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Comprehensive Insights into Lipid Nanocarriers: Preparation, Characterization and Applications

Ravi Goyal[1*], Gurpreet Kaur[2], Sumit Sharma[3], Deepika Raina[4] and Nitin Chitranshi[5]

[1]*Herbovive Private Limited, Hisar, Haryana, India.*
[2]*Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab, India.*
[3]*School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, New Delhi, India.*
[4]*School of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, India.*
[5]*School of Biomedical Science, University of New England, Australia.*

[*]herbovive.2021@gmail.com (Corresponding Author)

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ABSTRACT

Background: Lipid nanocarriers have emerged as a novel alternative to traditional drug delivery systems such as emulsions, liposomes, and microparticulate systems. These are spherical nano-sized (1–1000 nm) colloidal carriers dispersed in an aqueous surfactant solution. Their biodegradable, biocompatible, and non-toxic nature has led to extensive exploration in clinical medicine for multiple routes of administration, including oral, parenteral, and topical delivery. They offer high stability, large drug-loading capacity, and the ability to deliver both hydrophilic and lipophilic drugs in a targeted and controlled manner.

Purpose: The purpose of this review is to provide a comprehensive overview of lipid nanocarriers, focusing on their fundamental principles, advantages, limitations, preparation methods, and characterization techniques.

Methods: The review compiles and analyzes literature from relevant publications from the last 15 years on lipid nanocarriers, covering their formulation approaches, different preparation techniques, and evaluation parameters used to assess their physicochemical and functional properties.

Results: Lipid nanocarriers demonstrate significant advantages, including enhanced stability, improved drug loading, controlled and targeted drug release, and adaptability to various formulation requirements. Their versatility makes them suitable for applications in pharmaceuticals, vaccines, nutraceuticals, and diagnostic systems.

Conclusions: A comprehensive understanding of lipid nanocarriers can open new avenues in the treatment of multifactorial disorders. Their safety, efficacy, and flexibility position them as promising candidates for advanced drug delivery systems and future therapeutic innovations.

1. Introduction

Lipid nanocarriers are submicron-size colloidal systems with mean diameters varying from 50 to 1000 nm. These are the new generation carriers that form a successful substitute for traditional colloidal carriers like liposomes, emulsions (micro/nano), polymeric nanoparticles, etc. It basically comprises a lipid phase dispersed in water (stabilized by surfactants) and does not employ organic solvents for its preparation as used for other colloidal carriers. Use of physiologically accepted lipids in the preparation of lipid carriers makes these preparations better skin compatible and tolerant than conventional colloids. Furthermore, hydrophilic, lipophilic, and poorly water-soluble drugs can be loaded using these systems (Salvi & Pawar, 2019).

Lipid nanocarriers have proved to be the clinically advanced system for the delivery of nonviral genes. They assist in safe and effective encapsulating and delivery of nucleic acid. LNPs have been reported to selectively target a specific cell type and overcome the main biological barrier, such as cell transfection, intracellular trafficking, and cell internalization. The use of small-sized, large-surface-area nanoparticles (NPs) as therapeutic tools is growing in the biomedical profession. Chitosan is a biopolymeric carbohydrate derived from crustaceans and is an effective carrier for diagnostic systems owing to its biocompatibility,

low toxicity, and versatility in various forms (Goyal *et al., 2024)*. Copper NPs (CuNPs) are gaining popularity as antibiotics for wound healing. Gold (Au) nanoparticles have also been identified as an anti-infection agent. Their inertness and non-toxicity make them ideal for use as the core of NPs (Saharan *et al.,* 2024).

Müller *et al.* (1996) developed solid lipid nanoparticles (SLNs), the first-generation colloids, in the 1990s. These dispersions are physically stable and have an average particle size of 40 nm and 1 µm. These systems mainly contain highly pure triglycerides or glyceride/wax mixtures stabilized with surfactants (e.g., lecithin, poloxamer 188, polysorbate 80).

SLNs are composed totally of solid lipid; on the other hand, NLCs are composed of a mixture of solid and liquid lipid in the proportion of 70:30 to 99.9:0.1. The second generation of lipid carriers—NLCs—differs from the SLNs mainly with respect to lipid composition and physical state. These are reported to possess higher drug loading with the absence of any incidence of drug expulsion or stability issues (polymorphic transitions during storage), as observed in SLNs (Figure 1). These act as a prototype for drug targeting at the secondary and tertiary levels, with the ability to deliver low-aqueous-solubility BCS drugs (Class II and Class IV).

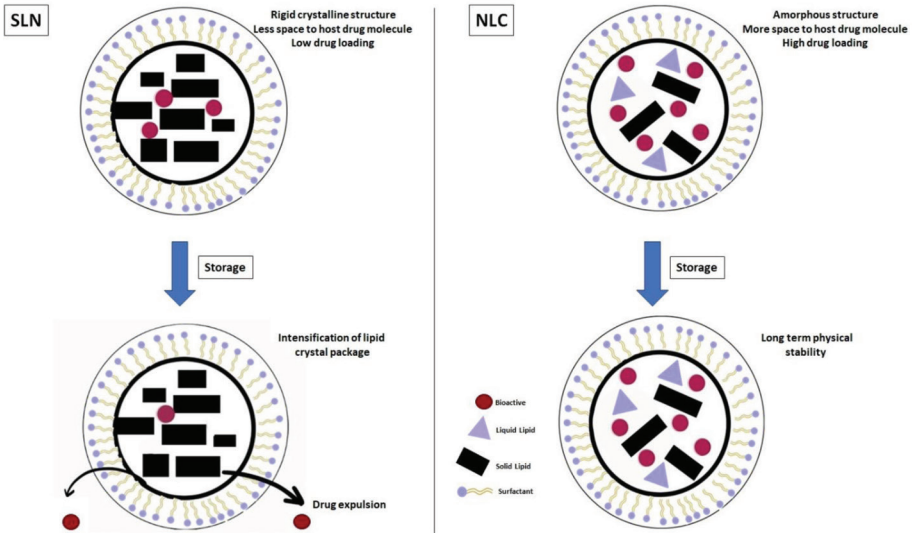

Figure 1: Structural Comparison of SLN & NLC

2. Methods of Preparation of Lipid Nanoparticles

Methods have been put forward for the development of lipid nanocarriers (Figure 2).

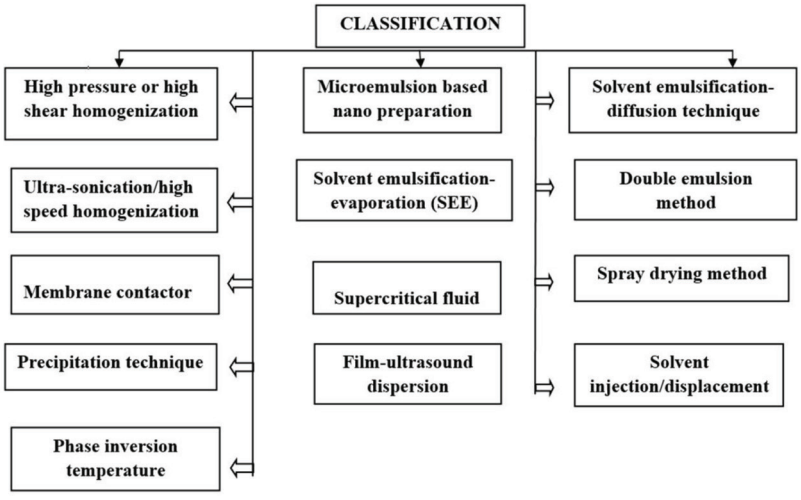

Figure 2: Methods of Preparation of Lipid Nanoparticles

2.1. High-Pressure or High-Shear Homogenization

High-pressure homogenization (HPH) is a durable, stable, and dependable method for producing lipid nanocarriers. The principle comprises subjecting particles to high shear stress followed by their passage through a narrow slit under high pressure ranging from 100 to 2000 bars. This leads to the generation of cavitation forces and the formation of particles of submicron size. Lipid content employed for the preparation of nano-dispersion usually ranges from 5 to 10% but can be extended up to 40%. Initially, this technique was employed for the production of lipid nano-dispersions. However, the presence of microparticles compromises the quality of the dispersion formed. In 2002, Olbrich *et al.* carried out an analysis in which they determined that certain process factors, such as emulsification duration, stirring rate, and chilling environment, directly affected the zeta potential and particle size of nano-dispersed particles (Olbrich *et al., 2002).* The two main methods that are used to create nanoparticles using HPH are the hot and cold techniques (Figure 3) (Mukherjee *et al., 2009).*

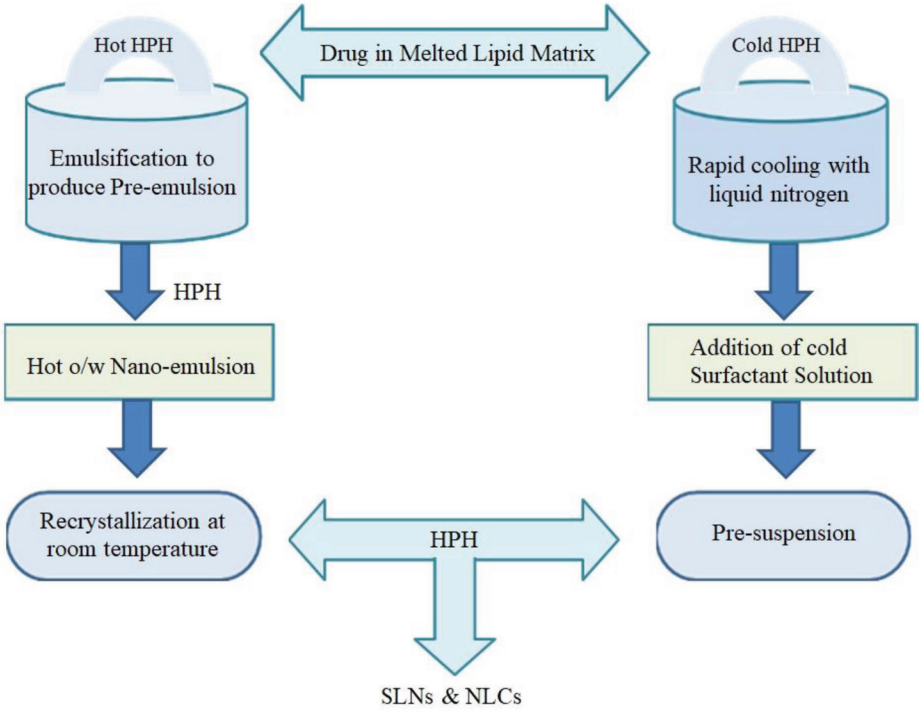

Figure 3: High Pressure/High Shear Homogenization Technique

2.1.1. Hot Homogenization Method

In this method, the drug is dissolved in a hot lipid sample, which is heated 5-10°C above the melting point of the solid lipid, and mixed with a preheated aqueous surfactant solution using high shear by means of an Ultra-Turrax. The pre-emulsion was consequently processed for 3-5 homogenization cycles at a pressure of 500-1500 bar until the formation of the desired quality. Indeed, the characteristics of the final product are determined by the quality of the pre-emulsion. The nanoemulsion is later cooled down to room temperature, where it undergoes lipid crystallization, leading to the formation of nanoparticles. Homogenization should be controlled, as it has a direct effect on particle size. An extensively used homogenizer is the rotor-stator (Hu *et al., 2019).*

- *Merits of Hot Homogenization Technique*: This technique is easy to scale up. They do not require any organic solvent for nano-preparations, and they also have a shorter production time in comparison to the other methods.
- *Demerits of Hot Homogenization Technique*: They are not suitable for thermosensitive drugs, as the high heating rate employed during nano-preparation may degrade the active compound. This technique is not recommended specifically for hydrophilic drugs, as these may get partitioned between the lipid melt and aqueous phase, leading to low drug entrapment efficiency. Surfactants employed for the nano-preparations (possessing low cloud points) may lose their emulsifying abilities upon heating, resulting in the

formation of unstable nano-preparations. An increase in temperature or frequency of homogenization cycles may influence the particles' kinetic energy, leading to their aggregation and formation of particles of larger size (Pardeike *et al.,* 2009).

2.1.2. Cold Homogenization Technique

The first preliminary step of drug dispersion in the melted lipid is the same for both the hot and cold HPH techniques. Dry ice or liquid nitrogen is used to treat the dispersion to cool the hot melt mixture that was formed. Afterwards, to create lipid particles with sizes ranging from 50 µm to 100 µm, the solidified mass is micronized using a ball mill or mortar (a homogenization procedure) (Hu *et al.,* 2024). These particles are then added to the ice-cooled surfactant solution and stirred to form a pre-suspension.

These suspensions, upon subjecting them to high-pressure homogenization, led to the formation of nanoparticles. As compared to other techniques, cold HPH forms larger particle sizes with wider size distribution (Mukherjee *et al.,* 2009). In cold homogenization, the exposure of the sample to thermal energy is reduced, though it cannot be eliminated because the initial step in this process involves melting of the lipid/drug mixture and contains a hot-melt mixture.

- *Merits of Cold HPH over Hot HPH*: They are suitable for thermo-labile and hydrophilic drugs, and this method is used to avoid drug degradation that is mainly due to temperature (Hu *et al.,* 2024).
- *Demerits of Cold Homogenization Technique*: The main limitation of cold homogenization is that here the production of particles is with a high polydispersity index, and it is an energy-intensive process.

2.2. Microemulsion-Based Nano Preparation

A wide variety of techniques have been used to produce non-material. These techniques mainly contain physical methods such as inert gas condensation and mechanical milling along with chemical methods such as photochemical reduction, chemical reduction, electrodeposition, hydrothermal, and sol-gel synthesis (Arbain *et al.,* 2011; Mohanty, 2011; Hayashi & Hakuta, 2010; Song *et al.,* 2009; Pérez-Tijerina *et al.,* 2008*;* Sonawane & Dongare, 2006; Ghosh *et al.,* 2002). To control the nanoparticle size and to get yields with a narrow size distribution, the microemulsion method is used, which is very accomplished and replicable and comes under the category of chemical methods. The production of lipid nanocarriers by the microemulsion method was first reported by Gasco (Gasco, 2009). Microemulsions are transparent, thermodynamically stable, and isotropic mixtures comprising a lipid (e.g., stearic acid), an emulsifier (e.g., taurodeoxycholic acid, polysorbate 60, etc.), a co-emulsifier (e.g., sodium mono-octyl phosphate), and water. The technique involves the mixing of appropriate ratios of lipid and aqueous phases, containing emulsifiers or co-emulsifiers, at temperatures above that of the melting temperature of solid lipid. The micro-emulsion so formed is later diluted with water to achieve the ratios of two phases in the range of 1:10 to 1:50 (Naseri *et al.,* 2015). Figure 4A illustrates the steps involved in the preparation of nanocolloids by the microemulsion method. Microemulsion techniques do not employ an external energy source to achieve particles of smaller size. Subsequently, formulated nanoparticles are washed with distilled water and filtered to remove unwanted lipid particles. The size and shape of the nanoparticle produced majorly depend on the type of surfactants and the addition of co-surfactants, so this should be taken into consideration.

- *Merits of the Microemulsion Technique*: The microemulsion prepared is thermodynamically stable. There is no specialized equipment or energy requirement for this method, and it is easy to scale up and economical.
- *Demerits of the Microemulsion Technique*: It is a very sensitive method, and any minor changes in composition cause phase transitions. They also show toxicity issues due to the incorporation of high surfactant concentrations during production. This method demands the removal of excess surfactant through ultra-centrifugation, ultrafiltration, or dialysis processes, which increases the production cost.

2.3. Solvent Emulsification-Diffusion Technique

Quintanar-Guerrero and his co-workers were the 1st to demonstrate the solvent emulsification-diffusion method for preparing polymeric nanoparticles (Quintanar-Guerrero *et al.,* Figure 4B). Afterwards, many amendments were done by various researchers to meet the formulary conditions required for the preparation of optimised lipid nanocarriers. The method involves the dispersion of lipid(s) in the partially miscible solvent (benzyl alcohol, isopropyl acetate, isobutyric acid and tetrahydrofuran). Initial thermodynamic equilibrium between solvent and water is achieved by pre-saturating them. Then in the lipid phase there is the addition of an aqueous phase containing surfactant at an appropriate temperature with continuous stirring. The prepared emulsion (oil in water; o/w) is diluted using water in the proportion of 1:5 to 1:10. This, due to solvent diffusion, causes precipitation of particles and results in the formation of lipid nanoparticles (Figure 4B).

Vacuum distillation or ultrafiltration can be employed to remove the excess of solvents diffused into the system. This method is commonly utilised for the encapsulation of peptides/proteins in lipid nanocores.

- *Merits of Solvent Emulsification-Diffusion Technique:* It is a very simple method, and particles exhibit fast drug release. They are suitable for thermo-sensitive drugs.
- *Demerits of Solvent Emulsification-Diffusion Technique:* The method is not suitable for the preparations that require slower release of drugs. The product generated by this technique is prone to contamination with organic solvent residues.

2.4. Ultra-Sonication/High-Speed Homogenisation

Ultra-sonication is a method where sonic waves/high shear (*via* cavitation) are used to reduce the particle size. When ultrasound waves are passed through the emulsion, then the cavitation phenomenon (2004) takes place. Figure 4. This comprises emergence (Creal., 2009) and implosive collapse of microbubbles/cavities in the medium. Above the melting point of the solid lipid, this technique involves the addition of an aqueous phase containing surfactant to the lipid-drug melt under high-shear mixing at the temperature. The emulsion formed is ultra-sonicated using either a probe sonicator or a bath sonicator until the desired-sized nano-emulsion is achieved (Wissing *et al.,* 2004). The last step involves cooling hot nano-emulsion at room temperature to obtain nano-sized lipid carriers. Figure 4C Studies are being done to form a stable formulation, and it has been concluded that ultrasonication and high-speed stirring are used in combination at high temperatures (Mukherjee *et al.,* 2009).

- *Merits of the Ultrasonication Technique*: This method is simple and economical with no utilisation of organic solvents.
- *Demerits of the Ultra-sonication Technique*: There are many issues of metal contamination and incidence of physical instability issues. Particles agglomerate in storage, leading to the formation of broad-sized particles.

2.5. Solvent Emulsification-Evaporation (SEE) Technique

The SEE technique (Figure 4D) was first elucidated by Sjostrom and Bergenstahl for the preparation of lipid nanocarriers (Sjöström & Bergenstahl, 199). A size < 30 involves mixing the drug with lipids in an organic solvent that is immiscible at low boiling temperatures, for example, chloroform. The aqueous phase is then added while stirring it mechanically. Organic solvent extraction from the emulsion by rota-evaporation at a low pressure of 40 to 60 mbar. This eventually leads to precipitation and the formation of nanoparticles having an average size of less than 50 nm. Figure 4D. Siekmann and Westesen further confirmed the reproducibility of this method by formulating cholesterol acetate nanoparticles with a size < 30 nm (Siekmann & Westesen, 1996).

- *Merits of Solvent Emulsification-Evaporation Technique*: This is a simple, scalable and continuous process which is appropriate for thermo-labile drugs.
- *Demerits of Solvent Emulsification-Evaporation Technique*: This technique exhibits low therapeutic yield. It is an extremely energy-intensive process which is prone to biomolecule damage. Moreover, the method leads to the generation of polydisperse nanocolloids contaminated with residual solvents.

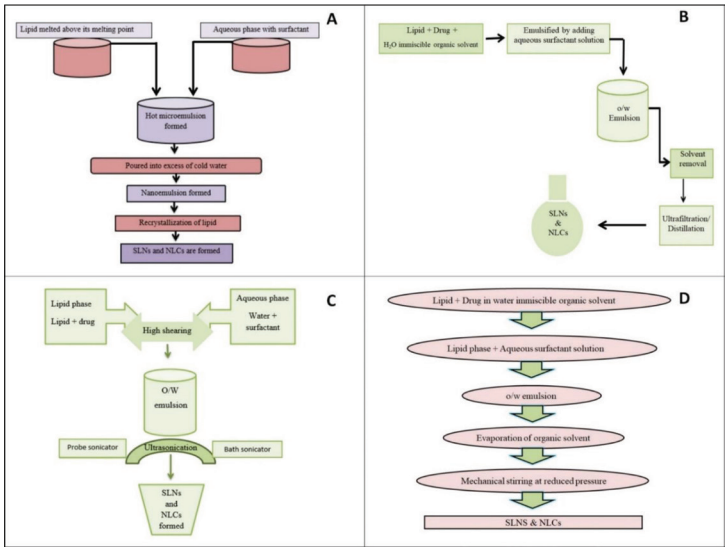

Figure 4: Method of preparation of Lipid Nanoparticles; A) Microemulsion technique for nano preparation, B) Solvent emulsification-diffusion technique, C) Ultra-sonication/high speed homogenization method and D) Solvent emulsification-evaporation method

2.6. Double Emulsion Method

Double emulsion, a water-in-oil emulsion dispersed in water (w/o/w), is a novel method that has been used for encapsulating the proteins and hydrophilic drugs. The process involves the dispersion of an aqueous drug solution to the lipid phase containing a stabilizer (poloxamer-407). This causes the formation of a w/o emulsion, which is subsequently treated with an aqueous solution under continuous stirring, which further leads to the formation of a double emulsion (w/o/w) of a nanometric size range. During solvent evaporation in the external aqueous phase of a w/o/w double emulsion, the encapsulation of the drug with a stabilizer is required, as with this there is prevention of drug partitioning to the external water phase (Olbrich *et al., 2002).* Li and co-workers loaded bovine serum albumin to lipid nanoparticles by using the double emulsion method (Li *et al.*, 2010). This technique is apposite for hydrophilic and thermo-sensitive drugs but limited in applicability due to the generation of polydisperse particles of micro-size range. The main limitation of using double emulsion is the production of homogenous droplet size using optimization of different processes. Techniques based on double emulsion are frequently used to encapsulate hydrophilic compounds, which have low encapsulation efficacy due to fast drug partitioning into the external aqueous phase when utilizing a single emulsion (Iqbal *et al.*, 2015).

2.7. Membrane Contactor Technique

The membrane contactor technique is a simple, economical, and novel method that is used for preparing lipid nanocolloids. This procedure involves the passage of the melted lipid phase through the microporous membrane under high pressure. This ultimately yields small droplets, which upon cooling to room temperature form nanoparticles. Different process parameters, viz., membrane pore size, flow rate, and organic phase pressure, have been reported to influence organic phase flux and size of nanoparticles (Andreozzi *et al.*, 2011).

- *Merits of Membrane Contactor Technique:* The method is versatile and allows control over particle size. As compared to other processes for nanoparticle preparations, this technique is easily scalable and can be tailored to achieve controlled particle size by selecting an appropriate membrane.
- *Demerits of Membrane Contactor Technique:* The disadvantages of ultrafiltration and microfiltration—two traditional membrane techniques—are connected to those of the membrane contactor. For every synthesis run, the experimental setup should be cleaned properly, and the initial permeability must be regained before initiating the next run. It takes a lot of time to clean. A run of synthesis may result in membrane fouling, which is the accumulation of inorganic and organic molecules in the membrane pores and on the membrane surface. The mechanisms cause the flux to diminish with time, which lowers the process's yield and efficiency. The velocity of the fouling processes can be limited by appropriately selecting the process parameters, such as high pressure, high crossflow, and concentrations that are not too high.

2.8. Supercritical Fluid Technology (SCF)

This technology was given in the late 1980s and early 1990s. Carbon dioxide (CO_2; 99.99%) and its miscible organic solvents (e.g., dimethylformamide) are generally employed for the study. CO_2 is selected as a solvent of choice due to its low toxicity, low cost, and low critical temperature. CO_2 behaves as a solubilizing agent with low viscosity, high diffusibility, and low surface tension. The technology further includes various processes for preparing nanoparticles, viz., supercritical fluid extraction of emulsions (SFEE), rapid expansion of supercritical solution (RESS), gas/supercritical anti-solvent (GAS/SAS), particles from gas-saturated solution (PGSS), aerosol solvent extraction system (ASES), and solution-enhanced dispersion by supercritical fluid (SEDS). However, amongst these, PGSS is the primary method explored widely for the preparation of nanoparticles (Wai & Wang, 1997).

- *Merits of SCF Technology:* This technology involves many favorable conditions: low temperature and high dissolving property for the desired particle size distribution.
- *Demerits of SCF Technology:* A small proportion of residual solvent persists in the final preparation.

2.8.1. Particles from Gas-Saturated Solution (PGSS)

The PGSS method involves the mixing of lipid melt containing drug with supercritical CO_2. The formation of nanoparticles takes place with the help of evaporation and precipitation when the mixture is subjected to atomization (rapid expansion) under high pressure. Some of the studies have mentioned the application of the PGSS method, and it has been commonly used for the production of liposome-forming lecithin formulations and encapsulation of vaccines (Patel *et al.*, 2012).

- *Merits of Supercritical Fluid Technology*: They are suitable for thermolabile drugs and products, exhibiting enhanced shelf life as the particles obtained by this method are in dried powder form.
- *Demerits of Supercritical Fluid Technology*: It is an expensive method with issues of frequent nozzle blockage with hydrophilic drugs.

2.9. Spray Drying Method

Spray drying is an alternative to lyophilization, which is used for the transformation of lipid nano-dispersion from a hydrous to an anhydrous state. In this method there is a single step, which involves the conversion of liquid into fine, dust-free, dry powder. It basically comprises 4 stages:

- Atomization (conversion of solution into spray).
- Contact of spray with hot air.
- Drying of sprayed particles.
- Separation of the product (dried powder).

Spray drying is a method that the pharmaceutical industry has been using since the early 20th century to produce amorphous solid dispersions, encapsulate drugs and essential oils in excipient matrices, and dry biopharmaceuticals (such as proteins, vaccines, deoxyribonucleic acid, antibodies, etc.) (Malamatari *et al*., 2020; Freitas & Müller, 1998).

- *Merits of the Spray-Drying Method*: This process is cheaper in comparison to lyophilization and applicable for lipids with melting points higher than 70 °C.
- Demerits *of the Spray-Drying Method*: They have physical instability issues, as the implication of high temperature and shear rates causes particles to aggregate.

2.10. Precipitation Technique

The precipitation technique is an alternative approach to prepare nanocarriers in which glycerides are added in an organic solvent to dissolve it, and the aqueous phase is added afterwards, leading to the formation of an emulsion. For the preparation of nanoparticles, removal of the organic solvent is required, which is done by subjecting the emulsion to rotary evaporation, which ultimately precipitates the lipids (Roy *et al*., 2017).

- *Merits of the Precipitation Technique:* High penetration rate ensures effective therapy. It aids in the penetration of unabsorbable drugs through the skin.
- *Demerits of Precipitation Technique:* Different drugs have varying concentrations, making it impossible to administer the same dose. Multiple concentrations of permeation enhancers should not be administered simultaneously (Roy *et al*., 2017).

2.11. Film-Ultrasound Dispersion

The film-ultrasound method involves the addition of the lipid phase containing the drug to a suitable organic solvent. The organic phase is rotated, decompressed, and evaporated to form a thin lipid film along the walls of the container. The film is then treated with an aqueous solution of surfactant and subjected to cycles of ultra-sonication using a probe sonicator to form lipid nanoparticles (Chavan *et al*., 2013). This method is simple and economical. But the method is limited by the issues of metal contamination and the formation of particles with a broad size range.

- *Merits of the Film Ultrasound Dispersion:* The method is simple and economical.
- *Demerits of the Film Ultrasound Dispersion:* It is limited by the issues of metal contamination and the formation of particles with a broad size range.

2.12. Solvent Injection/Displacement Technique

Solvent injection is a novel technique that is principally equivalent to the solvent emulsification diffusion method. The main difference between the solvent displacement method and the emulsification-diffusion method is that it avoids the use of dilution of the system (Noriega-Peláez *et al*., 2011). With this technique, the aqueous phase is injected with solid lipids that have been in water-miscible disseminated in water-miscible solvent mixtures (e.g., acetone, isopropanol, etc.) that are injected into the aqueous phase that may or may not contain surfactant under continuous stirring. The mixture is then subjected to filtration to remove excess lipids from the suspension (Chavan *et al*., 2013). One should consider various variables like stirring rate, oil-to-aqueous-phase ratio, and concentration of lipids and stabilizer, which affect the overall quality of the formulation (Noriega-Peláez *et al*., 2011).

- *Merits of the Solvent Injection Technique:* It is a simple method in which no sophisticated instrument is required.
- *Demerits of the Solvent Injection Technique:* Solvent removal is difficult, and remaining solvent can be removed by using an additional procedure.

2.13. Phase Inversion Temperature (PIT) Technique

The PIT technique involves the principle of inversion of phases of a system, i.e., conversion from an o/w emulsion to a w/o emulsion. The method involves dropwise addition of a surfactant-containing aqueous solution to the oil phase (lipids and non-ionic surfactants) at a constant temperature (usually above the PIT) under agitation; on cooling under continuous shear, an emulsion is formed w/o it. This method is applicable for thermo-labile drugs, as when these drugs are subjected to short heating periods, the degradation of the drug is not expected to occur (Heurtault *et al*., 2002).

Because of PIT's low intensity, it is simple to produce food-grade nanoemulsions. Lipophilic functional components are encapsulated and protected by nanoemulsions in the food and beverage sector. Creating reliable nano-emulsion-based delivery systems appropriate for the food sector is a revolutionary method.

- *Merits of the Phase Inversion Temperature (PIT) Technique:* Low energy consumption and lack of organic solvents.
- *Demerits of the Phase Inversion Temperature (PIT) Technique:* Instability of emulsion.

Table 1 depicts the varied SLN/NLC formulations in research and their preparation methods adopted with their advantages and shortcomings.

3. Characterisation of SLNs and NLCs

For quality assurance and stability study of nano carriers, SLNs and NLCs must be adequately or suitably characterized. Particle characteristic decides the overall therapeutic performance and stability profile of the formulation. Table 2 illustrates Various SLN & NLC Preparations in research and Table 3 enlists the major parameters and their characterising techniques essential for the evaluation of SLNs and NLCs.

3.1. Physiochemical and Biological Characteristics

Physio-biochemical properties of nanocarriers *viz.* particle size, surface charge and morphology, determines the solubility, stability, biological performance and release profile of formulation.

3.1.1. Particle Size and Size Distribution

- *Photon correlation spectroscopy (PCS) and laser diffraction (LD)*- the most common techniques for the analysis of particle size are PVCS and LD. Another name of PCS is dynamic light scattering (DLS) technique, in which particle size can be evaluated by measuring the fluctuation in the intensity of the light scattered due to particle movement. The method is sensitive over the size range of 3 nm to 3000 nm (Douglas & Davis, 1986). System with larger micro particles (100 nm to 180 μm) can be detected employing LD. Both analysis methods are based on particle beam diffraction angle on particle radius (Fraunhofer spectra) and produce a wide angle spread with smaller particles (Severino *et al.*,2012)
- *Polydispersity index (PDI)* – PDI is used to indicate degree of uniformity/non-uniformity of particles distribution. PDI value ≤0.5 indicates homogenous and monodisperse nature while values ≥0.7 designates broad size distribution. Different techniques employed for its determination include microscopy, photon spectroscopy, laser diffraction and hydrodynamic technique (Danaei *et al.*,2018).

3.1.2. Particle charge

- *Zeta analyser or zeta meter* - Zeta analyser is used to determine the zeta potentials of the diluted (c.a. 50 times) dispersions. Zeta potential determines the storage stability, release kinetics and biological fate of the colloidal dispersions.
- *Acoustic spectroscopy* - Acoustic spectroscopy is a technique employed for the evaluation of particle surface charge. It determines the charge by analysing the oscillating energy generated by particles moving under influence of acoustic energy (Bonacucina *et al.*,2016).

Table 1: Techniques for the Preparation of Lipid Nanoparticles

S. No.	Preparation Method	Drugs Loaded	Application	Advantages	Limitations	References
1	Hot high-pressure homogenization (Hot HPH)	Tamoxifen; Clotrimazole; Nile Red; Coenzyme Q10; Flurbiprofen; Clozapine; Etomidate; Retinol; Podophyllotoxin	Topical; Topical; Topical; Topical; Transdermal; Topical/Oral; Parenteral; Topical; Topical	Avoids the use of organic solvents; short production time.	Not suitable for heat-sensitive or hydrophilic drugs; particle aggregation; burst drug release due to high emulsifier concentration; drug leakage.	Reddy & Shariff, 2013; Tamjidi *et al.*, 2013; Bhaskar *et al.*, 2009; Junyaprasert *et al.*, 2009; Teeranachaideekul *et al.*, 2008; Souto *et al.*, 2004; Venkateswarlu & Manjunath, 2004; Jenning *et al.*, 2000.
2	Cold high-pressure homogenization (Cold HPH)	Vinorelbine bitartrate	Oral	Suitable for thermolabile and hydrophilic drugs.	Produces particles with high polydispersity index (PDI); energy-intensive process.	Lopes, 2014; Tamjidi *et al.*, 2013; Noriega-Peláez *et al.*, 2011.

3	Microemulsion-based SLN preparation	Valdecoxib; Minoxidil; Tretinoin; Methotrexate; Paclitaxel; Idarubicin	Topical; Topical; Topical; Topical; Parenteral; Oral/Topical	Thermodynamically stable system; no specialized equipment required; easy to scale up.	Toxicity associated with high surfactant/ co-surfactant concentrations; highly sensitive to formulation parameters; labor-intensive process.	Agrawal *et al.*, 2020; Mukherjee *et al.*, 2009; Joshi & Patravale, 2006; Cavalli *et al.*, 2000.
4	Solvent emulsification–diffusion technique	Tretinoin; Valproic acid; Isoniazid; Rifampicin; Insulin	Topical; Nasal; Oral; Oral; Oral	Avoids heat during production; suitable for thermolabile drugs.	Organic solvent residues in the final product; difficult to scale up.	Bhandari & Kaur, 2013; Mukherjee *et al.*, 2009; Zhang *et al.*, 2008; Cavalli *et al.*, 2000.
5	Ultrasonication/ high-speed homogenization	Ketoprofen; Naproxen; Nitrendipine; Thiolated PEG stearate; Vinpocetine; Insulin	Percutaneous; Percutaneous; Oral; Ocular; Oral; Oral	Avoids the use of organic solvents; easy to scale up.	Metal contamination; physical instability (particle size increases during storage); broad particle size distribution.	Mukherjee *et al.*, 2009; Shen *et al.*, 2009; Puglia *et al.*, 2008; Shah *et al.*, 2007.
6	Solvent emulsification–evaporation technique	Loperamide HCl; Insulin; Docetaxel	Parenteral; Oral; Parenteral	Simple and scalable procedure; suitable for thermolabile drugs.	Energy-intensive process; formation of polydisperse particles; possible biomolecule degradation.	Pérez-Tijerina *et al.*, 2008; Shen *et al.*, 2009; Akiyoshi *et al.*, 1998; Ueda & Kreuter, 1997.
7	Double emulsion technique	5-Fluorouracil; Alendronate; Bovine serum albumin; Raloxifene HCl	Oral; Oral; Oral; Oral	Suitable for hydrophilic drugs; avoids thermal stress.	Produces highly polydisperse particles with a high percentage of microparticles.	Nabi-Meibodi *et al.*, 2013; Yasin *et al.*, 2010.
8	Membrane contactor technique	α-Tocopherol	Oral/Topical/ Parenteral	Versatile, simple method; easy to scale up.	Membrane clogging.	Patil *et al.*, 2013.
9	Supercritical fluid technology	Indomethacin; Ketoprofen; Bovine serum albumin	Parenteral	One-step process; avoids organic solvents; produces dry powder particles.	Frequent nozzle blockage with hydrophilic drugs; expensive process.	Patil *et al.*, 2013; Chattopadhyay *et al.*, 2007.
10	Spray-drying method	10-Hydroxycamptothecin	Parenteral	Cost-effective; scalable process.	Particle aggregation due to high shear forces and elevated temperature.	Noriega-Peláez *et al.*, 2011; Zhang *et al.*, 2008.

11	Precipitation technique (solvent displacement/ ethanol injection/ microfluidic rapid mixing)	Fenofibrate; siRNA (Patisiran); mRNA (COVID-19 vaccines by Moderna and Pfizer-BioNTech); hydrophobic drugs	Intravenous; Intramuscular	Suitable for hydrophobic drugs; simple, rapid, scalable; high encapsulation efficiency.	Requires organic solvents; sensitive to mixing conditions; solvent removal required; possible particle aggregation; limited stability without optimization.	Umeyor *et al.*, 2026; Wilson & Geetha, 2022; Noriega-Peláez *et al.*, 2011; Mukherjee *et al.*, 2009.
12	Film–ultrasound dispersion	Budesonide; Doxorubicin; Paclitaxel; siRNA; Curcumin	Intranasal; Intravenous	Simple technique; no specialized equipment required; suitable for stimuli-responsive functionalization and high drug loading.	Metal contamination; broad particle size distribution; scale-up is challenging and often requires additional size reduction.	Chaturvedi & Kumar, 2012; Noriega-Peláez *et al.*, 2011.
13	Solvent injection technique	Rizatriptan; Hepatitis B surface antigen	Intranasal; Subcutaneous	Simple and easy to perform; rapid production process.	Residual organic solvents in the final formulation.	Shelake *et al.*, 2018; Mishra *et al.*, 2010.
14	Phase inversion technique	Idebenone	Topical	Suitable for thermolabile drugs; avoids organic solvents; minimizes particle aggregation.	Emulsion instability.	Montenegro *et al.*, 2012.

Table 2: Various SLN & NLC Preparations in Research

S. No.	Drug	Disease	Target Region/Problem	Inference	References
Topical Route					
1	Clarithromycin (SLNs & NLCs)	Bacterial infections; glaucoma; cataract	Target: Corneal tissues Problem: Poor bioavailability	Significant improvement in clarithromycin bioavailability ($p < 0.0001$) was observed with CL10.	Singh & Lillard Jr., 2009.
2	Colchicine (SLNs)	Gout	Target: Mitotic cells Problem: Poor penetration	The area under the curve (AUC) increased by 2.8-fold.	Balguri *et al.*, 2016.
3	*Zataria multiflora* essential oil	Fungal infections	Target: Microbial plasma membrane Problem: Low stability	Improved formulation stability was achieved.	Naseri *et al.*, 2020.
4	Citral (NLCs)	Cancer	Target: Tumor cells Problem: Poor stability	Increased stability, prolonged drug release, and reduced chemical degradation were observed. The instability index remained very low (0.032 after preparation and 0.042 after one month of storage), indicating excellent long-term stability at 25°C.	Nair *et al.*, 2021.

Oral Route					
1	Quercetin (SLNs & NLCs)	Obesity	Target: Inflamed cells Problem: Poor bioavailability	Oral bioavailability was significantly improved.	Cunha *et al.*, 2021.
2	Triptolide (SLNs & NLCs)	Cancer	Target: Lesions/tumor site Problem: Gastric irritation	Improved absorption and oral bioavailability with reduced gastric irritation.	Cunha *et al.*, 2021.
3	Puerarin (SLNs & NLCs)	Hypertension	Target: Endothelial nitric oxide synthase (eNOS) Problem: Poor bioavailability	Enhanced absorption and oral bioavailability were observed.	Cunha *et al.*, 2021.
4	Enrofloxacin (SLNs)	Bacterial infections	Target: Bacterial DNA topology Problem: Poor stability, palatability, and oral bioavailability	Enhanced bioavailability, sustained drug release, prolonged residence time, and a 1.92-fold increase in AUC were achieved.	Li *et al.*, 2021.
5	Lurasidone (SLNs)	Schizophrenia and bipolar depression	Target: Dopamine D_2 receptors; serotonin 5-HT_2A and 5-HT_7 receptors Problem: Poor absorption and bioavailability	Oral bioavailability increased by 5.6-fold.	Patel *et al.*, 2019.
6	Tilmicosin (NLCs)	Respiratory infections	Target: Gram-positive aerobic bacteria Problem: Low permeability and limited bioavailability	NLCs improved solubility, permeability, and oral bioavailability.	Duong *et al.*, 2019.
7	Donepezil (NLCs)	Alzheimer's disease	Target: Hippocampus Problem: Blood–brain barrier permeation	Nanocarriers with a particle size of 100–200 nm and a zeta potential of approximately +30 mV demonstrated improved brain delivery.	Zhang *et al.*, 2020.
Parenteral Route					
1	Baicalein (NLCs)	Neurodegenerative diseases	Target: Cerebral cortex and brain stem Problem: Short half-life	Compared with the free drug, baicalein-loaded NLCs significantly increased plasma concentration and prolonged half-life. Drug accumulation increased by 7.5-fold in the cerebral cortex and 4.7-fold in the brain stem.	Tsai *et al.*, 2012.
Pulmonary and Nasal Route					
1	Curcumin (NLCs & SLNs)	Cancer	Target: Tumor site Problem: Limited therapeutic activity	Improved antitumor activity and enhanced brain targeting were demonstrated *in vitro*.	Cunha *et al.*, 2021.
2	Montelukast sodium (NLCs)	Chronic asthma	Target: Cysteinyl leukotriene receptor-1 ($CysLT_1$) in the lungs Problem: Poor drug release and bioavailability	Sustained drug release, 96.1% entrapment efficiency, and a 143-fold increase in bioavailability were achieved.	Souto *et al.*, 2004.
Implants					
1	Estradiol valerate	Menopausal symptoms	Target: Sex hormone-binding globulin (SHBG) Problem: Uncontrolled drug release	A 16.8-fold increase in AUC and a 40-fold increase in Cmax were observed.	Fang *et al.*, 2013.

Table 3: Various Parameters and their Characterization Techniques Essential for the Evaluation of SLNs and NLCs

S. No.	Parameter	Purpose	Methods
1	Particle size and morphology	Determines the particle size distribution, morphology, and structural characteristics of nanoparticles.	a. Photon Correlation Spectroscopy (PCS)/Dynamic Light Scattering (DLS) b. Laser Diffraction (LD) c. Scanning Electron Microscopy (SEM) d. Transmission Electron Microscopy (TEM) e. Nuclear Magnetic Resonance (NMR) f. Atomic Force Microscopy (AFM) g. X-ray Diffraction (XRD)
2	Particle charge (zeta potential)	Determines the surface charge and predicts the physical stability of nanoparticle dispersions during storage.	Zeta potential analyzer (Zeta potentiometer)
3	Entrapment efficiency	Determines the drug-loading capacity of nanocarriers and evaluates the efficiency of the preparation method.	a. Ultracentrifugation b. Microfiltration c. Ultrafiltration d. Size-Exclusion Chromatography (SEC)
4	In vitro drug release	Determines the drug release profile and release kinetics from nanocarriers.	a. Dialysis bag diffusion technique b. Reverse dialysis bag technique c. Franz diffusion cell
5	Surface charge	Determines the electrical charge on the particle surface.	a. Acoustic method b. Zeta potential measurement
6	Coexistence of additional structures	Determines the presence of nanocompartments, phase separation, and dynamic phenomena in colloidal lipid dispersions.	a. X-ray Photoelectron Spectroscopy (XPS) b. Laser Doppler Anemometry (LDA) c. Surface Element Analysis by Electrophoresis d. Spectrofluorimetry
7	Crystallinity and lipid modifications	Determines the degree of crystallinity and polymorphic transitions of the lipid matrix.	a. Differential Scanning Calorimetry (DSC) b. Nuclear Magnetic Resonance (NMR) c. Powder X-ray Diffraction (PXRD)
8	Drug content	Determines the amount of drug encapsulated in the nanocarrier formulation for dosage determination and quality control.	a. UV–Visible Spectroscopy b. High-Performance Liquid Chromatography (HPLC) c. Spectrofluorimetry

3.1.3. Particle Morphology and Crystallinity

- *Electron Microscopic Techniques: The* two commonly used methods to directly observe the nanoparticles are transmission electron microscopy (TEM) and scanning electron microscopy (SEM). SEM provides the 3-D morphological and surface information of specimens over a wide particle size range, while TEM provides the high resolution. A 2-D image of particles briefing the detailed information of their internal structure *viz.* morphology, crystallization, stress, or even magnetic domains (Ready *et al.*, 2013; Klang *et al.*, 2012).
- *Atomic Force Microscopy* (AFM): It is a technique for physical scanning of particles at submicroscopic sizes with extremely high resolution, which, besides determining their size, can map the sample as per its properties.
- *X-ray Diffraction: The* lipid changes and crystallinity of the particles can be determined using the powder X-ray diffraction technique. It is based on the principle of processing and analyzing radiation dispersed from the crystalline planes of the solid sample to determine the specimen's degree of crystallinity (Dorset, 1998).
- *Optical Tweezers* (OT): OT is an advanced spectroscopic technique which, via implication of a single focused gradient beam, assists in restricting the movement and manipulating dielectric particles of micron/nanometric size range. The time and nature of a particle that gets entrapped within the electric zone depend upon the size and refractive index between

the particles and molecules in its surroundings. Holding of particles and confinement of their motility have been employed in determining the 3D physio-morphological characteristics of particles, viz., particle size, morphology, etc. Besides these, OT has been utilized for analysis of viscoelastic characteristics of biopolymers, cell motility, cell sorting, and cancer diagnosis (Lekka *et al*., 2012; Jores *et al*., 2003).

3.1.4. Chemical and Thermal Characterization of Nanoparticles

- *Nuclear Magnetic Resonance (NMR): NMR* could be used to qualitatively analyze the particle size as well as the nature of the nanoparticles (Mukherjee *et al*., 2009).
- *Co-existence of Additional Structures: The* magnetic resonance methods such as NMR and electron spin resonance (ESR) are useful for determining the compartmentation and the dynamic phenomena in the nanocolloidal dispersions (Müller *et al*., 1996).
- *Differential Scanning Calorimetry (DSC): DSC* is used to evaluate the nature, crystallinity, and thermodynamic stability of the particles by analyzing their thermal behavior (melting temperatures and enthalpy) (Gill *et al*., 2010).

3.1.5. Drug Entrapment and Release Profiles

- *Entrapment Efficiency (EE)*: EE signifies the amount of drug that is entrapped/encased within a colloidal carrier. The EE of the drug is commonly determined by the ultracentrifugation technique (Centrisart) and the dialysis membrane method (Wissing & Müller 2003). Both techniques employ a membrane (molecular weight cutoff >12 kDa) to separate out nanocarriers (blank/drug-loaded) from the free drug in suspension. The ultracentrifugation technique, in addition, employs an external centrifugal force to separate the particles. This further refines the filtration and accelerates the process. This is followed by detection of the drug (either free/entrapped) spectrophotometrically employing a UV spectrophotometer or HPLC.
- *In Vitro Drug Release Profile: These* studies are used for quality control and for the determination of the impact of process parameters on drug release. Dialysis tubing or a Franz diffusion cell (with a dialysis membrane) can be employed for the evaluation of drug release, subsequently processed, and quantitatively analyzed using a UV spectrophotometer or HPLC.

4. Applications of SLNs & NLCs

SLNs enable the controlled release of drugs for an extended period. The drugs can also be re-engineered to zero in on particular tissues or cells, increasing efficacy and decreasing collateral damage. SLNs have been used widely in the cosmetic industry to increase the solubility and stability of poorly water-soluble drugs. These are exploited for sustained release of active substances to enhance skin moisture and protection in skin care products. They are used in sunscreen to prolong their effect and stabilize UV protection. SLNs protect the vitamins and nutrients from degradation by adding them through encapsulation, hence facilitating better entrance of these molecules into the system. SLNs are being explored as gene delivery carriers, which provide protection and offer efficient transmission of genetic material in specific target cells. Since their crystal structure is not perfect, NLCs have a higher EE than SLNs, making them useful for delivering larger amounts of drugs. They are more stable in the NLC due to them being encapsulated, hence suffering less breakdown (Saharan *et al*., 2024; Mukherjee *et al*., 2009; Naseri *et al*., 2015; Wissing *et al*., 2004).

5. Recent Innovations and Novel Preparations of SLNs And NLCs

Formulating SLN and NLC has several advantages, including targeting, high bioavailability, good tolerance, and a lower risk of toxic product formation. The different formulations that provide these benefits are listed below that are helpful in treating various diseases. Table **4** summarizes patents related to Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC).

Table 4: Patents Related to the Study of SLN & NLC

Patent No.	Title	Description	Date of Issue	Reference
US 5785976	Solid Lipid Particles, Particles of Bioactive Agents, and Methods for the Manufacture and Use	Drug release can be controlled by modifying the lipid carrier. Solid lipid particles (SLPs) possess a lipophilic matrix that facilitates the encapsulation and solubilization of lipophilic and poorly water-soluble drugs.	28-07-1998	Westesen & Siekmann, 1997.

WO/2000/006120A1	Lipid Emulsion and Solid Lipid Nanoparticle as a Gene or Drug Carrier	The invention describes lipid emulsions and solid lipid nanoparticles as carriers for genes or drugs. Monoanions or polyanions may be incorporated to modify the interaction between the lipid carrier and DNA.	10-02-2000	Jeong *et al.*, 2000.
DE19952410B4	Sunscreen Preparations Comprising Solid Lipid Nanoparticles	The invention relates to sunscreen formulations containing solid lipid nanoparticles incorporating one or more ultraviolet (UV) filters to improve stability and performance.	17-05-2001	Heppner *et al.*, 2007.
WO/2006/128888A1	Use of Solid Lipid Nanoparticles Comprising Cholesteryl Propionate and/or Cholesteryl Butyrate	The invention describes the use of SLNs prepared from heated microemulsions containing cholesteryl propionate and/or cholesteryl butyrate for the prevention and treatment of vascular and inflammatory diseases.	07-12-2006	Gasco, 2009.
WO2006044660A2	Functionalized Solid Lipid Nanoparticles and Methods of Making and Using the Same	The invention relates to functionalized SLNs designed for magnetically guided targeting, thermoresponsive drug delivery, multimodal diagnostic–therapeutic applications, and tumor-targeted therapy.	26-05-2006	Shastri *et al.*, 2006.
WO2011116963A2	Lipid Nanoparticle Capsule	The invention describes a polymer-coated lipid nanoparticle delivery system comprising solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), each encapsulating at least one active pharmaceutical ingredient.	29-09-2011	Viladot Petit *et al.*, 2011.
WO/2013/105101A1	Solid Lipid Nanoparticles Entrapping Hydrophilic/ Amphiphilic Drugs and a Process for Preparing the Same	The invention relates to SLNs comprising one or more lipids selected from fatty acids and glycerides, together with hydrophilic or amphiphilic drugs and one or more emulsifying agents for efficient drug encapsulation.	30-01-2014	Kaur & Bhandari, 2012.

6. Future Direction

Lipid nanocarrier-based drug delivery has advanced remarkably, but before its clinical and commercial applicability, the following issues need to be addressed. Since it is technically challenging to maintain constant particle size, encapsulation efficiency and batch-to-batch consistency throughout the scale-up process, large-scale manufacturing continues to be a major challenge. The absence of standardised procedures for the characterisation, quality assurance, and safety assessment of lipid nanocarriers presents an additional challenge for regulatory approval. To assure the products' shelf life, additional optimisation is needed for long-term physical and chemical stability, including medication leakage, lipid oxidation and nanoparticle agglomeration during storage. Even though lipid nanocarriers are usually regarded as biocompatible, thorough research into their long-term toxicity, immunogenicity and biodistribution is still required, especially for chronic therapy and cases where repeated administration is conducted. Furthermore, the high cost of specialised lipids, sophisticated equipment and quality assurance processes add an additional barrier to its commercialisation.

Thus, research focussing on the development of scalable, cost-effective manufacturing technologies; standardised regulatory frameworks; advanced stabilisation strategies; and safer lipid-based formulations with improved targeting efficiencies is required.

7. Conclusion

Lipid nanoparticles, a rapidly growing colloidal system, are the young delivery devices and carriers of the future which have proved to be effective, promising, economical and patient-friendly in terms of the overall therapeutic index and safety profile of the drug. These are highly flexible structures with high loading and encapsulation efficiency, exhibiting

controlled and targeted drug delivery. These can be employed to incorporate varied drug moieties to target multiple disorders. But a thorough understanding and further research are required to investigate and exploit varied measures to improve the therapeutic and safety profile of the drug with the exploration of unrealised potentials of delivery systems.

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Authors Contribution

Ravi Goyal contributed to the methodology and prepared the original draft of the manuscript, with additional involvement in manuscript review and editing. Gurpreet Kaur was responsible for data curation and validation. Sumit Sharma carried out the experimentation and investigation. Deepika Raina contributed to data curation and validation. Deepinder Singh Malik conceptualized the study, developed the methodology, validated the findings, and critically reviewed and edited the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest related to this study.

Declarations

The authors declare that this work is original and has not been submitted elsewhere for publication. All data, methodologies, and system components have been developed and reported in adherence to academic standards. All referenced materials have been duly cited, and the authors accept full responsibility for the integrity and accuracy of the findings presented.

Ethical Approval

This study is a comprehensive literature review based exclusively on previously published articles and publicly available information. Therefore, ethical approval and informed consent were not required.

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This article does not contain any studies with human and animal subjects performed by any of the authors.

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