY OF GLYCERYL MONOSTEARATE IN BUTYL LACTATE AND IN BENZYL ALCOHOL AT DIFFERENT TEMPERATURES

Temperature (ºC)	**Solubility (mg/mL)**	
	butyl lactate	**Benzyl alcohol**
40	54	46
45	102	1370
50	1450	1920
55	2025	2830

Encapsulation using the injection-diffusion approach is just as effective as encapsulation through the emulsification-evaporation technique, despite the fact that the particles exhibit minor variations. As a result of their low diffusion capacity during the process of solvent evaporation7,18, the load increases with medications that have a low solubility in water but a high solubility in the organic solvent. Due to the rise in zeta potential, the emulsification of Lipoid S100 (in methylene chloride) with an aqueous solution of saccharide esters of fatty acids, which is accomplished using the emulsification-evaporation process that makes use of ultrasound, results in the production of SLNs that are both smaller and more stable. The injection of Lipoid S100 that has been dissolved in acetone into the aqueous solution of the surfactant (using a tiny jet with a needle measuring 0.45 millimeters) likewise results in the formation of monomodal spherical particles, but these particles are bigger in size and have a lower zeta potential. The addition of filler (paclitaxel) does not change the size of the nanoparticles created through evaporation; however, it does change the IP of the nanoparticles. In contrast, the size of the nanoparticles grown through the injection process can rise by up to three times. The approach does not have any impact on the lipid crystal structure that is included within SLNs. The efficiency of the encapsulation process is often improved when the solvent diffusion process is carried out at low temperatures, which range from 0 to 25 degrees Celsius. The quick precipitation of the lipid in the form of droplets, which occurs before the particles can coalesce, is beneficial to the deposition of the drug at the interface between the lipid and the water, and it lowers the amount of drug that escapes into the aqueous phase. The encapsulation of peptides using this method provides a number of extra challenges. This is due to the fact that the majority of peptides contain a significant hydrophobic component that makes it easier for them to adhere to the walls of the apparatus. Both the formulation and the parameters of the process will have an impact on the amount of peptide that is incorporated into the SLN. Due to the quick diffusion of the solvent, the influence of temperature on the particle size is not sufficient to be considered relevant.

Because hydrophilic polymers are quickly absorbed by the surface of the droplets that are generated during the diffusion of the solvent, the presence of hydrophilic polymers in the aqueous phase induces the spontaneous production of particles that are smaller than one millimeter. When the aqueous medium is acidic, polyvinyl alcohol (PVA) causes the SLN to aggregate. This is due to the fact that the zeta potential of the system is close to zero, which makes it easier to separate the particles using centrifugation. In the absence of acidification of the medium, neither the coacervation nor the precipitation of the lipid will take place. The parameters under which NL dispersions are prepared and applied are determined by the effect that pH has on the stability of NL. It is possible that the particle size could increase up to a certain limit value from the concentration of the aqueous phase. It is the amount of charge that is present in the lipid droplets that determines the size of the NL when the concentration is low, but when the concentration is large, the size of the NL

will be dictated by the mass of the droplets. It is possible that the presence of co-surfactants in the water, such as Pluronic F68, could reduce the impact of this effect. This is because co-surfactants improve the thermodynamic stability of the SLN20. The viscosity of the external aqueous phase, on the other hand, has the potential to alter the diffusion kinetics of the solvent as well as the hydrodynamic size of the particles.

One of the advantages of using the solvent emulsification-diffusion process is that it makes it easier to generate LN dispersions that are suitable for IV administration. A semi-transparent product with particles smaller than 100 nm, with low IP, zeta potential of -31.6 mV, high charge capacity (4.6%), and a trapping efficiency of 87.7% can be obtained by slowly injecting a solution of stearic acid into acetone and soy lecithin in ethanol, within an aqueous phase containing poloxamer 188 and glycerin, and then evaporating the mixture under vacuum. This process can be repeated until the desired results are achieved.

THE TECHNIQUE OF MICROEMULSIFICATION

When SLN is prepared using the microemulsification method, it is possible to obtain particles that are thermodynamically stable, optically isotropic, and have a size that can be regulated at the moment of emulsification. With a low amount of energy usage and the ability to readily scale up without the need for specialist equipment, the process will be successful. Because of the high quantities of surfactants and cosurfactants that are present in the nanoemulsions that are generated using this approach, the usage of these nanoemulsions in human beings is subject to health laws.

The crystallization of lipid droplets within the aqueous medium is what allows for the synthesis of SLN through the process of microemulsification. The size of the particles will mostly be determined by the type of surfactants and co-surfactants, as well as the conditions under which the experiment is conducted. When it comes to optimizing the process, the first step is to conduct solubility tests of the medication in lipids and solubilizers. These studies are performed with pseudoternary phase diagrams, which enable the selection of components for a stable microemulsion. This microemulsion is one that can withstand cooling-heating cycles ranging from -4 degrees Celsius to 40 degrees Celsius. Twenty-four hours for a week. Procedures that have a high loading efficiency, NL with an average size of less than 200 nm, and an IP of less than 0.6 are the types of procedures that are produced by this selection mechanism.

The formation of NL with bimodal profiles often occurs when the conditions of microemulsification are particularly severe. The formation of structures in which the liquid lipid forms nanocompartments within the solid matrix is typically the consequence of ultrasonic stirring. These structures have the ability to increase the loading capacity of the particles. The rate of development of the medication will be determined by its affinity for the oil.

Table 3. Comparison of the characteristics of the SLNs obtained by microemulsification and precipitation

	Size (nm)	IP	Zeta potential (mV)	Burden (%)
Microemulsification at 70°C	118	0.16	-39.6	30.8
Precipitation from ethanol	69	0.12	-44.8	28.3

in accordance with the partition coefficient that exists between the nanocompartments and the solid lipid as well as between the solid lipid and the aqueous medium releases. 10% melted solid lipid, 15% surfactant, and 10% co-surfactant are the components that are typically used to create a microemulsion that is used to obtain SLN. To accomplish the creation of lipid droplets and subsequent precipitation, the warm oil phase is added to an excess of cold water (1:50) using a slow flow or by injection with a heat-sealed syringe. The mixture is then dispersed using high agitation or ultrasound until the desired results are reached. Both ultrafiltration and lyophilization are utilized in order to remove excess water. Glyceryl behenate and capric-caprylic triglycerides are used in the manufacturing of certain NLCs. These triglycerides are combined with an aqueous solution of Lutrol F68 that contains 1.35 percent and is stirred at a speed of 8,000 revolutions per minute for

one minute. In order to prevent recrystallization, the pre-emulsion that was created needs to be ultrasonicated until it is completely homogenized. This should be done while keeping the temperature at 5 degrees Celsius above the melting point of the lipids.

Microemulsification and precipitation are two methods that are commonly used to prepare SLN dispersions. These dispersions produce particles that have comparable physical features. These particles can be sterilized through filtration using a 0.2 µm membrane and purified through dialysis. Microemulsification at 70 degrees Celsius (with Epikuron and sodium taurocholate, emulsifier and co-surfactant respectively) and precipitation of the ethanolic solution are the two methods that were used to manufacture the SLN that contains tamoxifen. The features of this SLN are presented in Table 3.

The encapsulation percentage of some peptides in SLN obtained from o/w microemulsions can be increased up to three times compared to that obtained in a w/o/w microemulsion, if its lipophilicity is increased by the formation of an ion pair. of the polypeptide with an anionic ion (sodium taurodeoxycholate-sodium hexadecyl phosphate, 4:1). Both techniques result in drug release characteristics that are comparable to one another.a 24 It is also possible to encapsulate other types of low lipophilic components through the process of microemulsification, provided that these components have been rendered more lipophilic through the addition of a protective colloid. The colloid would be dissolved in the medium that was used for dispersing, and it would be heavily adsorbed on the surface of the phase that was being dispersed25.

There are two stages involved in the process of encapsulating magnetite, which is a biological marker that is formed by ferrous-ferric hydroxides. The first stage involves the formation of an o/w emulsion, which is composed of ethyl oleate and soy lecithin at a temperature of 60 degrees Celsius in an aqueous solution of Tween 80. After this, a lipophilic suspension of magnetite in oleic acid is added to the oleic acid. The second stage involves dispersing the o/w emulsion in five parts of water at a temperature of seven degrees Celsius. This process results in the precipitation of nanoparticles with a size of less than sixty-two nanometers, which are then cleaned using ultrafiltration and lyophilized.

A method of emulsification that makes use of contact membrane Recently, contact membranes (Figure 1) have been utilized in the process of SLN preparation. This is due to the fact that they are simple to employ, make it possible to control the particle size through the selection of production parameters, and facilitate the process of scaling up with ease26. They are made of ceramic and typically measure forty centimeters in length, with an external diameter of one centimeter and an internal diameter of six centimeters. They have a surface area of seven and a half times ten to the power of three square meters with pores that range from one to forty-five millimeters in size. A ZrO_2 active layer is positioned on top of an Al_2O_3-TiO_2 support in these structures. Through the pores, the oil phase that is held within a pressurized container that is surrounded by a nitrogen atmosphere and is maintained at a temperature that is determined to be higher than the melting point is transferred to the membrane module. It is at one end that the aqueous phase is fed, and it is also at a temperature that is controlled. The aqueous phase flows tangentially within, making contact with the lipids and releasing the little droplets. A stirring motion brings the flow that is leaving the system down to room temperature. It is possible to renew the membrane till it comes back to having a permeability that is greater than 80 percent before it may be used again.

As can be seen in table 4, the elements that have the most influence on the size of the SLN that is formed in the contact membranes are as follows: a) the quantity of the lipid phase, which, when increased, causes the pores to become saturated, resulting in a decrease in flow and an increase in particle size; and b) the temperature of both phases. An increase in pressure leads to a rise in the productivity of the process, which has the potential to be useful in industrial applications. A higher speed in the aqueous phase only helps to facilitate the detachment of the droplets and the homogeneity of the dispersion. As far as the pores of the membrane are concerned, when they are larger, they enhance the flux, but they do not have an effect on the size because the surface tension is the primary factor.

Figure 1. Schematic representation of the contact membrane for the preparation of SLN

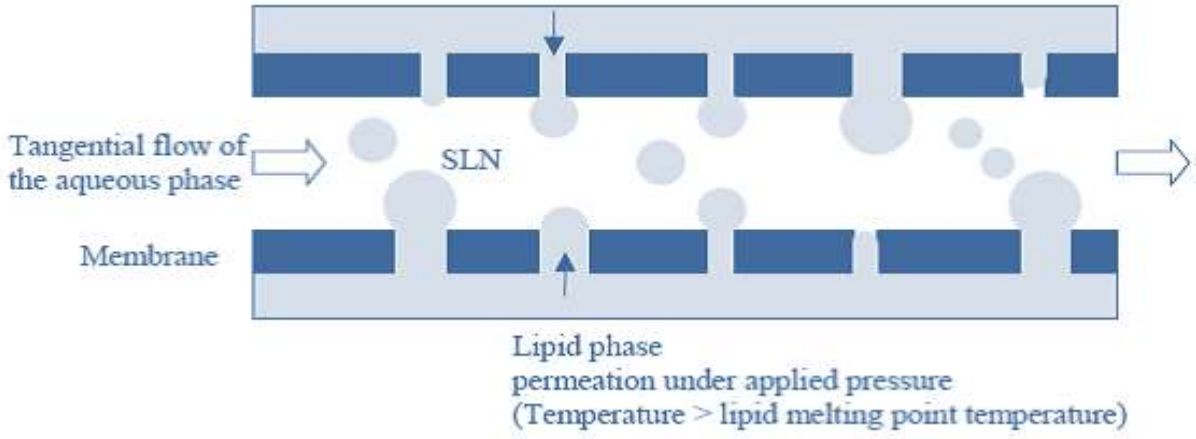


Table 4. Effect of temperature on phase flow lipid content and the size of SLN obtained by the contact membrane process

F.L (ºC)	F.L. Flow (m3/h.m2)	Size (nm)	Observations
55	0.19	200	This factor impacts the viscosity of molten lipids. A greater flow decreases process time.
65	0.21	175	
78	0.28	100	
F. A. (ºC)	0.20	190	The drops solidify instantly when the aqueous F. has a temperature below the p.f. of fats. If it is higher, it heats the lipid, decreasing its viscosity and making smaller droplets.
50	0.22	170	
60	0.25	125	
70			

COMPARATIVE ANALYSIS OF THE VARIABLES INVOLVED IN THE PREPARATION PROCESSES FOR SLN AND NLC:

The variables that interact in the various phases of the procedure of acquiring SLN and NLC and that affect their final features should be brought to light and analyzed. It is essential to ensure that these variables are properly identified and analyzed. These are the primary variables:

• Pressure and the number of cycles are important factors in homogenization and emulsification. Various types of stirring, include mechanical and sonication speeds Different ways that surfactants can be added The temperature This refers to the nature of the solvent used in the emulsification process. How the aqueous phase behaves in nature The presence of polymers that are hydrophilic Temperature of the phase Shock and awe

•The concentration and purification of the dispersion through the use of ultrafiltration, centrifugation, and/or drying:

The rate of temperature The type of membrane

•The use of cryoprotectants throughout the freeze drying process At a temperature of freezing Both the pace and temperature of sublimation When homogenization and emulsification conditions are present, the effect There is no overarching guidelines to follow when choosing the sort of homogenization to use. The ability of the apparatus to break up the mixture is determined by the shear force and cavitation that it generates. Equipment that operates with horizontal flow may experience floating of the material and frequent blocking of the valve, but equipment that operates with vertical flow does not experience one of these characteristics.

The homogenization pressure and the number of cycles both have a considerable impact on the characteristics of the SLN. This impact is exceptionally significant. As the pressure increases and the number of cycles increases, the particle size decreases significantly, which results in the formation of suspensions that are almost completely transparent and have the ability to easily

flocculate and precipitate during storage10. Operating parameters for the hot homogenization process typically range from 5,000 to 20,000 pounds per square inch and consist of 1-4 cycles. The best conditions are determined by the level of the other factors involved in the process. It is possible to obtain particles with a size range of 180-330 nm when the pressure is 6,000 psi and there are five cycles. Because of the different temperatures that exist at the nanoscale, the number of homogenization cycles could result in the formation of different types of NL. This could be due to the fact that the nanoscale temperature could either favor or not favor the solidification of the lipid in a particular crystalline structure and/or the formation of intermolecular spaces with nanocompartments of oil. This could result in the drug being expelled while it is being stored. The homogenization technique known as sonication is a straightforward approach that is frequently utilized in the process of preparing liposomes, nanoparticles, and SLN. However, it is not very efficient when it comes to decreasing huge particles, but it is quite successful when it comes to lowering the size of particles in tiny batches. Utilization of this substance for an extended period of time raises the probability of degradation (of the lipid or medication) as well as contamination with titanium from the probe28. When it comes to the preparation of NL, this particular method of homogenization is not always successful since, when it is carried out at high temperatures, it encourages the particles to agglomerate. Ibuprofen microemulsions that have been manufactured at 70 degrees Celsius using Precirol ATO 5, sodium cholate, and Pluronic F68 and then sonicated at 400 watts, 20 hertz, for twenty minutes can experience a size growth of up to thirty percent.

Sonication carried out in conjunction with other techniques has the potential to be an extremely efficient way of homogenization. After evaporating the drug-lipid solution (in chloroform-methanol), melting the residue, and then emulsifying the mixture with ultrasonic for a period of twenty-five minutes, SLNs with a high loading efficiency (more than ninety percent clozapine), a size of less than three hundred and eighty nanometers, and a low immunopotency can be generated. The crystallinity of various types of lipids is reduced to a greater or lower amount as a result of this process (Table 5), while the medication continues to exist in an amorphous state28. However, when SLN dispersions are lyophilized, the amount of lipid crystallinity that is lost is significantly greater.

Table 5. Effect of evaporation-sonication and lyophilization on the crystallographic characteristics of some lipid mixtures with clozapine.

	Parameter	**Physical Mix**	**Evaporated and sonicated mixture**	**Freeze Dried SLN**
Trimiristina	p. f. (ºC)	57.92	57.4	55.46
	ΔH (J/g)	156.67	154.41	6.58
	% cristalinidad*	99.5	98.12	64.3
Tripalmitina	p. f. (ºC)	65.09	65.66	62.83
	ΔH (J/g)	185.91	164.45	8.20
	% cristalinidad*	98.71	87.3	66.9
Triestearina	p. f. ºC	72.69	73.43	68.76
	ΔH (J/g)	170.8	157.83	11.10
	% cristalinidad*	98.69	91.2	98.6

Table 6. Effect of the form of addition of the surfactant on the characteristics of b-elemene-loaded SLNs

Lipid (% w/w)	**Size (nm)**	**Zeta potential (mV)**	**Encapsulation efficiency (%)**
100 P-L	106.5	-32.5	99.3
100 P-A	149.7	-29.8	97.2
(70 P+30 M)-L	46.7	-34.9	99.8
(70 P+30 M)-A	51.5	-32.7	96.9
100 M-L	26.5	-33.7	99.9
100 M-A	32.8	-35.3	98.2

P = Percitrol, M = monostearin, L = surfactant in lipid, A = surfactant in water.

The use of ultrasound combined with high shear speed during emulsification results in high quality SLN, with 2% loading, 88% encapsulation efficiency, 106 nm and IP of 0.2830. The combination of the probe sonication procedure with extrusion through a membrane allows the sonication time to be reduced and the quality of the NL to be improved. This combination would decrease the degradation and/or volatilization of some volatile oils (such as b-elemene) during their encapsulation in SLN.

It is important to note that the features of the SLN are largely determined by the manner in which the surfactants are presented. It comes out that the particle size is substantially smaller when it is put to the lipid phase as opposed to when it is brought into contact with water8. The reason for this would be the increased rate of fat disintegration as well as the rapidity with which the droplets are coated with the surfactant. This speed must compete with the pace at which the uncoated lipid particles agglomerate. The creation of the protective layer is made easier by the dispersion of the surfactants in the lipid matrix. This is accomplished by directing the hydrophilic portion of the surfactant towards the surface. This method is less effective when the surfactants are dissolved in water since they would be in a lower concentration compared to the lipid. This would be a problem because it would not promote their adsorption on the new surfaces that are formed during the homogenization process, which would result in larger particles.

It is possible that the presence of the surfactant in the water could limit the efficacy of the encapsulation of highly lipophilic components. This would result in the drug being distributed in both phases, and it would also favor the deposition of the drug on the surface of the particles. It is not possible to observe this partition when the surfactant is in the lipid phase8. Table 6 illustrates the impact that the type of surfactant addition has on the properties of SLN that is produced with varying proportions of lipid according to the aforementioned criteria. The zeta potential of the particles is not significantly affected by the manner in which the surfactant is added to the mixture. What the temperature and lipid concentration do to the effect Therefore, the particle size, encapsulation efficiency, and loading are all greatly impacted by the temperature at which SLN and NLC are prepared. This is because the temperature alters the kinetic energy of the system. As a result of the fact that the loading capacity of NLCs is determined by the liquid lipid concentration, the change is not as large in these materials. It has only been observed on a very infrequent basis that temperature is responsible for a significant change in the size of SLNs formed by the emulsification-diffusion process. This change can be attributed to the rapid diffusion of the solvent. In general, the hot high-pressure homogenization method is carried out at a temperature that is 10 degrees Celsius higher than the melting point of the lipid. When the process is carried out at lower temperatures, larger particles with a greater degree of dispersion are obtained. It is possible to obtain particles with an IP less than 0.3 if the system is maintained at room temperature and the homogenization pressure is increased. These particles would be smaller than 50 nanometers. Particles with a size range of 400-800 nm and an intensity of 0.87 are formed when SRMS are prepared by hot homogenizing and then cooling in an ice bath. In contrast, particles with a size range of 130 nm and an intensity of 0.46 are obtained when homogenization is carried out at ambient temperature.

Depending on the formulation, the influence of temperature on the physical features of SLN will be different from one variation to another. SLNs with a bimodal distribution and a somewhat lower loading capacity are obtained by dispersing a monostearin phase in acetone-ethanol at 0 degrees Celsius in an acidic aqueous solution of polyvinyl alcohol and poloxamer 188. This is in comparison to the SLNs obtained at 70 degrees Celsius, which were monomodal with a low interaction potential. The temperature does not significantly affect the size and distribution of the particles when the formulation comprises different proportions of liquid lipid (miglyol: capric-caprylic triglycerides). However, the temperature does have an influence on the loading capacity, and this effect is determined by the percentage of liquid lipid. In comparison to the particles obtained at 70 degrees Celsius, the zeta potential of the particles obtained at 0 degrees Celsius is larger and more dependent on the percentage of oil present (see table 7 and graph 2 for more information). Temperature will also have an effect on the crystallinity of the lipid matrix as well as the distribution of the liquid within the solid matrix. This will lead to distinct in vitro release patterns,

with the NLCs made at 70 degrees Celsius exhibiting a biphasic profile.111 It is possible to optimize the particle size distribution and facilitate the dispersion of the oil phase by adding a less viscous oil, such as miglyol, in situations where the circumstances of thermoregulation and homogenization are not sufficient to regulate the features of NL. When large quantities of liquid lipid are present, the surface viscosity of the NL increases, and the zeta potential of the NL decreases. This results in an increase in the growth rate of the NL while it is being stored at 25 degrees Celsius.5. With a temperature increase of twenty degrees Celsius over the melting point and an increase in the concentration of the lipid, it is feasible to generate SLN dispersions that have a semi-solid consistency, with colloidal particles forming a structured lipid network.

Table 7. Effect of temperature and liquid lipid content on some characteristics of LN loaded with clobetazole propionate.

Temperature C		Lipid content liquid (%)		
		0	12.5	25
0 C	Encapsulation (%)	45.14	60.12	67.17
	Load (% w/w)	2.26	3.01	3.35
	Zeta potential (mV)	-27.6	-25.1	-21.2
70 C	Efficiency	52.7	59.24	69.91
	Load (% w/w)	2.63	2.96	3.48
	Zeta potential (mV)	-20.5	-20.7	-21.8

Table 8. Effect of temperature on the average diameter and PI of dried SLN dispersions

Temperature (ºC)	**Time (h)**	**Diameter (nm)**		**Polydispersity index**	
		Home	**SLN dried**	**Home**	**SLN dried**
2	96	65	72	0.18	0.12
5	88	69	76	0.20	0.13
8	70	72	84	0.15	0.10
10	56	71	80	0.08	0.04
15	48	72	224	0.20	0.20
20	24	70	390	0.15	0.38

After being homogenized at 85 degrees Celsius for three cycles at 500 bars, they produce high viscosity oil-in-water nanoemulsions. These nanoemulsions maintain their colloidal size as a result of the recrystallization of the lipids and the low likelihood of diffusion3 that they exhibit. It is possible to generate an internal network that contains a high concentration of particles by homogenizing fifty percent of the lipids by applying high pressure, and then adding repeated amounts of twenty percent of the lipid while continuing to stir at a high speed until the total concentration reaches ninety-five percent (Figure 2). These types of dispersions are simpler to concentrate and can be used as granulating or wetting agents in the manufacturing of pellets or tablets without requiring any additional steps.1.

CONDITIONS OF DRYING, DIALYSIS, ULTRAFILTRATION, AND CENTRIFUGATION IMPACT THE RESULTS OF THE EXPERIMENT

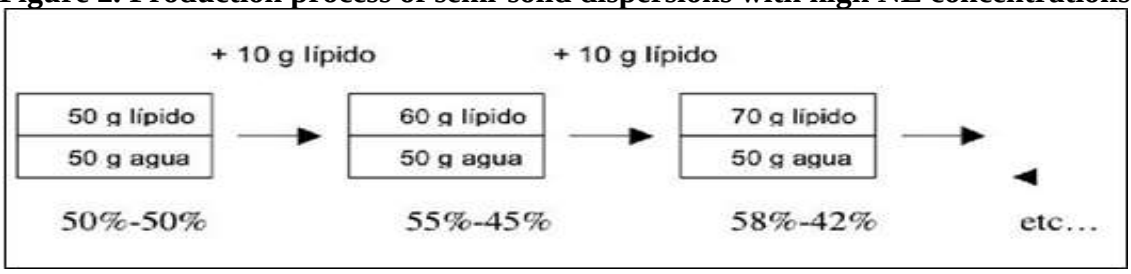
Due to the fact that SLN or NLC dispersions typically include a low fraction of particles, they need to be treated with drying, ultrafiltration, and/or centrifugation in order to achieve a final product that is more concentrated.

Freeze-drying is a process that does not require a freezing stage and reduces the agglomeration phenomenon33. A low-cost cold drying method has been described as an alternative to freeze-drying, which can be used to generate a powder with controlled particle size. This method can be utilized as an alternative to freeze-drying. The apparatus consists of a mini-desiccator made of Plexiglas that is divided into two chambers. One of the chambers is furnished with basic alumina,

which serves as a desiccant, and the other chamber is furnished with miniature trays, which are used to place the NL dispersions. In addition to operating in a vacuum, it is thermoregulated within a temperature range of 2 degrees Celsius to 20 degrees Celsius, using a mixture of water and propylene glycol.

It has been reported that the drying kinetics of 20% SLN dispersions in this apparatus are not affected by the removal of surfactants and co-surfactants (Epicuron 200 and taurocholate) in advance, nor is it affected by the utilization of cryoprotectants. Whenever the operation is carried out at temperatures lower than 10 degrees Celsius, the size of the particles stays practically exactly the same as it was when it was first carried out; The size of the product is significantly increased at higher temperatures (Table 8), although it is still relatively smaller than the size that is produced during the freeze-drying process. The increase in vapor pressure (0.4 Pa at 20 degrees Celsius) is a direct result of the temperature, which means that the drying process is significantly accelerated. In terms of the amount of water present, the process exhibits dynamics that are very close to being of zero order.

Figure 2. Production process of semi-solid dispersions with high NL concentrations



In most cases, NL dispersions are concentrated by either filtration through 0.45 mm membranes or by evaporating superfluous water under decreased pressure (10-30 mbar, 30 minutes). When the product is formed by the process of emulsification and evaporation, it is necessary to filter it immediately after the evaporation of the solvent and then promptly decrease its temperature to between 0 and 2 degrees Celsius in order to achieve solidification of the SLN.21. Considering that the particles that are present in the aqueous phase sediment at the same rate as the majority of colloids (40,000-100,000 g for 0.5 to 1.5 hours), ultracentrifugation is the procedure that is utilized the most frequently in the process of nanoparticle separation. Centrifugation under conditions that are not as extreme (20,000 revolutions per minute for three minutes) might be effective for certain kinds of goods.

For the most part, ultrafiltration is utilized to get rid of surplus surfactants and co-surfactants, the presence of which could lead to the instability of LNs during the sterilizing process, and to make certain that the dispersions are in accordance with the rules that govern health. The most common method of ultrafiltration is centrifugal ultrafiltration or low-pressure ultrafiltration, which involves the utilization of several membranes with pores ranging from 10 to 20 nanometers diameter. • TCF2 or TCF10A with a Diaflo YM 100 membrane, 100,000 Da is the system that is recommended the most as the best option. In most cases, 100 milliliters of the initial dispersion are concentrated to a volume of twenty milliliters, and then the same volume of water is added to it. The water is then reconcentrated to twenty milliliters, and the washing process is repeated three times. A residue of around 30 parts per million is left behind after this process, which also eliminates practically all of the benzyl alcohol that was utilized in the emulsification-diffusion approach. Minitan is outfitted with a polysulfone membrane (PTMK) that has a density of 300,000 Da. By doing so, it is possible to generate a microemulsion that is stable and may be frozen and dried. Millipore apparatus equipped with a PM 100,000 PXB100C50 membrane are included. When it comes to the purification of dispersions that contain lipid nanoparticles that are either very small or low density, it is not effective.

The purification of NL dispersions has also included the use of dialysis against water, which was carried out for a period of five days at room temperature in a Visking tube measuring 18/32 inches

and containing 12,000-14,000 Da. In the case of many dispersions that contain lipid nanoparticles that are either extremely tiny or have a low density and cannot be entirely separated using ultracentrifugation or ultrafiltration, lyophilization might be a more suitable alternative. Examples of dispersions that are prepared using the solvent diffusion method in an aqueous medium with PVA and whose SLN remain in a high proportion in the aqueous medium are examples of this type of dispersion. The process of freeze-drying could lead to the preservation of extra components, such as excess PVA, among the materials being dried.

INFLUENCE OF CONDITIONS INVOLVING FREEZE-DRYING

Through the process of lyophilization, liquid NL dispersions can be converted into powders that have favorable physical properties, are chemically stable, and are easily redispersible in aquatic environments. In most cases, the treatment calls for the incorporation of cryoprotectants, which are hydrophilic compounds that enhance the rate of lyophilization and prevent growth that is brought on by the pressure that is imposed by the frozen water that is contained inside the particles. Additionally, the circumstances of the freeze-drying process and the lipid matrix of the NL also play a role in determining its effectiveness.

The effectiveness of the cryoprotectant shines through when it safeguards the nanoparticles throughout the freezing process, which is the initial stage of the freeze-drying process. As a result of its existence, the osmotic activity of water in frozen samples is reduced, which favors the amorphous state. Additionally, it forms barriers that prevent particles from coming into contact with one another and interacts with the polar heads of the surfactants, functioning as a pseudohydrated envelope. Compounds such as 10% mannitol, 5% glucose, 5-15% trehalose, fructose, and poloxamer 188 are the cryoprotectants that are used the most frequently. Although it has been stated that trehalose is the most effective, fructose has demonstrated superior performance following the reconstitution of the powder.10-34. Because they are able to create a steric barrier around the particles, some types of fatty acid esters and the high concentration of surfactants are beneficial to the stability of the lyophilization process in specific systems.

One of the most important parameters in lyophilization is the cooling rate, which is an impact that is determined by the cryoprotectant that is utilized. The formation of small crystals with heterogeneous or amorphous structures is favored by rapid freezing, which can be accomplished by submerging the vial in liquid nitrogen or by dripping the dispersion into the nitrogen. These crystals allow water vapor to escape at a high speed at the beginning of the process, and then at a slower rate as a solid mass with fine pores is produced. During the drying process, a crystalline structure with wide holes would be left behind if the cooling process was slow. This structure would be favorable for the quick sublimation of water.

It is possible to achieve the creation of larger crystals with a more homogenous structure as well as the transition of a metastable or amorphous form into a stable crystalline one by freezing the substance at a temperature that is suitably low and then rapidly raising the temperature until the solid particles begin to collapse. For a period of time, the temperature is maintained at a steady level, and then it is cooled once more until it reaches the conditions necessary for the drying process. In order to prevent the sample from becoming thawed, it is recommended that the ideal temperature be determined by the use of DSC35 analysis. In the process of powder reconstitution, the production of a greater number of aggregates is a consequence of the utilization of extremely low temperatures (-196 degrees Celsius) during the freezing process. Freeze-drying of NL dispersions is often performed under the following conditions: freezing at temperatures ranging from -25 degrees Celsius to -75 degrees Celsius, drying at 20 degrees Celsius, and applying a pressure of 3 millimeters of mercury or 45 millibar over a period of 24 to 36 hours. As can be shown in Table 5, the freeze-drying procedure has a general impact on the crystallinity of some lipids that are responsible for the formation of the particles.

EFFECTS OF THE CONDITIONS OF THE STERILIZATION

NL dispersions that are going to be used for this purpose are either submitted to a sterilization process after concentration and purification, or they are created under sterile conditions. This is because products that are intended for parenteral or pulmonary administration are required to be sterile. Due to the fact that the procedure of sterilization should not alter the physical properties, chemical stability, or release kinetics of the NL, many formulations are unable to be sterilized using the conventional methods.

Heat sterilization is without a doubt the most widely used technique for NL dispersions. However, heating the particles in an autoclave at 121 degrees Celsius, two bars of pressure, for fifteen minutes might cause the particles to deteriorate to a greater or lesser degree, depending on the components of the particles and the medium in which they are dispersed. Because of the coalescence that the nanodroplets may have prior to solidification, the lipids that are present in the NL matrices melt when they are heated, and this melting process has the potential to alter the particle size when the matrices are cooled. After the autoclave sterilization process, recrystallization in those LNs that have been given special characteristics with the intention of modulating the release profile through the control of the production parameters would be out of control, and the characteristics that were given would be lost. This issue would be mitigated if the cooling was slow 34. When the excess of emulsifiers in the dispersions has been eliminated in the past, either through dialysis or ultrafiltration, the increase in the frequency of the loss of physical stability of the particles that is induced by the heat sterilization process is increased.

As a result of the fact that temperature has an effect on the mobility and hydrophilicity of emulsifiers and polymeric stabilizers, it is essential that these components be carefully chosen in order to ensure that the NL is physically stable after being sterilized by heat. It is possible for the temperature that is achieved during autoclave sterilization to be higher than the critical flocculation temperature of some poloxamer type polymers, which is 75.5 degrees Celsius. This causes the molecules of the adsorbed polymer to become dehydrated, which in turn causes the coating layer to collapse and makes it easier for particles to aggregate. It is possible that this phenomena could be considerably mitigated by lowering the temperature and increasing the amount of time that it is exposed to. At a temperature of 110 degrees Celsius, the likelihood of SLNs containing poloxamer aggregating in the absence of ions would be significantly reduced than it would be otherwise.

Table 9. Effect of stearylamine on the size and zeta potential of SLN loaded with clozapine, before and after heat sterilization.

Formulation by SLN	Size (nm)		Zeta potential (mV)	
	Before	after	Before	after
Trimyristin	225	516	1.1	-3.9
Tripalmitin	223	536	0.2	-5.7
Tristearin	266	616	4.1	-4.3
Trimyristinstearylamine	150	289	33.2	-6.0
Tripalmitinstearylamine	163	354	23.2	0.7
Tristearinstearylamine	97	287	21.3	-7.2

By changing the zeta potential of the particles, the presence of electrolytes in the NL formulation can have a significant impact on the critical temperature of the poloxamers and the properties of the particles. This is the reason why ions are considered to be agents that reduce stability. Tetracaine and etomidate are two examples of medications that have the potential to create a distortion in the mechanical properties of the interfacial coating of surfactants in LNs when they are subjected to heat sterilizing. It is possible for the inclusion of stearylamine, which is employed as a filler stabilizer in certain formulations, to produce an increase in size of up to three times in SLN that contains clozapine. Furthermore, depending on the triglyceride, the zeta potential of the SLN can be significantly altered (Table 9). The size and number of microparticles in steam-sterilized NL

dispersions, on the other hand, only exhibit a minor increase. This is because various stabilizers, such as lecithin, have been added to these dispersions.

By altering the surface of the glass vials and using a low concentration of lipids (2%), which prevents gelation of the dispersion, it is possible to limit the effect that temperature has on the growth of particles during the sterilization process. There is a protective effect that is generated by the utilization of an inert environment that eliminates carbon dioxide and raises the pH of the medium. This shows that certain chemical processes that are carried out in an acidic medium can contribute to the instability of the particles. Therefore, SLN that contain behemic acid and stearic acid double in size when they are sterilized by steam. This is a problem that does not occur when SLN are created with other types of components.

Table 10. Characteristics of different types of homogenizers used in scaling up NP dispersions

Characteristic	**Lab 40**	**Lab 60**	**Gaulin 5.5**
Number of pistons/valves	1/1	2/2	3/2
Operating pressure (bar)	100-1500	50-500	50-500
Ability	40 mL/cycle ----	60 L/h 10 L (max)	150 L/h 50 L (max)
Lot type	discontinue	continue	continue
Operation scale	Laboratory	clinical batch	Production batch

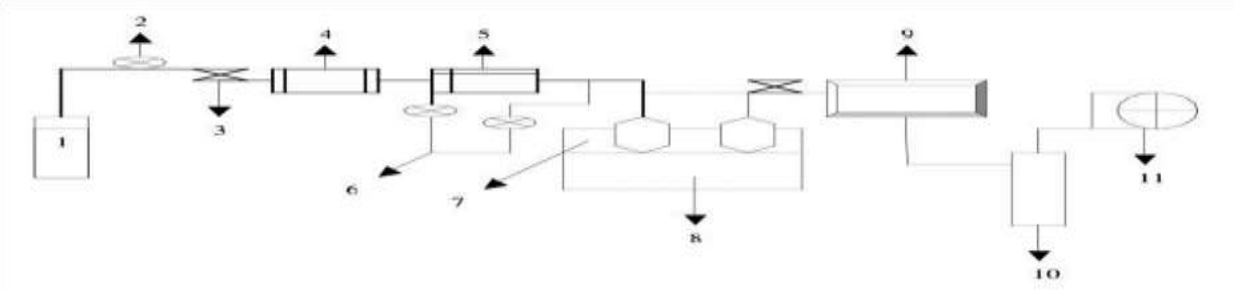
It is possible that filtration is a sterilization method that can be applied to SLN dispersions. This process is comparable to the one that is utilized in microemulsions for parenteral nutrition. It is necessary to filter the nanodispersions while they are in a liquid condition by applying pressure. This should be done in such a way that makes it possible for all particles to pass through the filter, regardless of whether or not they become larger than the pores after cooling. It is not recommended to filter dispersions that contain particles that are larger than 0.2 μm.1. Sterilization by the use of gamma rays is an alternate way that can be utilized for the treatment of products that cannot be treated using other methods. In this process, the size of SLN that is formed with poloxamer and stabilized with lecithin increases. This rise is smaller than the one that is induced by water vapor at 121 degrees Celsius, and it is comparable to the one that is produced at 110 degrees Celsius. It has been conjectured that the process of gamma-ray sterilization can bring about chemical alterations in the constituents as a result of the generation of free radicals, as well as bring about instability in the particles. However, this assertion has not been entirely verified. The production of species such as lysophosphatides or free fatty acids would be beneficial to the preservation of tiny particles, despite the fact that these species might result in some toxicological issues. Presentation of the SLN and NLC dispersions; the final presentation By incorporating NL dispersions into gels or o/w creams for topical treatment, the administration of these dispersions is made easier, and their long-term physical stability is improved. Additionally, controlled release characteristics are imparted to the pharmaceutical presentation.

It is more stable, easy to lyophilize without the addition of cryoprotectants, and can be used in the preparation of tablets or capsules for sustained drug administration. The oral administration system that is produced as a result of conditioning SLN dispersions in dextran-methacrylate hydrogels is characterized by the absence of the typical characteristics that are associated with nanosuspensions.29 NLC dispersions that have been conditioned in carbopol hydrogels and then neutralized with triethanolamine have a greater degree of stability than those that have been neutralized with electrolytes. This is due to the fact that the ionic effect on the zeta potential is reduced when triethanolamine is involved. Triethanolamine, on the other hand, has the potential to cause the precipitation of nonionic surfactants and other components that are present in considerable proportions. The decrease in the zeta potential is beneficial to the growth of the particles and the production of a pseudogel, which is strongly dependent on the crystallinity of the lipid phase.

INCREASING THE SIZE OF THE PROCESS IN ORDER TO RECEIVE LIPID NANOPARTICLES

When a product is going to be manufactured on an industrial scale, scaling must be considered an essential component of the product development process. The scaling up of the methods for generating NL by high-pressure homogenization and microemulsification has been successful and complies with the health regulation of Good Manufacturing Practices, which makes it possible to use them for the production of LN dispersions up to a medium level2. Using piston homogenizers with varying capacities (Lab 40, Lab 60, and Gaulin 5.5) that operate under controlled temperature and pressure settings, several formulas have been ramped up to a higher level. Table 10 exhibits the primary properties that it possesses. When trying to homogenize the product in Lab 40 for multiple cycles, it is necessary to feed the product each time. Lab 60 is equipped with a continuous feeding system, and the dispersion is fed through two homogenization valves by means of this system. To generate a rebound pressure that would redistribute the droplets that have collected or aggregated, the first operates at a pressure of 500 bar, and the second operates at a pressure of 50 bar. Both of these pressure adjustments are made. Both the temperature adjustment in the feed tank (which is the production temperature) and the temperature adjustment in the product container (which is the cooling temperature) are separately carried out.

Figure 3. Schematic representation of a vacuum drying equipment



In batches of two kilograms, the continuous circulation method would be more effective than the discontinuous process. This is due to the fact that the dead volume in the discontinuous process is comparatively considerable. The amount of time, the pressure at which the homogenization occurs, and the number of cycles are the variables that influence the particle size throughout this process. In most cases, the particle size becomes stable after 15 minutes and after four cycles; under these circumstances, the drug loading has only a marginal effect. When batches of 10 kilograms are processed in Lab 60 using continuous circulation, the amount of time required to complete the process is doubled. Overheating of the fats in the feeding tank, loading of the drug in the particle size of NL obtained in a continuous process, at a pressure of 500 bar because it is required to reach a temperature 10 degrees Celsius above the melting point, and then cooling to room temperature are all outcomes of the homogenization of batches that are larger than 20 kilograms. This is because the homogenization process requires a very long exposure time. When the Gaulin 5.5 is utilized, this issue does not arise because the product is not recirculated, which results in a reduction in the amount of time spent heating and producing the product.

In addition to having three pistons, the Gaulin 5.5 apparatus also features two homogenizers connected in series and stirring in an inert atmosphere both throughout the cooling process and during the recrystallization process. Time, pressure, and cooling rate are the factors that are used in the operation. When the Lab 60 is paired with the Gaulin 5.5, the variability of the pressure is controlled, feedback is avoided, and the amount of time spent storing after a cycle is cut down. The particle size and distribution are both within a range that is considered to be highly acceptable when each homogenizer is operated at a pressure of 500 bar.

A vitally important parameter is the rate of cooling. If it is carried out by circulating water at a temperature of 18 degrees Celsius, the product has a small particle size and little distribution. On the other hand, if the water is at a temperature of 8 degrees Celsius, the cooling is drastic in the first

liters of the dispersion, which causes the separation of the lipid, its deposit on the walls of the container, and a significant number of micrometric particles. There is a variance of 10 nm in particle size and a minor variation in charge between batches during the large-scale hot homogenization process that is carried out in these pieces of equipment. This method has good reproducibility. Alumina was used as a desiccant substance in the equipment that was used to carry out the drying process in 1 L batches of SLN dispersions that were created by microemulsification. The drying process was carried out with minimum fluctuation in particle size being carried out. It operates in an atmosphere that is inert and has a low pressure of 1.5 mbar41. The apparatus consists of 12 glass containers that are placed inside a bath that is operated at a temperature ranging from 20 to 60 degrees Celsius. The apparatus is elaborated upon in Figure 3.

During the initial stages of the process, the nitrogen flow is optimized in accordance with the drying kinetics, the temperature, and the concentration of the dispersion. The overall drying time is impacted by each and every experimental condition. Within the context of heat transmission, the circulation of the inert gas acts as a driving force, and the effect that it has on the agglomeration of particles is quite insignificant. At the lowest initial concentration and the greatest temperature (for approximately five hours), the optimal size of the SLN can be reached. Alternatively, the optimal size can be obtained at a high concentration and a lower temperature, which involves an increase in both the amount of particles and the amount of time required for operation (ten hours). only a little. The influence of temperature in this process is three times less than the effect that it has in the freeze-drying process. Additionally, this technique results in less particle agglomeration and reduced operating costs when compared to other processes that have a capacity that is comparable. A production level of 26 has been reached by the scaling up of the SLN production process that utilizes the contact membrane technology. The aqueous portion of the effluent is cooled to room temperature at a rate of five degrees Celsius per hour. Through the utilization of its volume (V), the interaction time (t), and the surface area of the membrane (A), the optimization of the lipid flow rate (J) is determined. This is accomplished by utilizing the equation $J=V/(\Delta t*A)$. The amount of time necessary for the creation of SLN is directly proportional to the lipid flux. The worth of it enables a comparison to be made between the outcomes produced with various membranes and surfaces 42. An efficiency of 1.2 liters per minute is achieved by injecting the aqueous phase into a membrane with a surface area of 0.0075 square meters at a speed of 1.7 meters per second. From the circumstances for a membrane with a surface area of 0.34 square meters, 55 liters may be made in the same amount of time.

CONCLUSION:

A high pressure homogenization technique is the primary method that has been documented in recent years for the purpose of generating lipid nanoparticles. As well as being able to be carried out with either heating or cold, it is easily scaled to production levels. The most significant drawback of the heated approach is that it hastens the process of the drug's breakdown during the process. The encapsulation of thermolabile and hydrophilic medicines is made possible through the processing of high cold pressure homogenization.

Emulsification of lipid solutions involves either the evaporation of the solvent or the diffusion of the solvent. It takes place in conditions with a lower temperature and does not require any specialized apparatus to be brought into play. The potential for the retention of solvent residues and the low concentration of NL in the dispersions are the two disadvantages that are most significant with this method. Because of its adaptability, the diffusion approach makes it possible to generate NL dispersions of a high sufficient quality.

Microemulsification is second. It can be accomplished through the use of high cutting force, through mechanical agitation, or through ultrasound. Because of the fact that it is possible to create stable nanoparticles from high concentrations of surfactants and co-surfactants using this technology, the use of these nanoparticles for the delivery of drugs to people is restricted.

In general, the circumstances of homogenization and temperature are the parameters that have the most impact on the features of NL. This is because these conditions define the degree to which

particular disintegration occurs. High pressure homogenization and ultrasound are the two procedures that are utilized the most frequently. Conditions of operation that are extremely severe are favorable to the coalescence of the particles.

The factors that affect the drug loading efficiency and occasionally the particle size both play a role in determining the properties of the solid state that is contained within the NL. These conditions include temperature and the type of lipids that are employed in the formulation. Synergistic effects are produced by emulsifiers, co-emulsifiers, and protective polymers in general. These effects result in the formation of a layer that has a high coating capacity. It is possible to incorporate them into either the oil or the aqueous phase. These particles are more effective when they are in the oil phase because they encourage the production of droplets and the protective coating, which results in particles that have a greater capacity for loading.

In most cases, NL dispersions are required to go through a process that eliminates surplus surfactants and concentrates the NL. In order to accomplish this goal, centrifugal ultrafiltration or low-pressure ultrafiltration is typically utilized, with a variety of membranes, including Diafo YM 100 and 100,000 Da, being utilized.

Because heat encourages the growth of particles, it is not always possible to sterilize LN dispersions in an autoclave. This is because heat makes it easier for particles to proliferate, which restricts the usage of goods that are meant for parenteral administration. The utilization of membrane filtration is an alternate method of sterilizing. For the purpose of enhancing the particle size stability of dispersions while they are being stored, it is recommended to freeze-dry the mixture while cryoprotectants are present.

In the case of high-pressure homogenization and microemulsification techniques, process scaling has proven to be effective, and its deployment can be in accordance with Good Manufacturing Practices.

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