REVIEW ARTICLE

Solid lipid Nanoparticles and Nanostructured Lipid Carrier: A Novel Approach for Lipid-Based Drug Delivery System

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ABSTRACT

Lipid nanoparticles, or LNPs, including nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs), attracted a lot of attention lately. SLNs were formed to circumvent the confines of the most common colloidal carriers because of their benefits, which include a favorable profile of release and precise administration of the drug with great physical stability. NLCs are the succeeding group of lipid nanoparticles with better capacity loading and durability. There are three possible NLC structural models. These LNPs may find usage in clinical medicine, research, cosmetics, and drug delivery.

Keywords: Drug delivery systems, Nanoparticles, Nanostructured lipid carriers, Solid lipid nanoparticles.

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INTRODUCTION

In the past few years, several drug-delivery technologies have attracted academic attention. One interesting aspect of this is the advancement of nano-delivery systems.[1,2] Several nanoparticulate systems can be utilized to increase drug bioavailability by various methods, such as increasing drug penetration, controlling the first-pass effect; or increasing P-glycoprotein (P-gp) efflux. The majority of lipids are biocompatible, biodegradable, and have low chronic toxicity. During *in-vivo* breakdown, several polymeric nanoparticles have demonstrated harmful consequences.[3,4] Lipids biocompatibility, physiochemical diversity, and capacity to increase drug bioavailability have made them viable options for drug delivery. Also, lipid-based formulations can increase intestinal drug dilution, enhance membrane permeability, increase solubilization capacity, inhibit P-gp efflux transporters, decrease CYP enzymatic activity, and increase lymphatic transport rate to improve drug absorption.[5]

Solid lipid nanoparticles (SLN) and nanostructured lipid carrier (NLC) are the 2 foremost categories into which lipid nanoparticles fall (Figure 1). They combine the merits of emulsions, liposomes, and polymeric nanoparticles.[6,7] The largest degree of flexibility in modifying the drug release patterns can be obtained from the solid matrix, which can shield the integrated active ingredients from chemical deterioration. The use of lipidic stabilizers or biodegradable physiological lipids that remain "generally recognized as safe (GRAS)" or have regulatory approval status, as well as a potentially broad treatment spectrum (oral, intravenous, and cutaneous), are advantages of SLN and NLC.[8] An example of drug orientation in NLCs and SLNs as shown in Figure 2.

Forms of Lipid Nanoparticles

Lipids that are compact at body temperature make up emulsifiers, which stabilize the lipids.[9] Submicron (less than 1000 nm) is the size of SLNs. SLNs are comprised of 0.1 to 30 (% w/w) of solid fat distributed in an aqueous phase. To increase stability, surfactants are used at doses extending from 0.5 to 5%. Triglycerides, waxes, and fatty acids are among the lipids used in the synthesis of SLNs.

They can protect medications against harsh environmental conditions, facilitate large-scale production by utilizing a high-pressure homogenization process, and be both biocompatible and biodegradable, among other advantages.[10] However, SLNs have several disadvantages: low drug loading efficacy and the likelihood of drug eviction owing to crystallization throughout storage because of their

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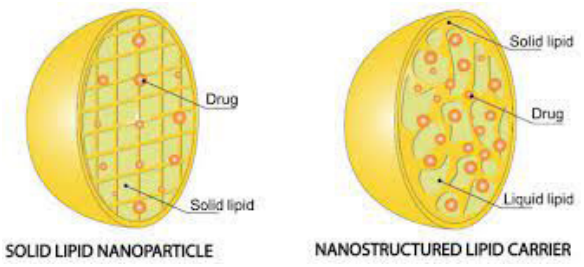

Figure 1: Representation of SLN & NLC

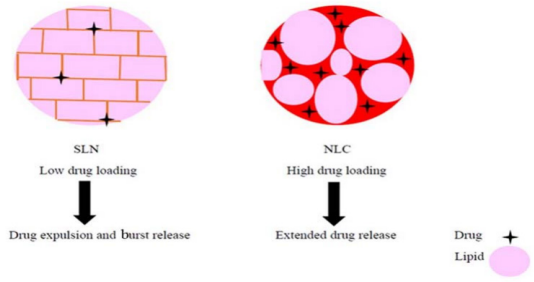

Figure 2: An example of drug orientation in NLCs and SLNs

perfect crystalline structure. Initial burst release is another disadvantage. Table 1 provides a detailed description of each model depicted in Figure 3.[11,12]

Because the elements of NLCs contain distinct moieties, they have an unstructured matrix.[13,14] NLCs were established to circumvent SLN limitations. Liquid lipids included in the preparation of NLCs decrease the amount of loaded drug removal during and after formulation. Compared to SLNs, NLCs can display better-regulated release profiles and increase the solubility of drugs in lipid matrices.[15]

NLCs possess a low melting point compared to SLNs despite being solid at body temperature.[16] The first form of lipid structure is imperfect, containing a mixture of liquid and solid fats or oil. The extreme disorder is formed during the crystallization process by certain conditions. The next class of NLCs is called formless type (non-crystalline matrix), which is sometimes referred to as amorphous type because it lacks a crystalline structure and hereafter inhibits the removal of loaded drugs. In this type, crystals occur while cooling, and to prevent them, a certain lipid combination needs to be used. The third kind is known as the multiple type; drugs in this class are more solvable in liquid lipids than in solid lipids, protecting them from solid lipid breakdown. w/o/w emulsions and this type of NLC are comparable (Figure 4).[17,18]

Recent Progress in SLNs

Solid lipids with a width extending from 50 to 1000 nm make up SLNs, a particular kind of nanosphere. These lipidic components can be complicated mixes of glycerides, refined triglycerides, or even waxes that are dissolved in an appropriate surfactant and solid at room temperature (25ºC) as well as the temperature of the human body (about 37ºC). SLN positions itself as an alternative drug delivery strategy in comparison to more conventional carriers, including liposomes, emulsions, and polymeric particles.[19,20]

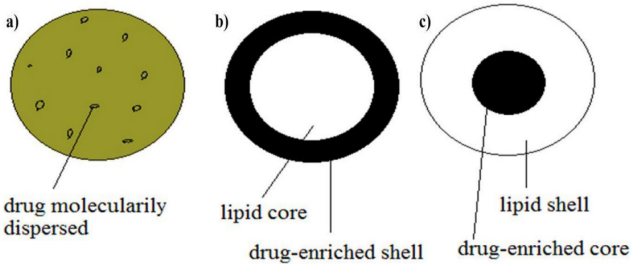

Figure 3: a) Solid solution model, b) Core-shell model, c) Core-drug model.

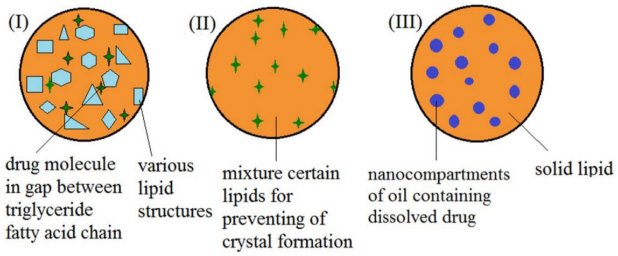

Figure 4: Class I (imperfect type), class II (formless type), class III (multiple type)

SLNs are exceptional lipid-based drug carriers for a variety of reasons, such as:

- The materials utilized are biodegradable, low toxicity, and biocompatible;
- Following drug encapsulation, the particles' average size is between 50 and 1000 nm; and
- The particle production process is inexpensive and can be scaled up quickly.

They can give simultaneous diagnosis and treatment by carrying anti-tumor drugs and contrast chemicals, as demonstrated by the results of ongoing research projects. SLNs have been examined for the incorporation of different contrasting agents, with carbon dots and iron oxide.[21] The current cancer therapy options were made possible by using a quantum dot as a contrast agent to encapsulate an SLN.

For particular uses, SLNs can contain small-sized pharmacological molecules made up of proteins and peptides as well as biomacromolecules.[22,23] SLNs have several drawbacks, including limited loading efficiency, drug leakage as a result of polymorphic modification, and comparatively high water content in the dispersions.[24]

Recent Progress in NLCs

NLC systems were introduced to fix the issues with SLN. The core matrix of the NLCs is often collected as a combination of lipids, both liquid and solid. They consist of a variety of lipid molecules. Compared to SLNs, these induce defections in the matrix structure to provide room for additional drug molecules. Both at ambient and at body temperature, the NLC matrix is solid despite the liquid lipid structure.[25,26] NLCs have a better ability to stop particle amalgamation via the solid matrix than emulsion. The virtues of SLNs, including biodegradation,

reduced toxicity potential, sustained drug release, shield against hostile conditions, and avoidance of organic solvents throughout manufacture, are also present in NLCs.[27]

Methods of Preparation

High-pressure homogenization technique

- *Hot homogenization*

The method entails heating the lipid phase to 90°C and then dissolving it into an aqueous phase that is surfactant-containing and at an identical temperature. Three high-pressure homogenizer cycles are achieved on the pre-emulsion at 90°C and 5 × 107 Pa. To solidify SLNs or NLCs, the formed emulsion is finally cooled to room temperature (Figure 5).[28]

- *Cold homogenization*

This method includes cooling the molten lipid phase till it sets, then crushing it to make lipid microparticles. To create pre-suspension, attained lipid microparticles are distributed in a cold aqueous phase holding surfactants. Subsequently, the pre-suspension undergoes five cycles of high-pressure homogenization at ambient temperature and 1.5 × 10^8 Pa of pressure (Figure 6).[29]

- *Solvent emulsification/evaporation*

By means of an organic solvent, the lipid segment is dissolved. Subsequently, the aqueous phase (surfactant solution in water) is mixed continuously at a temperature of 70 to 80°C while the organic phase is introduced. Up till the organic phase fully evaporates, the stirring will be done. Lipid nanoparticles are subsequently hardened by cooling the resulting nanoemulsion to less than 5°C (Figure 7).[30]

- *Microemulsion formation method*

After melting the lipids, an aqueous phase comprising surfactants is heated to a similar temperature. Then, the melted lipids are stirred at that identical temperature while the hot aqueous phase is added. Lipid nanoparticles are solidified by adding the hot O/W microemulsion in cold water at a temperature of 1:50 (Figure 8).[31]

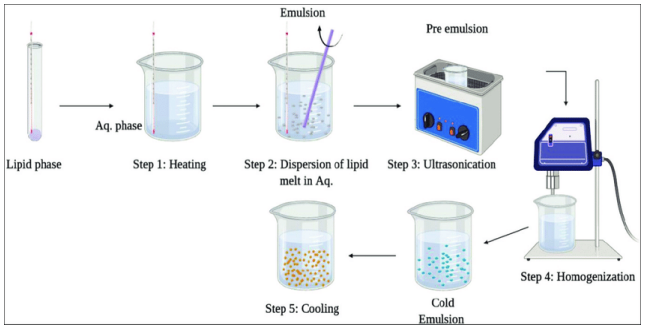

Figure 5: Hot homogenization technique

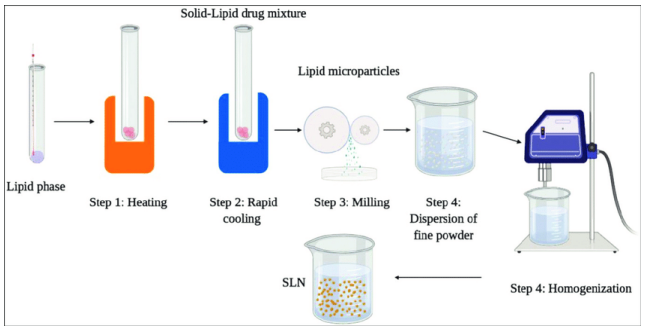

Figure 6: Cold homogenization technique

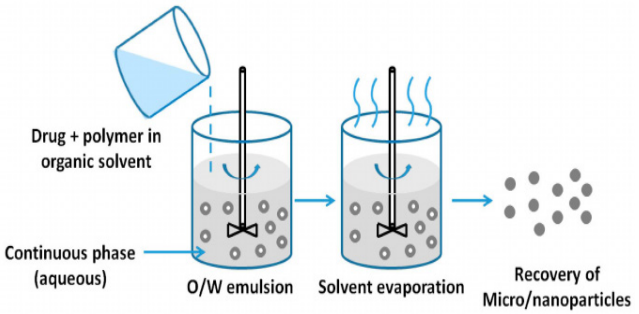

Figure 7: Solvent emulsification/evaporation technique

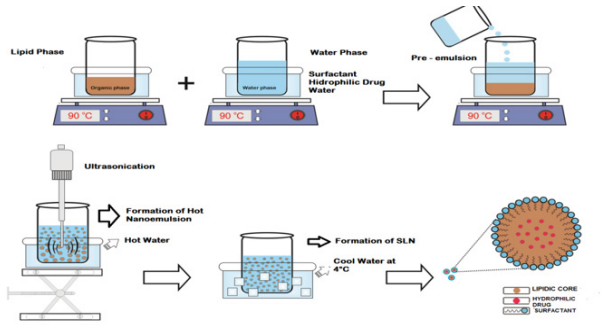

Figure 8: Microemulsion formation technique

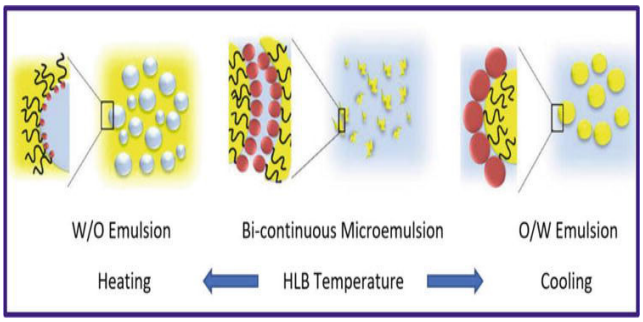

Figure 9: Phase inversion temperature (PIT) technique

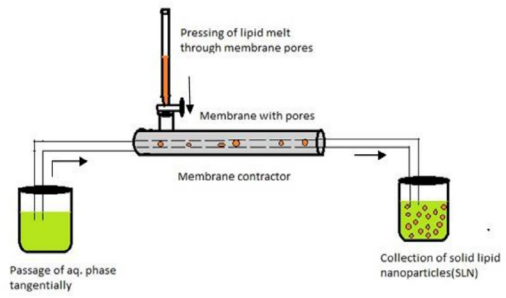

Figure 10: Membrane contactor process

Table 1: Differentiation between models

Solid solution model	*Drug-enriched shell*	*Drug-enriched core*
Cold homogenization method	hot homogenization technique	The drug that dissolves in the lipid turns into supersaturated as an outcome of dispersion cooling.
Using no drug-solubilizing surfactant	At the temperature at which lipids recrystallize, the lipid core forms.	Drug precipitation in melted lipid
Drugs dispersed in a lipid matrix	When dispersion cools, the active ingredient re-partitions into the lipid phase.	Lastly, additional cooling headways to recrystallization of the lipid

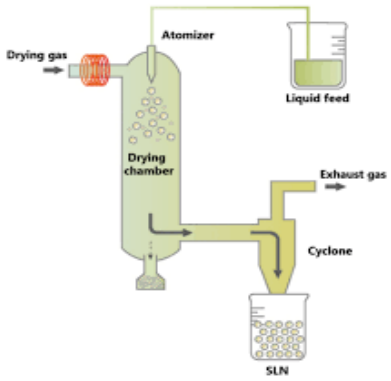

Figure 11: Spray drying

Ultrasonic solvent emulsification

The lipid phase is heated to 50°C throughout this procedure after dissolving it in an organic solvent, such as dichloromethane (DCM). Following that, the aqueous phase (emulsifiers and surfactants) is heated to a similar temperature.[32] DCM is partially evaporated, and then the organic phase and aqueous phase are combined at 50°C while being stirred. Lipid nanoparticles are solidified by cooling the obtained emulsion in an ice bath after it has been sonicated for the proper amount of time.

Phase inversion temperature (PIT) technique

It has proven possible to create SLNs, NLCs, and nanoemulsions using the phase inversion temperature (PIT) approach.[33] The method relies on the changes of w/o to o/w emulsions and conversely caused by temperature (Figure 9).[34]

The temperature at which the surfactants have identical affinity for the lipid and aqueous phases is known as PIT. The surfactants preferentially produce w/o emulsions at temperatures > PIT; although they also create o/w emulsion at temperatures < PIT.[35] The initial temperature of the oil, water, and surfactant is > PIT while stirring to generate w/o emulsions before being used to make SLNs and NLCs. They are then rapidly chilled while being stirred continuously, which encourages the disintegration of w/o microemulsions and causes o/w nanoemulsions to develop. Low-temperature precipitation of lipids results in the development of SLNs and NLCs.

Membrane contactor process

A lipid phase is enforced over membrane holes, although the temperature is reserved above the melting point of the solid lipid. Tiny droplets are formed as a result of this phase. Surfactant-containing aqueous phase is concurrently circulating on the membrane's opposite side. It travels laterally toward the membrane's surface, eliminating droplets that originate from pore outputs. The emulsion is heated; and then cooled to room temperature to produce SLNs and NLCs (Figure 10).[36]

Table 2: Recent work on SLN and NLC

Drug	*Category/Indication*	*Delivery route*	*Year*	*Reference*
Ribociclib	Anticancer	Oral	2022	54
Celecoxib	Non-steroidal anti-inflammatory drug (NSAID)	Topical	2021	55
Acitretin	Anti-psoriasis	Topical	2021	56
Nisoldipine	Antihypertensive	Topical	2020	57
Simvastatin	HMG CoA reductase inhibitor	Topical	2019	58

Spray drying

This approach produces pharmaceutical products from aqueous SLN dispersion as a substitute for the lyophilization method.[37] Despite being less expensive than lyophilization, spray drying is not widely used in the lipid manufacturing process. This process involves high temperatures and shear pressures, which lead to particle aggregation (Figure 11).

Applications

Topical application

The ineffectiveness of drugs in passing through the skin is the foremost obstacle. Changing the pervasion from follicular or transcellular to paracellular can, however, circumvent this.[38,39] Skin penetration has been improved through the manufacture of SLNs and NLCs. With a small modification, a novel solvent diffusion process was used to create topical amphotericin B SLNs, which were then lyophilized both with and without cryoprotectants to test their stability. It was noted that when lyophilized without cryoprotectants, the SLN formulations' particle sizes significantly increased.

Oral application

The primary issue is inadequate oral bioavailability, which can be accredited to fractional drug solubility or a hepatic first-pass impact. Using drug delivery methods based on nanoparticles results in increased oral bioavailability. The chitosan surface

modification of nanoparticles enhanced oral drug absorption.[40] Enzymatic or chemical degradation, as well as P-gp efflux pumps, are other major issues. Lipid nanoparticles may reduce the first-pass hepatic impact and enhance lymphatic transfer. To increase bioavailability, consider an oral baicalin-NLC carrier system. The low-temperature solidification method and emulsion evaporation were used to create the NLC. The entrapment and drug loading efficiencies were 59.51 and 3.54%, respectively.

Ocular application

Ocular drug administration presents several challenges.[41] Lipid nanoparticles can shield drugs from lacrimal enzymes, regulate drug release, and pass the ocular blood barrier. Non-viral gene delivery has been utilized in gene therapy to target specific retinal illnesses. The purpose of creating indomethacin (IN)-SLNs and NLCs was to investigate their possible application in topical ocular administration. The chitosan surface modification of the SLNs enhanced the ocular penetration of IN. NLCs (0.8% w/v) and IN SLNs (0.1% w/v) were accomplished with success.

Parenteral application

Lipid nanoparticles loaded with drugs can be directed intravenously, subcutaneously, intramuscularly, or just next to the intended organs. NLCs are, therefore acceptable substitutes, whereas SLNs are inappropriate carriers due to insufficient drug loading. A warm microemulsion approach was used to manufacture carvacrol NLCs, taking into account the impact of component concentration and lipid matrix on NLC production. Using surfactant and beeswax, the NLC preparation with the small particle size, maximum encapsulation effectiveness, and finest size distribution was optimized.[42]

Pulmonary application

It is a non-invasive way to deliver drugs for together local and systemic therapy. This direct delivery profile may allow for a reduction in drug dosage, which would, therefore lessen the negative effects of the drug. For example, sildenafil citrate is one of the phosphodiesterase type 5 inhibitors that is important in the treatment of pulmonary hypertension.[43,44] Utilizing a modified melt emulsification technique, SLNs were created. Over 24 hours, there was a high payload encapsulation effectiveness (88–100%) and a prolonged release.

Brain application

Drug entry into the brain is one of the main issues brought on by the BBB. Insufficient drug penetration through the BBB and drug transporters' effluence from the brain into the bloodstream are the two key issues with brain drug delivery. Innovative SLNs loaded with levofloxacin and doxycycline (LEVO/DOX) were created using an emulsification technique that involved high-speed homogenization and ultrasonication.[45] Compared to the intranasal LEVO/DOX free solution, the brain peak concentration and AUC0–360 minutes of the improved SLN-HPMC gel exhibited a significant increase, according to the results of the pharmacokinetic investigation conducted in plasma and the brain.

Characterization of SLNs and NLCs[46,47]

Entrapment efficiency

The % of drug that is effectively encapsulated in the nanoparticles is known as encapsulation efficiency.[48]

$$\%EE = (\text{Mass of entrapped drug}/\text{Mass of drug included}) \times 100 \ldots\ldots\ldots\ldots(1)$$

Several methods, including ultracentrifugation, can be used to separate the drug that is entrapped in particles from the free drug. Analyzing the isolated supernatant will yield the free drug content.[49]

Particle size and distribution

Dynamic light scattering (DLS) is used for determining particle size. This technique is capable of measuring particle with sizes between 0.1 and 10 μm. A parameter resulting from DLS called the polydispersity index (PDI or PI) is used to show the distribution of particle size. To depict monodispersed nanoparticles, a PDI value of 0.3 or less is deemed appropriate.[50]

Zeta potential

It is the entire surface charge of the particle. Electrophoretic light scattering is a useful tool for measuring zeta potential. A ZP of ±30 mV produces an electrostatic repulsion force that is sufficient to improve the physical steadiness of dispersion.[51]

Degree of crystallinity

Lipid carrier crystallinity behavior is frequently measured using X-ray diffraction (XRD) and differential scanning calorimetry (DSC). The structural details of the lipid nanoparticles, including their phases, crystal alignments, defects, and crystallinity, are provided by XRD.[52]

In-vitro drug release

One practical method is the dialysis bag diffusion method. Fill a dialysis bag with lipid dispersion and continuously stir while it is submerged in a dissolving liquid at a regulated temperature in the dialysis process. The aliquots of the dissolving media are taken out at the appropriate intervals and substituted simultaneously with an equivalent capacity of fresh dissolving medium.[53] The drug content in the aliquots is determined with suitable approaches; like UV-vis spectrophotometer and HPLC (Table 2).

CONCLUSION

Comparing lipid nanoparticles to alternative polymeric and colloidal nanocarriers, they are unique drug delivery vehicles with numerous benefits. Lipid carriers offer several benefits, chief among them being their biocompatibility, biodegradability, scalability, and ability to have regulated and customized release patterns. NLCs, being the second generation, have demonstrated superior performance in targeted drug delivery and are increasingly being explored for alternative modes of administration. Several delivery methods are obtainable for their administration and each of these nanoparticles' administration routes has unique benefits

and drawbacks that need to be taken into account. Lipid nanoparticles have a lot of potential as a drug delivery system shortly for a variety of pharmaceutically important active ingredients, plus proteins, genes, and small compounds.

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