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Emerging Insights into SLNs and NLCs: Innovative Lipid-Based Drug Delivery Systems – A Review

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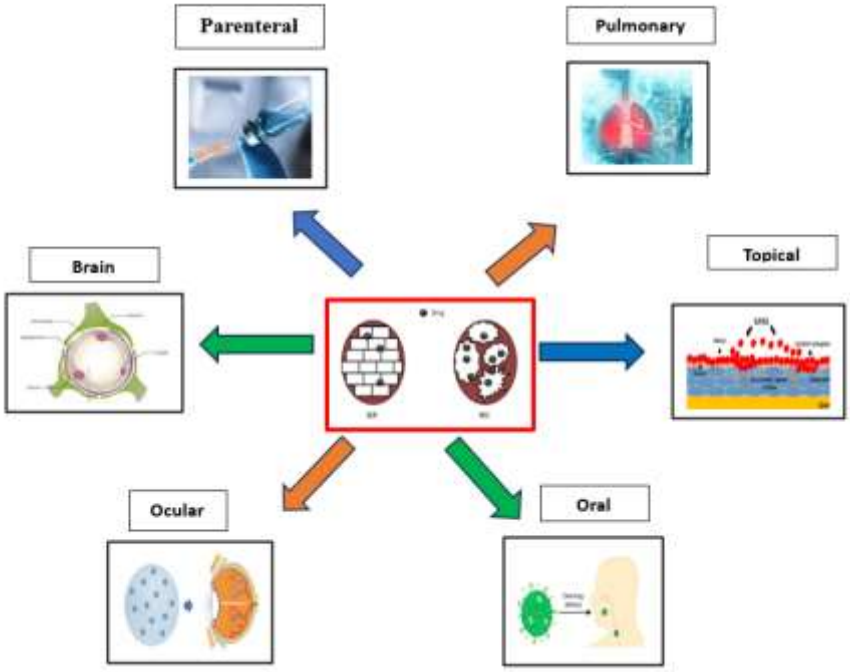
Graphical Abstract



Abstract

In the past few years, lipid nanoparticles, or LNPs, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have garnered particular attention. Since they have advantages like a promising release profile and targeted drug delivery with high physical stability, SLNs were designed to address the constraints of prevailing colloidal carriers. NLCs are the next group of lipid nanoparticles with better capacity loading and durability. There are three potential structural models of NLCs. These LNPs may find usage in the arenas of clinical medicine, research, cosmetics, and drug delivery.

Keywords: Drug delivery systems; Nanoparticles; Nanostructured lipid carriers (NLCs); Solid lipid nanoparticles (SLNs).

Introduction

In the previous few years, numerous drug-delivery technologies have attracted academic attention. One particularly interesting aspect of this has remained the advancement of nanomedicine and 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 trans-porters, decrease CYP enzymatic activity, and increase lymphatic transport rate to enhance drug absorption [5].

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are the two chief categories into which lipid nanoparticles fall. They combine the benefits 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 are 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].

TYPES OF LIPID NANOPARTICLES

Emulsifiers stabilize the lipids that make up solid lipid nanoparticles (SLNs), which are contained of lipids that are solid at body temperature [9]. Submicron (less than 1000 nm) is the size of SLNs. About 0.1 to 30 (% w/w) of solid fat that has been distributed in an aqueous phase makes up SLNs. To increase stability, surfactants are used at doses extending from 0.5 to 5%. Triglycerides, diglycerides, waxes, fatty acids, and steroids are among the lipids utilized in the preparation of SLNs.

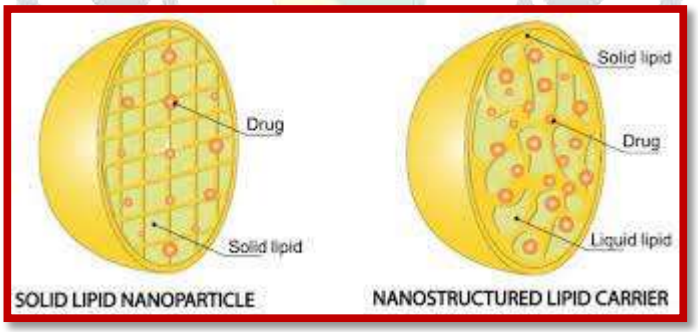


Figure 1: Representation of Solid Lipid nanoparticle (SLN) and Nanostructured lipid nanocarrier (NLC)

They can protect drugs 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]. SLNs also have several disadvantages, such as low drug loading effectiveness and the likelihood of drug expulsion as a result of crystallization during storage due to their flawless crystalline structure. Initial burst release is another disadvantage. Drug molecules in SLNs are directed among fatty acid chains or glycerides, and there is a propensity for formerly dissolved drugs to be expelled in SLNs throughout storage times and polymorphic fluctuations in solid lipid structures.

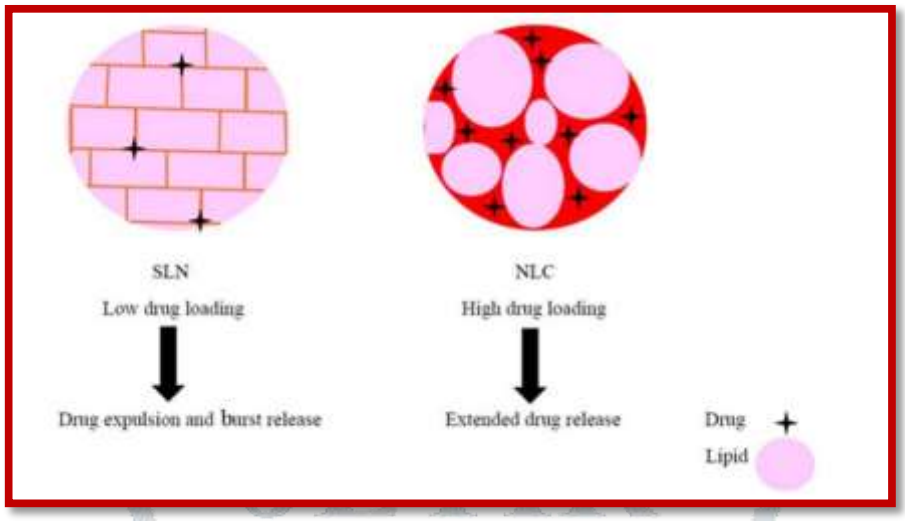


Figure 2: Illustration of drug loading and release in SLNs and NLCs

Three potential models of drug distribution in SLNs have been identified by several studies using transmission electron microscopy (TEM) and scanning electron microscopy (SEM) due to the production conditions, type, and concentration of excipients. Table 1 provides a detailed description of each model depicted in Figure 3 [11,12].

Table 1. Differentiation between Models

Solid solution model	Core-shell model (drug-enriched shell)	Core-shell model (drug-enriched core)
Development of this model in cold homogenization method	hot homogenization technique	The drug that dissolves in the lipid becomes supersaturated as a result of dispersion cooling.
Utilizing no drug-solubilizing surfactant	At the temperature at which lipids recrystallize, the lipid core forms.	Drug Precipitation in melted lipid
Drug dispersed in lipid matrix	When dispersion cools, the drug re-partitions into the lipid phase.	Lastly, additional cooling leads to recrystallization of the lipid
There is a strong contact among lipid and drug	Concentration of drug in nearby membrane	Formation of drug-enriched core

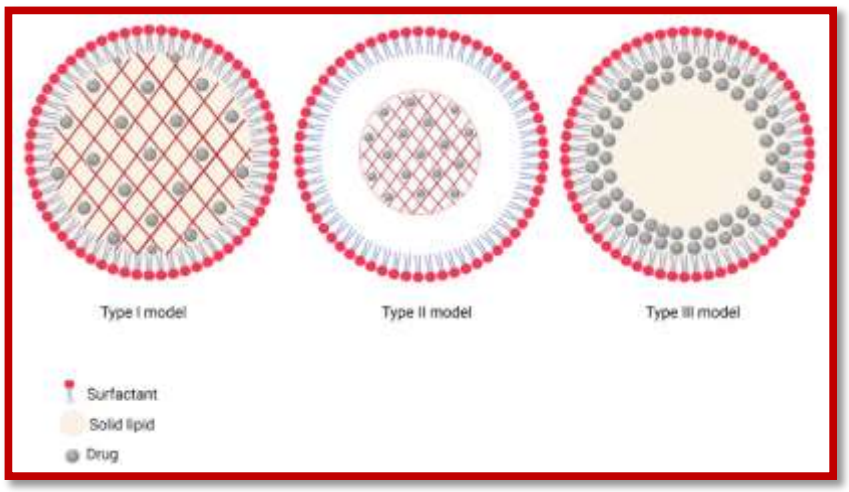


Figure 3. a) Solid solution model, b) Core-shell model, c) Core-shell model.

Because the elements of nanostructured lipid carriers (NLCs) contain distinct moieties, they have an unstructured matrix. NLCs are the next generation of lipid-based nanocarriers that are generated from a blend of

liquid and solid lipids [13, 14]. NLCs were formed to get around the restrictions of SLNs. NLCs have a higher drug-loading capacity and can circumvent drug expulsion by stopping lipid crystallization throughout the production and storage stages due to their flawed crystal structure. The formulation of NLCs contains liquid lipids, which minimize the removal of loaded drugs both during and after formulation. In contrast to SLNs, NLCs can exhibit more controlled release profiles and can also boost drug solubility in lipid matrices [15].

NLCs possess a low melting point compared to SLNs, despite being solid at body temperature [16]. NLCs have a higher loading capacity than SLNs.

The major three structures in which NLCs are found have been identified by studies using TEM and SEM microscopy:

- The first form of NLCs is called Amorphous type (non-crystalline matrix), which is sometimes referred to as formless type because it lacks a crystalline structure and hereafter inhibits the expulsion of loaded drugs. In this type, crystals occur while cooling, and to prevent them, a certain lipid combination needs to be used.
- The subsequent class of lipid structure is imperfect, containing of a blend of liquid and solid fats, or oil. The extreme disorder is produced during the crystallization process by certain conditions.
- The third kind is known as the multiple type; drugs in this class are more soluble in liquid lipids than in solid lipids, protecting them from solid lipid breakdown. w/o/w emulsions and this type of NLC are comparable [17, 18].

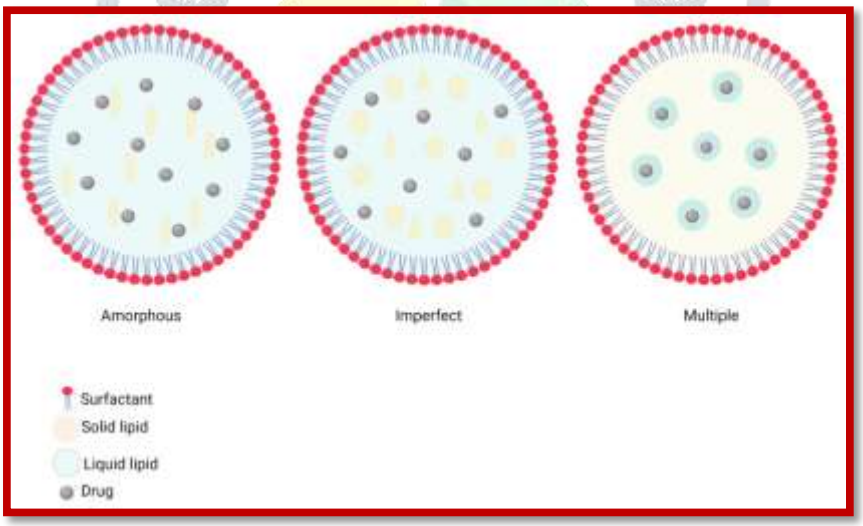


Figure 3. Class I (Amorphous), class II (Imperfect), class III (Multiple)

Recent progress in SLNs

Solid lipids with a diameter ranging 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 (25 ºC) as well as the temperature of the human body (about 37 ºC). SLN positions itself as an alternative drug delivery strategy in comparison to more conventional carriers including liposomes, emulsions, and polymeric micro- and nanoparticles [19, 20].

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

a. the materials utilized are biodegradable, low toxicity, and biocompatible;

b. following drug encapsulation, the particles' average size is between 50 and 1000 nm.; and

c. 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 investigated for the incorporation of different contrasting agents, including 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 relatively 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 [25,26]. NLCs have a better ability to stop particle coalescence via the solid matrix than emulsion. The advantages 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

1. High-pressure homogenization technique

a) Hot homogenization

The approach includes heating the lipid phase to 90 °C and then dispersing the hot lipid phase into an aqueous phase that also contains surfactants at the identical temperature. The pre-emulsion is homogenized in three high-pressure homogenizer cycles at 5×10^7 Pa at 90 °C. To solidify SLNs or NLCs, the formed emulsion is finally cooled to room temperature [28].

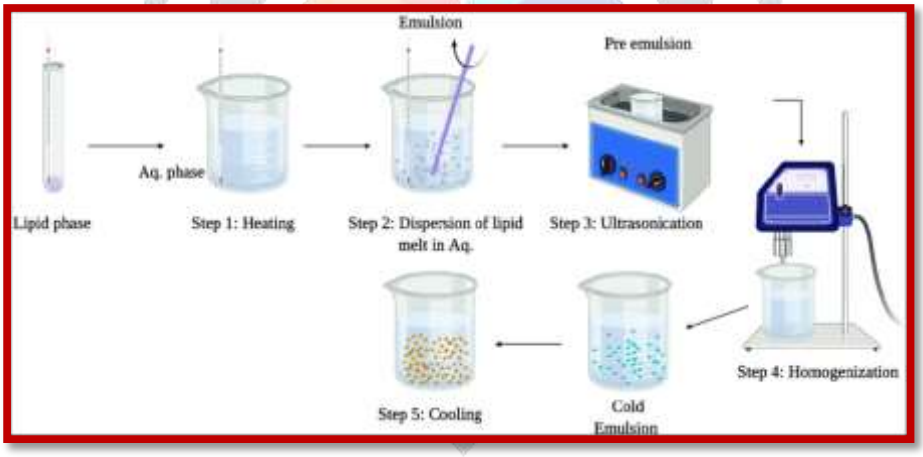


Figure 4. Hot homogenization technique

b) Cold homogenization

This process includes cooling the molten lipid phase till it solidifies, 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 [29].

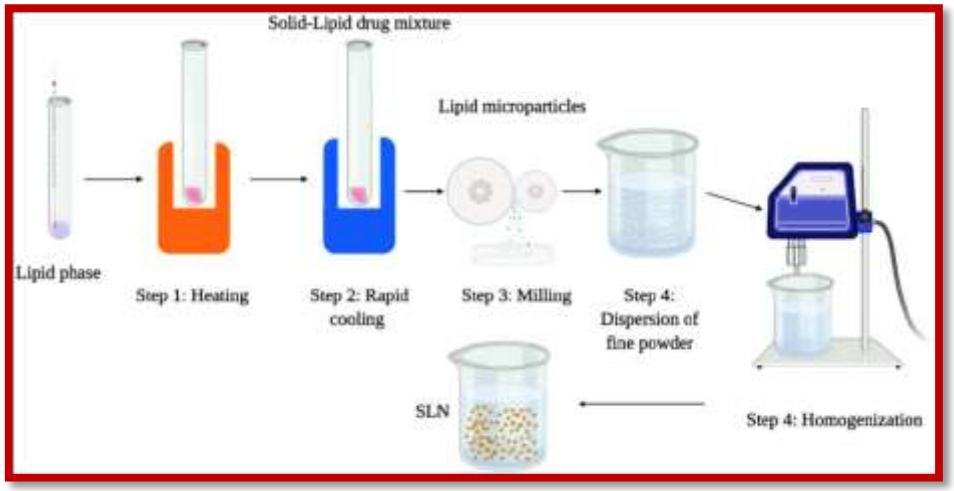


Figure 5. Cold homogenization technique

2. Solvent emulsification/evaporation technique

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

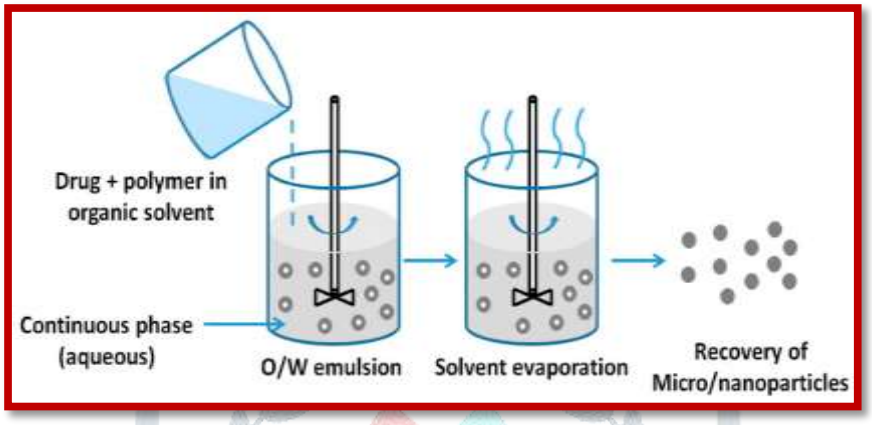


Figure 6. Solvent emulsification/evaporation technique

3. Microemulsion formation technique

This approach involves heating an aqueous phase comprising surfactants to the similar temperature as the lipids, which are melted at the proper temperature. After that, as the hot aqueous phase is added, the melted lipids will be stirred at the same temperature. Lipid nanoparticles are solidified by dispersing the hot oil in water microemulsion in cold water at a 1:50 ratio [31].

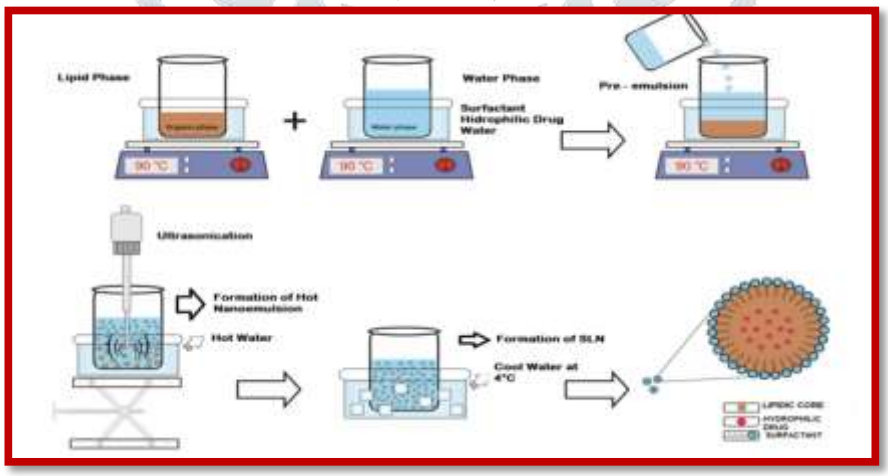


Figure 7. Microemulsion formation technique

4. Ultrasonic solvent emulsification method

This process includes heating the lipid phase to 50 °C after dissolving it in an organic solvent, such as dichloromethane. After that, the aqueous phase that comprises the emulsifiers and surfactants is heated to the same temperature [32]. Dichloromethane 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.

5. Phase Inversion Temperature (PIT) Technique

It has proven possible to create SLNs, NLCs, and nanoemulsions using the PIT approach [33]. The method relies on the inversions of w/o to o/w emulsions and vice versa caused by temperature. Non-ionic polyoxyethylated surfactants with temperature-dependent characteristics are needed for this approach [34].

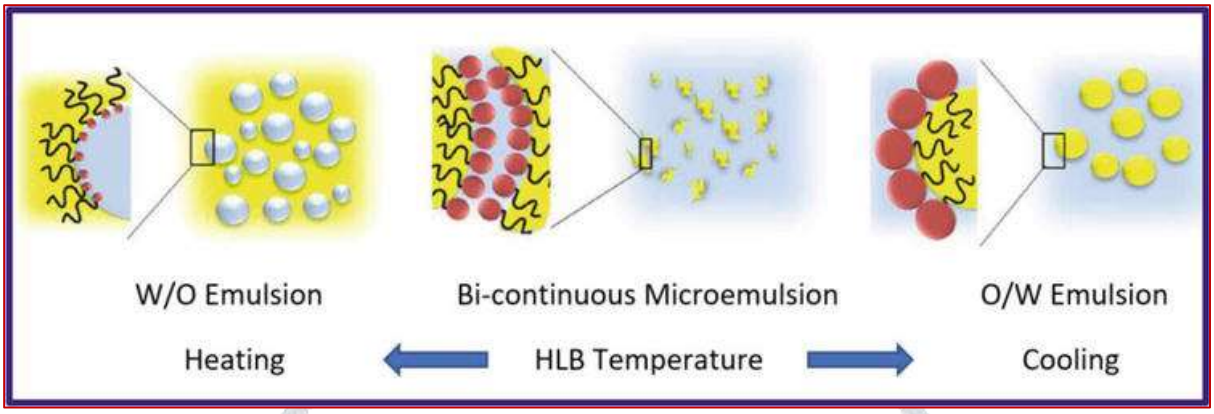


Figure 8. Phase Inversion Temperature (PIT) Technique

The temperature at which the surfactants' affinities for the lipid and aqueous phases are equal is known as PIT. The surfactants preferentially produce w/o emulsions at temperatures > PIT, although they also create o/w emulsions at temperatures < PIT [35]. Oil, water, and surfactant are initially heated to a temperature > 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.

6. Membrane Contactor Process

A lipid phase is enforced over membrane holes whereas the temperature is set above the melting point of the solid lipid. Tiny droplets are formed as a result of this phase. On the other side of the membrane within a module, an aqueous phase comprising surfactants is circulating concurrently. It travels tangentially toward the membrane's surface, eliminating droplets that originate from pore outputs. The hot emulsion is allowed to cool to room temperature to generate SLNs and NLCs [36].

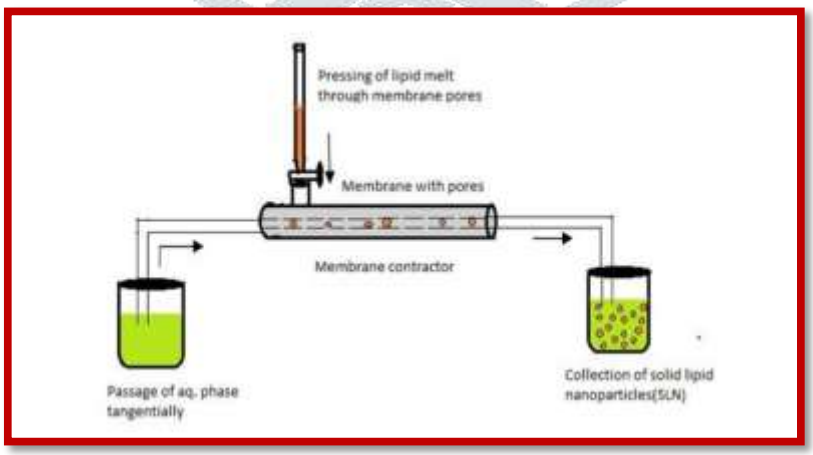


Figure 9. Membrane Contactor Process

7. Spray drying

This approach produces pharmaceutical products from aqueous SLN dispersion as a substitute for the lyophilization method [37]. Although spray drying is more economical than lyophilization, it is not frequently employed in the lipid synthesis process. Particle aggregation results from the high temperatures and shear pressures employed in this manner. Lipids that have a melting point higher than 70 °C are appropriate for spray drying, according to earlier research.

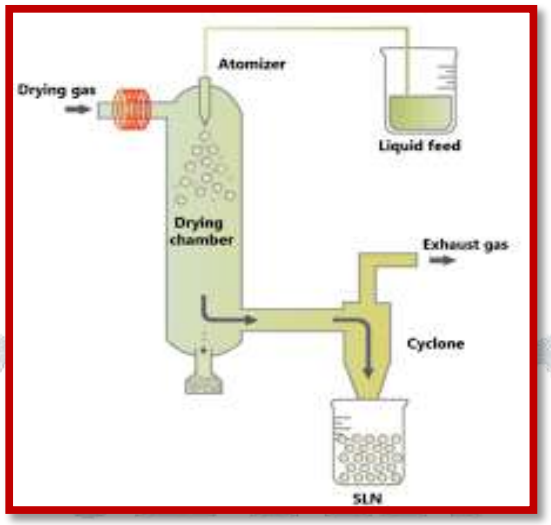


Figure 10. Spray drying

Applications of SLN & NLC

Topical application

Skin correlation is a worldwide ailment that is widespread. The ineffectiveness of drugs in passing through the skin is the primary obstacle to healing this sickness. The primary skin barrier is the stratum corneum. However, this can be avoided by switching the permeation from follicular or transcellular to paracellular [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 restricted oral bioavailability, which can be ascribed to fractional drug solubility or a hepatic first-pass impact. Using drug delivery methods based on nanoparticles results in increased oral bioavailability. Oral drug absorption was enhanced by the chitosan surface modification of nanoparticles [40]. Other key concerns are P-gp efflux pumps and enzymatic or chemical degradation. 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. Usually, the frontal portion of the eye receives drug administration. There are many obstacles to be overcome, including conjunctival blood flow, the ocular blood barrier, the corneal epithelium, and tear drainage [41]. Lipid nanoparticles can shield drugs from lacrimal enzymes, regulate drug release, and pass the ocular blood barrier. Non-viral gene delivery with SLNs and NLCs 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. SLNs loaded with IN were created using a hot homogenization method. The ocular penetration of IN was enhanced by the chitosan surface modification of the SLNs. 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 continuous release and greater encapsulation efficiency (88–100%) of the payload.

Brain application

One of the major problems caused by the BBB is the passage of drugs to the brain. Because nanoparticles can subsequently cross the reticuloendothelial system (RES), they are appropriate as candidates for brain drug delivery agents. Insufficient drug penetration and drug transporters' efflux from the brain into the bloodstream are the two chief issues with brain drug delivery. SLNs and NLCs have been used as colloidal drug delivery methods to allay these worries [45].

CHARACTERIZATION OF SLNS AND NLCS [46, 47]

Drug loading (DL) and Entrapment efficiency (EE)

It represents the mass of the nanoparticles that the encapsulated drug contributes to.

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

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

$$\% \text{ EE} = (\text{Mass of entrapped drug/Mass of drug added}) \times 100 \ldots\ldots\ldots\ldots (2)$$

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

Laser diffraction and dynamic light scattering (DLS) are well-established methods for determining particle size. These techniques are capable of measuring particles with sizes between 0.01 and 3500 µm and between 0.1 and 10 µm. Light is disseminated at small angles by bulky particles and at large angles by small particles. A parameter derived from DLS called the polydispersity index (PDI or PI) is used to show the distribution of particle sizes. To depict monodispersed nanoparticles, a PDI value of 0.3 or less is deemed appropriate [50].

Zeta potential

The zeta potential is the total charge on the particle surface. Electrophoretic light scattering is a useful tool for measuring zeta potential. It is commonly accepted that a zeta potential 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 studied using X-ray diffraction (XRD) and differential scanning calorimetry (DSC). In DSC, phase transition changes are tracked by comparing a sample's heat energy absorption to a reference. In X-ray reflectometry, the sample is exposed to X-rays, and the radiation strength dispersed at various angles is measured. The structural details of the lipid nanoparticles, including their phases, crystal orientations, crystallinity, and crystal defects, are provided by XRD [52].

Co-existence of dissimilar colloidal species

Nuclear magnetic resonance (NMR) can distinguish among dissimilar nuclei, elements, and isotopes [53]. Information on the quantity of nuclei and how they interact with their surroundings can be found in NMR spectra [54].

In vitro drug release

The dialysis bag diffusion technique is a useful tool. 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 replaced simultaneously with an equal volume of fresh dissolving medium [55]. The drug content in the aliquots is determined with suitable methods, like UV-Vis spectrophotometer and HPLC.

Table 1: Recent work on SLN and NLC

Drug	Category/Indication	Delivery route	Year	Reference
Ribociclib	Anti-cancer	Oral	2022	56
Celecoxib	Non-steroidal anti-inflammatory drug (NSAID)	Topical	2021	57
Acitretin	Anti-Psoriasis	Topical	2021	58
Diacerein	osteoarthritis	Topical	2020	59
Nisoldipine	Antihypertensive	Topical	2020	60
Simvastatin	HMG CoA reductase inhibitor	Topical	2019	61
20(S)-Protopanaxadiol	Anti-cancer, Anti-fatigue, and skin-whitening effects	Topical	2019	62
Hydrochlorothiazide	Antihypertensive	Oral	2018	63

CONCLUSION

Comparing lipid nanoparticles to other colloidal and polymeric 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 for a range of pharmaceutically important active ingredients, including proteins, genes, and small compounds.

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