



Solid lipid nanoparticles: Preparation techniques, their characterization, and an update on recent studies

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ABSTRACT

Solid lipid nanoparticles (SLNs) have emerged as a remarkable nanocolloidal system for drug delivery. This review presents contemporary information regarding various aspects about SLNs, i.e., SLN morphology, structural features, preparatory methods, and their characterizations. This carrier system allows advancing the therapeutic efficacy of drugs belonging to several categories. The present uses of SLNs include cancer therapy, infectious conditions, diabetes, central nervous system disorders, cardiovascular disorders, cosmeceuticals, and others. SLNs facilitate improved the pharmacokinetics and modify the drug releases. The prospect of surface modification, enhanced permeation against various biological barriers, the ability to resist chemical degradation, and the possibility of encapsulation of two or more therapeutic agents simultaneously has gained attention for SLNs universally. Simultaneously, this review emphasizes on recent research trends pertaining to this carrier system.

INTRODUCTION

In the past few years, there has been a fascinating development in nanoscale drug delivery technologies. Majorly biocompatible polymers and lipid excipients have been on the rise, which efficiently incorporated in the lipid nanosystems. These lipids are usually physiological lipids possessing little acute and chronic toxicities (Hadis *et al.*, 2019; Harde *et al.*, 2011). Solid lipid nanoparticles (SLNs) offer an amalgamating effect of several carrier systems such as liposomes and niosomes. Similar to other carrier systems, SLNs are also constituted by biocompatible excipients that are physiologically accepted and homology to polymeric nanoparticles. The solid matrix in SLNs also proposes to protect the loaded therapeutic molecules against the rough biological environment and also shield the other chemical degradations with maximum feasibility to alter the release profiles of the therapeutic molecule. Altogether, these proficiencies make the SLNs an exceptional carrier system (Das and Chaudhury, 2011).

SLNs are morphologically spherical with a smooth surface possessing mean diameter ranging between 50 and 1,000 nm. Both *in vivo* and *in vitro* behaviors are dependent on the physicochemical characterization of SLNs. Solid lipid (at 25°C–28°C), emulsifiers for certain times simultaneously, and along with appropriate solvent for solubilizing lipid and non-lipid components, together constitute the typical SLNs (Fig. 1).

While formulating SLNs, lipids listed in Generally Regarded as Safe are commonly employed (Weber *et al.*, 2014). These comprise of fatty acids/esters, cholesterol, triglycerides (e.g., compritol® 888 and caprylic), and waxes (bees, carnauba, etc.). Pluronic F68/F127, poloxamers, and sodium cholate are considered for emulsification. Organic salts, surface modifiers, and ionic polymers are served for PEGylation, specific targeting, surface charge modifications. SLNs are classified into (a) drug-loaded shell, (b) drug-loaded core, and (c) homogeneous matrix, based on entrenched site of the therapeutic molecule within the SLN structure. Advantages and applications are shown in Figure 2.

The process of cooling hot liquid droplets followed by phase separation yields a drug-loaded shell. This rapid cooling results in liquid precipitation that forms SLNs on complete cooling. This category of SLNs fits well for topical conditions. Unlike the shell model, drug-loaded core, the drug ought to crystallize much before liquid precipitate. The drug-loaded core model facilitates

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the sustained release of therapeutic agents and obeys Fick's law of diffusion. Highly lipophilic drugs are dispersed homogeneously within the lipid matrix employing cold homogenization. Hence, SLNs benefit in smooth production, employing simple homogenization techniques (Aleksandra *et al.*, 2018; Jenning *et al.*, 2000). A comprehensive understanding of various production techniques is further discussed in the following section.

PREPARATION OF SLN

High-pressure homogenization

High-pressure homogenization (HPH) has been used as a reliable technique for the preparation of SLN. Several manufacturers produce homogenizers of diverse sizes at a reasonable cost. The particles of the submicron range are obtained at elevated shear stress and cavitation compulsion. Nanoemulsions for parenteral nutrition

are produced by HPH. HPH pushes the liquid at high pressures (100–2,000 bar) through a narrow space (range of few microns). The fluid moves faster over a short distance with high velocity. With homogenization, even the high lipid concentration could be transformed into nanodispersions (Wolfgang and Karsten, 2001).

Hot and cold homogenization techniques are the means for the manufacturing of SLN. A preparatory step involves in both the cases. Lipid matrix used in this process is extracted from the physiological lipids which reduce the risk of acute and chronic toxicity.

Hot homogenization

Temperatures higher than the melting point of the lipid are selected for this process and can subsequently be considered as the homogenization of an emulsion. An aqueous surfactant is used for the combination of lipid and drug at the same temperature. A device for high shear mixing is used to prepare a hot pre-emulsion, resulting in an emulsion of oil in water type. Then, the product is left for cooling, and this leads to the initiation of crystals of lipid and then the formation of SLNs. For the production of perfect SLNs, 3–5 cycles of homogenization at a pressure of 500–1,500 bar are necessary (Akanksha *et al.*, 2012). One should always be aware that there is a rise in temperature with HPH. With the rise in the number of cycles or the pressure, there is a growth in the particle size. This is due to attractive forces between the particles which are due to the energy of moving the particles (Siekman and Westesen, 1994). Finally, cooling of the nanoemulsion to room temperature is done, where the recrystallization of lipids occurs and this leads to the formation of nanoparticles (Fig. 3).

Cold homogenization

This technique has been developed to combat the problems of hot homogenization such as faster deterioration due to high temperatures, loss of drug during homogenization into the aqueous phase, and undetermined polymorphic transformations of the lipid due to the complexity of crystallization.

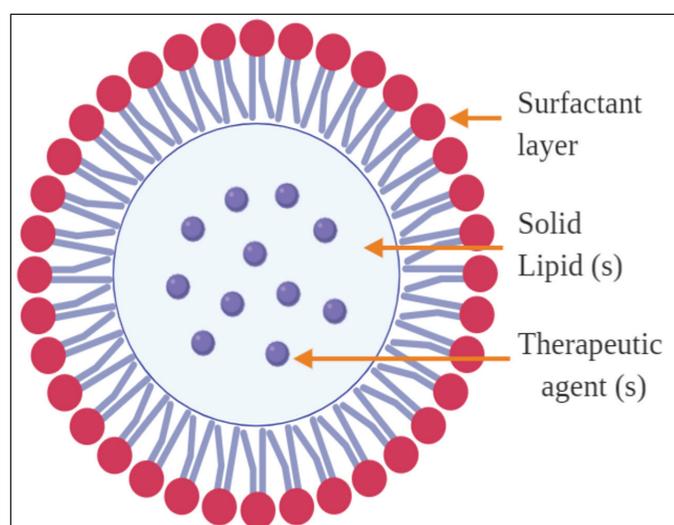


Figure 1. Structure of SLNs.

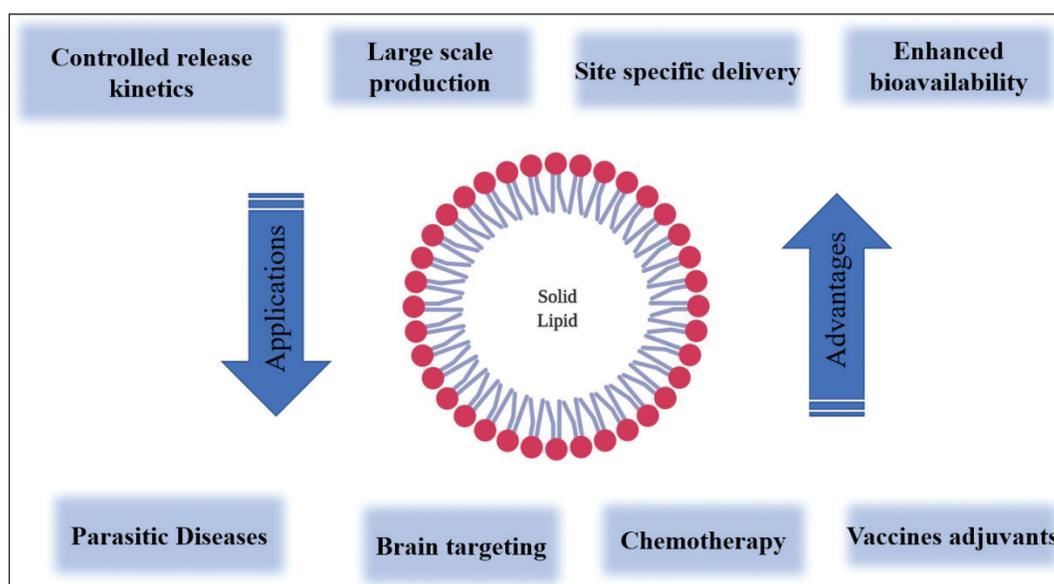


Figure 2. Representation of advantages and applications SLNs formulations.

The first elementary step is indistinguishable as in the hot homogenization technique which includes the solubilization of drug in the lipid melt. The successive steps are altered; the drug-containing melt is refrigerated speedily with the aid of solid carbon dioxide or liquid nitrogen for attaining a homogenous drug distribution lipid matrix. The solid is then levigated into a fine dust by using a ball mill. Typical dust size attained is in the range of 50–100 μm . In the chilled aqueous surfactant, the fine dust particles are dispersed. Now, the dispersion is subjected to HPH to initiate the SLN production (Fig. 4). However, compared to a hot homogenization technique, greater particle sizes and wider size distribution are typical of the cold homogenized product (Mehnert and Mäder, 2001)

Cold homogenization lessens the heat vulnerability, but it is not completely avoided due to the softening of lipid mixture in the opening step.

Ultrasonication

SLN was also produced by high-speed stirring or sonication (Eldem *et al.*, 1991). The impedimenta used for this method is prevalent in every single laboratory. The main drawback of this technique is wider particle size distribution ranging into micrometer range which is the main cause for physical instability (Svilenov and Tzachev, 2009). Particle gain on storage and potential metal decay are acute problems in this method. After many studies and intense research, it was proved that high-speed stirring and

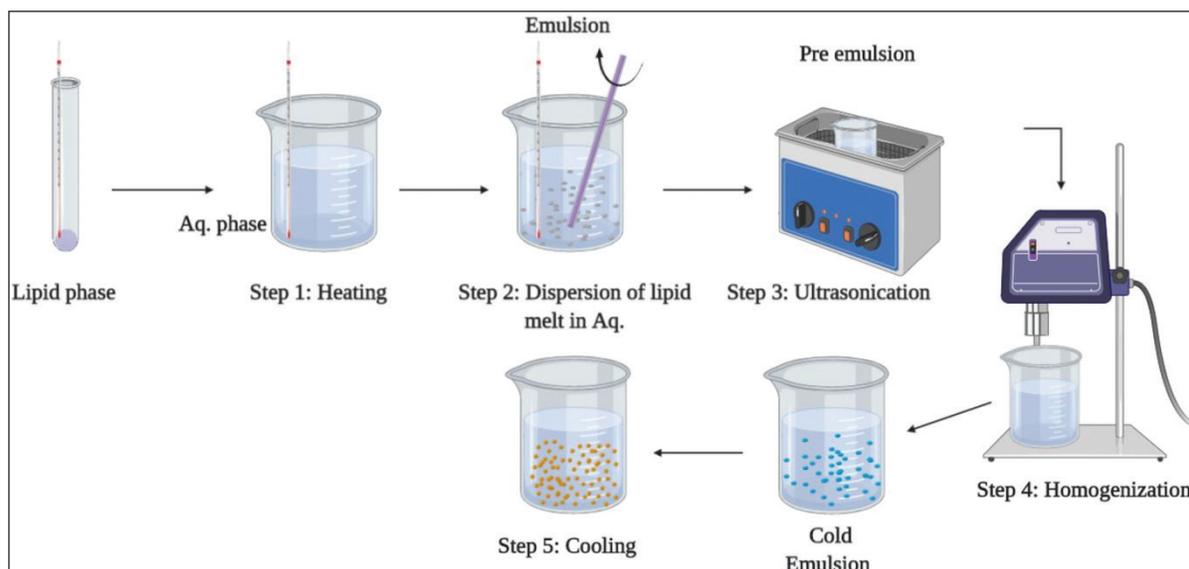


Figure 3. Hot homogenization technique.

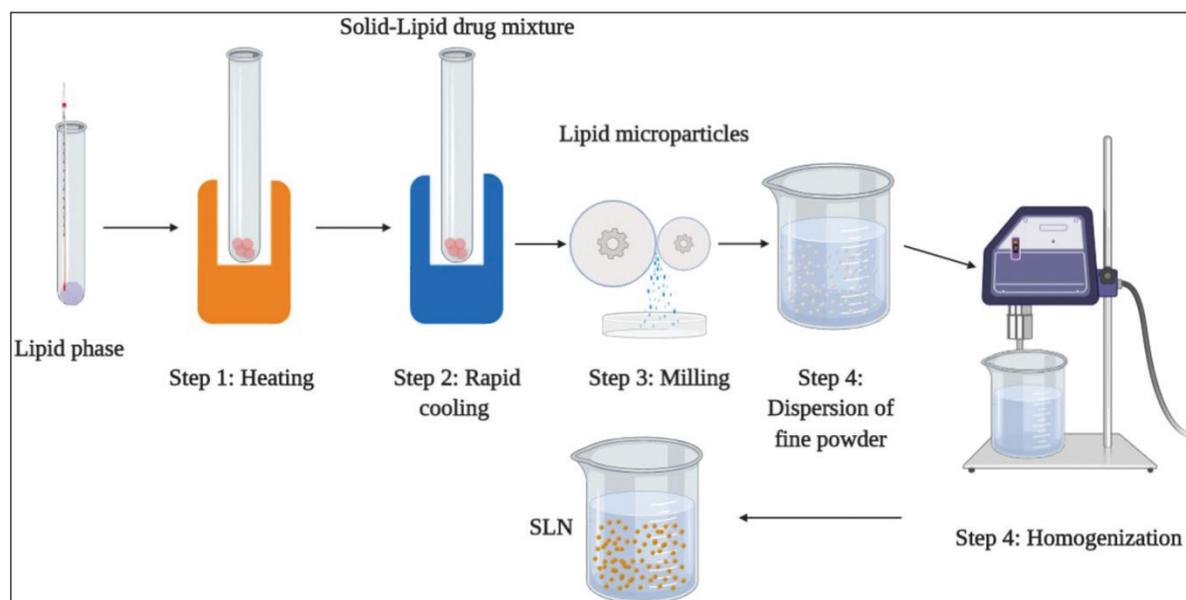


Figure 4. Cold homogenization technique.

ultrasonication, when operated combinedly at high temperatures, yield a steady formulation (Eldem *et al.*, 1991) (Fig. 5).

Solvent emulsification–evaporation

In this method, the lipophilic material and hydrophobic drug are dissolved in water-immiscible organic solvents such as cyclohexane, toluene, and chloroform. Now, by using a high-speed homogenization, the mixture is emulsified in an aqueous phase. The coarse emulsion is instantly allowed to flow through a microfluidizer. A rotary evaporator with mechanical agitation at room temperature and decreased pressure is used to evaporate the organic solvent (Ramteke *et al.*, 2012). The main mastery of this technique is bypassing the thermal stress. Therefore, now, there is a possibility for the incorporation of highly thermolabile drugs (Fig. 6). The clear-cut disadvantage is the use of an organic

solvent which may react with drug molecules (Sjostrom and Bergenstahl, 1992)

Supercritical fluid (ScF)

This is a comparatively advanced technique for the manufacturing of SLNs. The supercritical fluid has distinct thermophysical properties which can be finely adjusted by minute modifications in the pressure. It is solvent-free processing (Chen *et al.*, 2006; Kaiser *et al.*, 2001). With the elevation in pressure, the density and capability of fluid to liquefy compounds enhance, whereas the velocity remains the same. ScF is a substance above its pressure and critical temperature. The fluid has special properties at these conditions: liquid-like density, gas-like viscosity, and larger diffusivities than those of typical liquid (intermediate to that of a liquid and a gas), giving rise to its higher

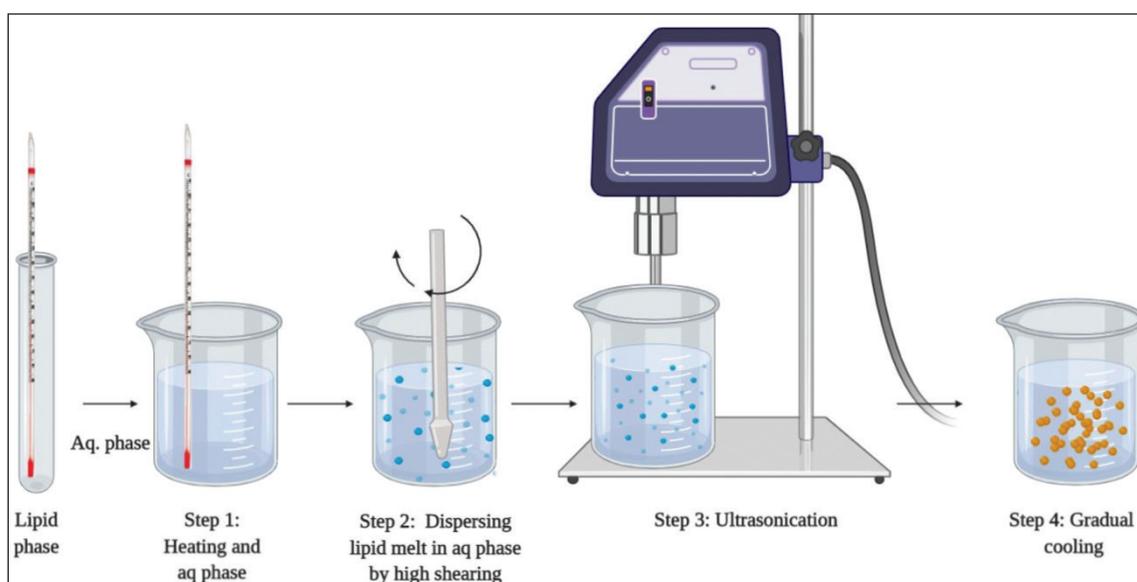


Figure 5. High shear homogenization or ultrasonication technique.

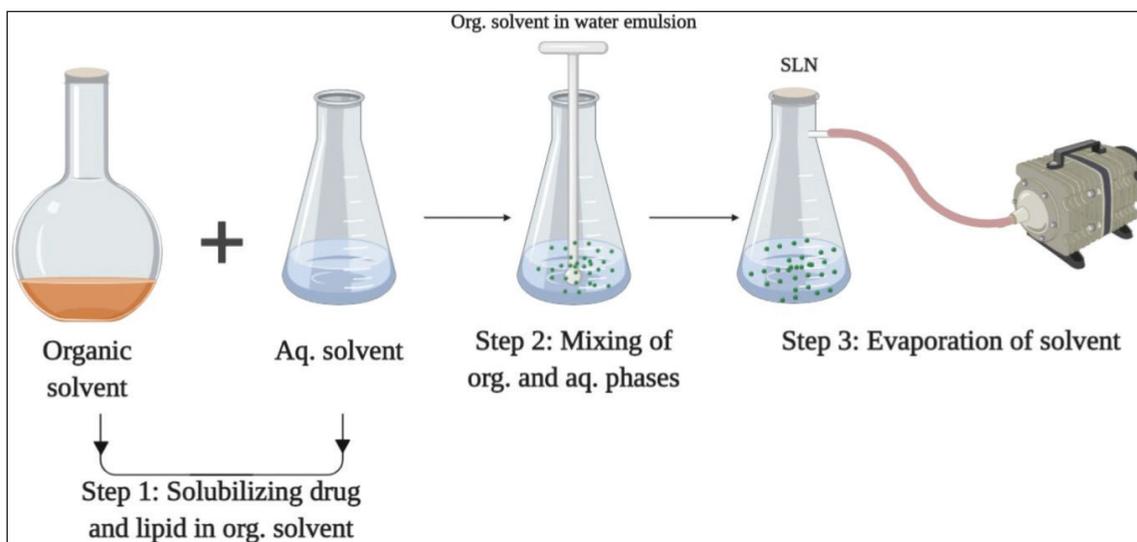


Figure 6. Solvent emulsification-evaporation technique.

mass-transfer rate. Various techniques such as rapid expansion of supercritical solutions (RESS), supercritical antisolvent process and precipitation with a compressed antisolvent process (PCA), particles from gas-saturated solutions/suspensions, and supercritical extraction from emulsions can be used.

The high solubility of the drug in ScCO₂ (solvent) is required for carrying out RESS technology. In this process, the supercritical fluid is quickly enlarged via a nozzle to convert the solute as micro- or nanoparticles. There are three major factors which regulate the particle, and the particle growth is a short residence time, not much time available for particle growth and maximum dilution of the particles in the expansion chamber (Garces *et al.*, 2018). Pure powder griseofulvin has been acquired using a cosolvent such as methanol which improves the drug solubility in ScCO₂ for about 28 folds. The usage of a simple capillary nozzle, griseofulvin NPs in the range of 50–250 nm has been derived (Thakur and Gupta, 2005).

In the PCA technique, an atomized drug solution along with compressed carbon dioxide is introduced into the chamber. After the solution gets supersaturated, fine crystals precipitate out. A supercritical fluid with poor drug solubility is selected and used. The drug is dissolved in the solvent. This solvent should be miscible with the supercritical fluid. The supercritical fluids pull out all the solvent, and then, the drug solution becomes supersaturated after introducing the drug solution into the supersaturated solution. The drug precipitates as fine crystals (Alessi *et al.*, 2012). The key advantage of this method is the particles which are acquired as a dry powder, instead of suspension (Fig. 7).

Microemulsion

SLN preparations were developed by Gasco and coworkers on the basis of reducing the concentration of microemulsions (Akanksha *et al.*, 2012). These microemulsions are biphasic units consisting of external and internal mediums. Combination consists of a low melting fatty acid (e.g., stearic

acid), an emulsifier (e.g., polysorbate 20, polysorbate 60, and soy phosphatidylcholine), coemulsifiers (e.g., butanol and sodium mono cetyl phosphate), and water. In the cold water (2°C–3°C), the hot microemulsion is diffused. Based on the combination of microemulsion, the dilution process can be fixed. In this method, there is no extra energy consumed for attaining the submicron size (Gasco, 1997; Ramteke *et al.*, 2012). The main criteria for the production of nanoparticles are that they can be produced only with certain solvents which rapidly distribute into the aqueous phase (Fig. 8), whereas more lipophilic solvents are utilized for obtaining the large particle sizes. The main advantage of this method is low mechanical energy input which is sufficient.

Spray drying

It is another procedure to lyophilization for the modification of an aqueous dispersion into a drug. It is an economical method when compared to lyophilization. There is a chance of particle gathering due to the elevated temperature, shear forces, and incomplete melting of the particle (Jawahar *et al.*, 2012). Freitas *et al.* (1998) recommended that the lipids with a boiling point higher than 70°C should be selected for spray drying. The best result was procured by spray drying with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol–water mixtures (10/90 v/v).

Double emulsion

This method is used for the preparation of hydrophilic-loaded SLNs based on solvent emulsification–evaporation (Svilenov and Tzachev, 2014). First, the drug is dissolved in aqueous-based solutions and then dissolved in a liquid melt. A stabilizer is used for the stabilization of the primary emulsion (He *et al.*, 2015). This primary emulsifier is dispersed in the aqueous phase composed of hydrophilic emulsifier. Now, the double emulsion is blended and then separated by sifting (Fig. 9). Poly (lactic-co-glycolic

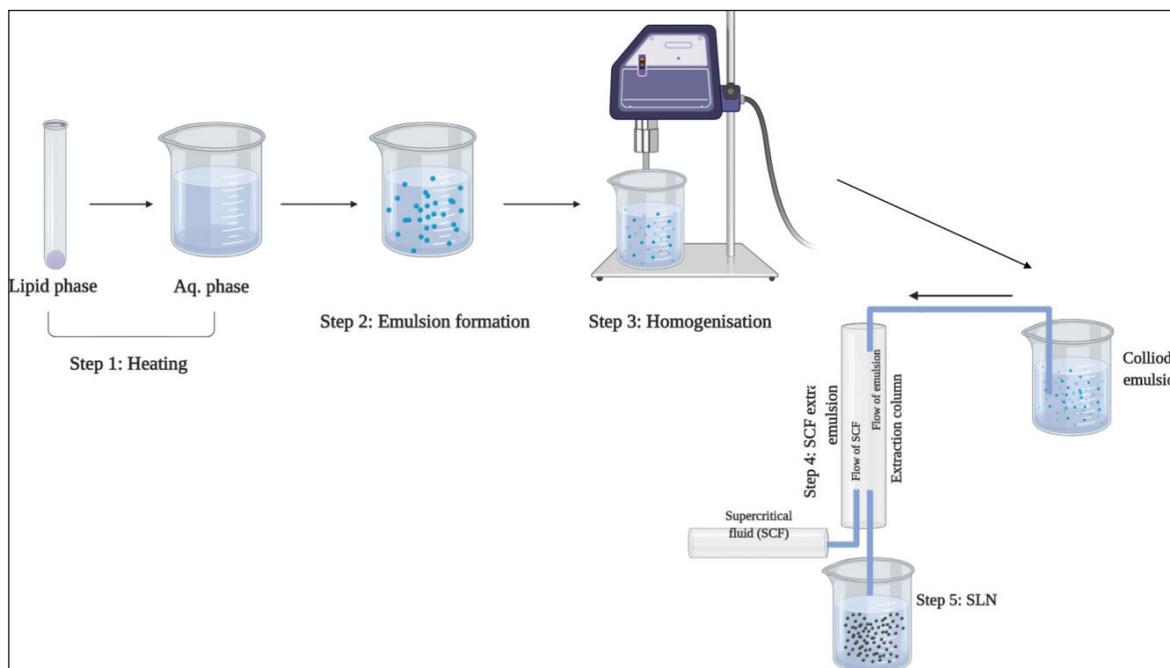


Figure 7. Supercritical fluid technique.

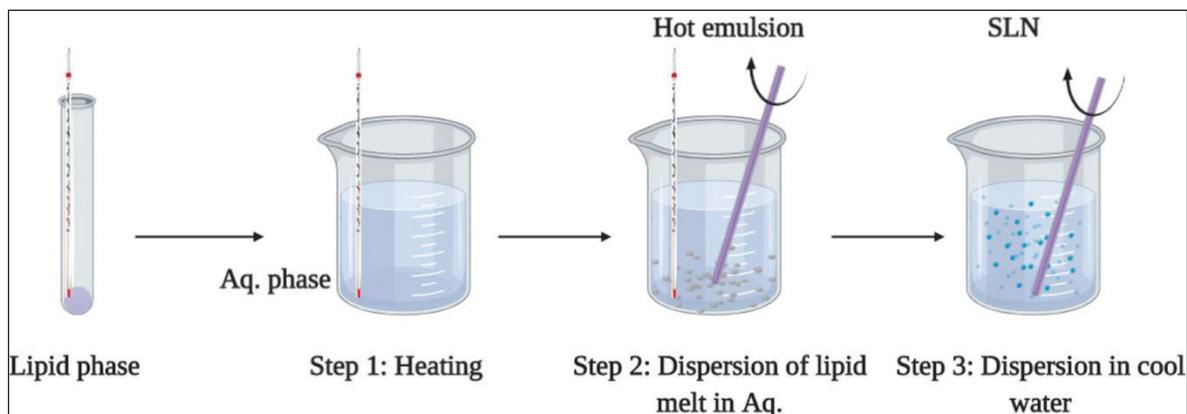


Figure 8. Microemulsion technique.

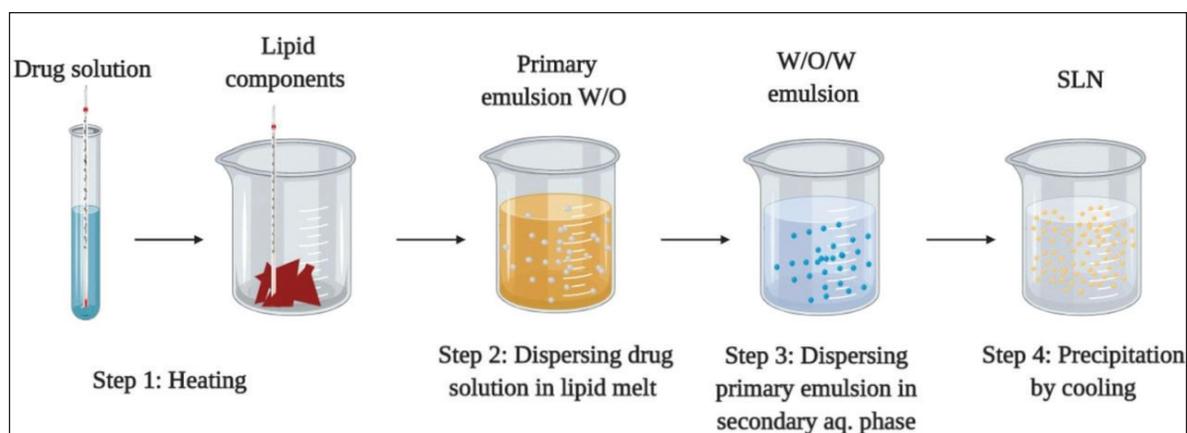


Figure 9. Double emulsion technique.

acid) (PLGA) is vital for the primary w/o emulsion emulsification process. It is observed that with the increase in the concentration of PLGA, there is an enhancement in loading capacity, w/o emulsion stability, and the encapsulation efficiency. PLGA has no impact on the SLN particle size, and with the increase in the concentration of PLGA, there is a significant decline in the zeta potential.

Characterization of SLNs

Several techniques and instruments employed for the characterization of SLNs are discussed as follows (Paurnima *et al.*, 2018; Poovi and Damodharan, 2017).

Visual size and distribution

Photon correlation spectroscopy (PCS)

PCS measures the variations of scattered light by means of particle movement. It measures a size range of about a few nanometers to 3 microns. It depends on the diffraction angle on the particle radius (Jerome *et al.*, 2004).

Laser diffraction (LD)

LD has a merit that it has a wide range from nanometer to lower millimeter. Polarization intensity differential scattering increased the sensitivity of LD to small particles (Mukherjee *et al.*, 2009).

Dynamic light scattering

It records the difference in the intensity of the scattered light in the time gap of microseconds. Light is scattered under Brownian motion and quantified by the compilation of an autocorrelation function. Few presumptions such as size, low concentration, and viscosity are measured by this coefficient (Van de Ven *et al.*, 2009).

Static light scattering (SLS)

It is also known as Fraunhofer diffraction. It is a method where the pattern of the scattered light is collected from a solution of particles and placed in an electromagnetic equation. It is a rough and quick method (Akanksha *et al.*, 2012).

Electrical surface potential and pH

Zeta potential

Its measurement can be analyzed using zeta potential analyzer or zetameter. Zeta potential gives information about the magnitude of the electrostatic repulsion or attraction between particles in the aqueous suspension of SLN (Mishra *et al.*, 2012).

pH-sensitive probes

A pH probe is a scientific device that determines the H⁺ ion activity in hydrophilic liquids. On the basis of pH, they give

information about the acidity and alkalinity of the substances. The magnitude of electrochemical potential is estimated by the Nernst equation (Karmen *et al.*, 2011).

Shape and surface morphology

Transmission electron microscopy

A high energy beam of electrons are excited across the analyte (very fine), and thus, interactions among these electrons and the atoms can be used to perceive the features such as the crystal structure and features in the structure such as dislocations and grain boundaries (Jores *et al.*, 2004).

Scanning electron microscopy

It produces sample images by scanning the surface with a focused beam of electrons. These electrons interact with samples and produce various signals that contain information about the surface topography and composition of the sample.

Atomic force microscopy

This involves colloidal or resistance across the sample. This movement between tip and surface is tracked by the topological map based on the forces that play. This approach helps us to obtain ultrahigh resolution by mapping the sample (Carrillo *et al.*, 2013).

Optical microscopy

Optical microscopy also referred to as light microscopy is a type of microscope, which utilizes the light of visible range along with an arrangement of magnifying lenses to observe the small objects. This type of microscope captures the image by normal, photosensitive cameras to obtain a micrograph (Majid *et al.*, 2019).

Crystallinity

X-ray diffraction

This process is used to measure the degree of crystallinity, and this is determined by the scattering of radiation from the crystal plane within a solid substance. X-ray diffraction method can be used to determine the crystallinity with a nanoparticle. This method is useful to test the bulk material (Andreas *et al.*, 2012)

Surface hydrophobicity

Two-phase partition

This method splits the compounds in two different immiscible fluids usually polar and nonpolar, on the basis of their relative solubilities. The chemical potential aids in the separation process. The two major types are polymer/polymer and polymer/salt systems. Some of the factors affecting the phase separation are pH, biomolecule concentration, polymer concentration, and biomolecule's surface properties. They impart sensitive conditions that do not damage liable biomolecules (Johanna *et al.*, 2018).

Contact angle measurement

The contact angle is the angle between solid-liquid interaction at interface or two vapors or two liquids. It is based

on Young's equation. The device used to measure is goniometer. A scale of maximum contact angle to minimum contact is seen in a dynamic phenomenon of contact angle hysteresis. Contact angle has been crucial in parameter to estimate the wetting capacity of the polymer membrane surface. There are a few factors affecting the contact angle such as heterogeneity, surface roughness, and size and shape of the particle (Kai *et al.*, 2017).

Examples of alternative instrument are radiolabel probe and synchrotron radiation X-ray (Poumellec *et al.*, 2016).

Density

Gas pycnometer

The gas pycnometer is an apparatus used to calculate the true density of a solid material by using Archimedes principle and Boyle's law. In this instead of a fluid an inert gas is used, mostly helium is used. There are a few advantages as it gives quick with accurate results.

Viscosity

Viscometer

A viscometer is a device used to calculate the viscosity of a fluid. For fluids with changes in flow conditions, another device named rheometer is used. Viscometer can only determine under a single flow condition. Usually, either the object passes through the fluid or the liquid stays without movement or vice versa. For the condition of flow, there need to have a slight value of Reynolds' number for laminar flow. There are different types of viscometers: u-tube viscometer, falling sphere viscometer, Krebs' viscometer, quartz viscometer, etc. (Vandana and Amit, 2019).

Molecular weight

Gel permeation chromatography

It is otherwise known as size exclusive chromatography that enables separation on the basis of analyte size.

In vitro release

Membrane diffusion method is broadly used to investigate *in vitro* drug dissolution. The methods including dialysis sac method, reverse dialysis sac method, and side-by-side dialysis method are used, in many devices (Ghada and Rania, 2009).

Sample and separation methods are used to separate the dispersed nanoparticles from the continuous phase. Amount of drug is examined. Because of the little size of nanoparticulate systems, it is very hard to segregate them from the media (Ramteke *et al.*, 2012)

Continuous flow methods were developed initially to alter the oral dosage release. The use of United States Pharmacopeia apparatus four method has a lot of advantages in restoring the *in vitro* surrounding (Junxian *et al.*, 2009).

Summarizing Studies on Lipid Nanoparticles for Their Therapeutic Benefits

Enhanced bioavailability

Nanomedicine is a credible approach in improving the therapeutic benefit of anticancer drugs (Fan *et al.*, 2014).

Intravenous administration has raised difficulties for patients undergoing chemotherapy as it requires professional supervision. The major advantage of oral chemotherapy is patient compliance and flexibility in timing and ease of administration. Unfortunately, due to the rough biological conditions and poor diffusion across gastrointestinal (GI) tract, many anticancer drugs are poorly bioavailable through oral administration (Mei *et al.*, 2013). Paclitaxel shows successful activity against breast, lung, and ovarian cancers. Cytochrome P450 activity and P-glycoprotein (P-gp) present in the stomach lining and liver limit the bioavailability of drug through oral route (Hendriks *et al.*, 2013). These difficulties in oral delivery of anticancer drugs, namely, drug-resistant tumors, toxicity, and low stability, are resolved by SLNs (Yadav *et al.*, 2014).

Some materials may be entrapped in the external layer of SLNs to enhance the therapeutic activity of the oral delivery systems. Wheat germ agglutinin (WGA) was coated by Pooja *et al.* (2016) to enhance the oral paclitaxel delivery. The incorporation of paclitaxel into WGA-covered SLNs led to a fold increase in mean residence time. Baek *et al.* improved the surface of paclitaxel with the aid of hydroxypropyl-beta-cyclodextrin (Baek *et al.*, 2012). The dextrin has a property to enhance the solubility and prevent the oxidation of lipids (Zafar *et al.*, 2014).

Docetaxel is a second-generation taxane enormously used for the cure of prostate, lung, breast, and neck/head cancers. Due to poor bioavailability, the designing of oral docetaxel is hindered. Tween 80 or D-alpha-tocopherol polyethylene glycol succinate-coated SLNs were developed to boost the oral delivery of the drug (Cho *et al.*, 2014). SLNs showed a sustained docetaxel release when set side by side with taxotere. Vorinostat is an inhibitor of histone deacetylase (HDAC) that effectively promotes apoptosis and cell cycle arrest for the cure of T-cell lymphoma (Ozaki *et al.*, 2008). Combination of HDAC and a variety of DNA destroying agents is a favorable chemotherapeutic plan for the death of tumor cells. Hashem *et al.* assessed the bioavailability through oral route and cytotoxicity of SLNs enveloping tamoxifen, the drug for dealing with breast cancer (Hashem *et al.*, 2014). The profiles for *in vitro* release testing gave out an instant preliminary release followed by sustained release. About a 1.6-fold increase in bioavailability was observed with SLNs administration.

Nowadays, oral SLNs are used in antitubercular therapy. Antitubercular drugs such as pyrazinamide, rifampicin, and isoniazid loaded in SLN were able to drop the dosage frequency and boost the patient compliance (Pandey *et al.*, 2005). The mechanism for the preparation of antitubercular drug-loaded SLNs is emulsion solvent diffusion technique. These drugs enhanced bioavailability. Paclimer is a standard formulation developed to assist in maintaining progressive and systematic levels of paclitaxel (PTX) for a long duration of time. The composition constitutes of polylactofate polymer-loaded PTX, which was developed by Harper in 1999 who later tested its efficiency in the treatment of non-small-cell lung carcinoma (Jain *et al.*, 2012). Expansile is another standard nanoparticle formulation used for lung cancer cells. This drug has a special feature of responding to the high acidic pH present around the

cancer cells. These nanoparticles act on the acidic-hydrophobic group that causes swelling of polymeric nanoparticle and release of the payload (Zubris *et al.*, 2012).

Disorders such as depression and anxiety which are treated by oral dose are constrained by aqueous solubility, first-pass effect, and short half-life (Jain *et al.*, 2012). Treatment for psychotic disorders needs regular dose administration, which can lead to less patient compliance and high cost (Zubris *et al.*, 2012). By mixing dopamine agonist, apomorphine is formed which is used in the treatment of Parkinson's disease. The quick breakdown of apomorphine in the GI tract has shown the results of 1.7% in a bioavailability (Subramony, 2006). SLNs gave the results of 13-fold higher in bioavailability than the reference solution. There are a few headache disorders such as migraines which carry symptoms of nausea, photophobia, etc. The first drug accepted by the US Food and Drug Administration was sumatriptan. Encapsulated sumatriptan chitosan-coated SLNs were used (Hansraj *et al.*, 2015). Rizatriptan-loaded SLNs exhibited an 18-fold increase in brain uptake in rats according to an *in vivo* study. The first-line antidepressant venlafaxine is used for the treatment of depressive disorders and anxiety. Since venlafaxine substrate at P-gp, its penetration is reduced across GI and blood-brain barrier (Minassi *et al.*, 2013). However, a marked increase in area under the curve (AUC) of about 1.5-fold was observed from SLNs in the brain venlafaxine solution.

For treating cardiovascular (CV)-related diseases, SLNs have been used orally, to enhance drug plasma concentration and prolong circulation duration. These features are important for attaining better therapeutic benefits. Under refrigeration at room temperature, the optimized SLNs were stable for 3 months (Hernandez *et al.*, 2002). A 2.2-fold increase in the oral bioavailability of SLNs was given by the pharmacokinetic study as compared with nisoldipine suspension. For hypertension and heart failure remission, a prodrug of candesartan called candesartan cilexetil and an angiotensin-2 type-I receptor antagonist is employed. Using dynasan as the solid-lipid, oral bioavailability was increased more than 2.8-fold by SLNs after inclusion of candesartan cilexetil (Dudhipala and Veerabrahma, 2016). An antihypertensive drug called carvedilol has a low oral bioavailability of 20% because of the first-pass effect. SLNs were developed with N-carboxymethyl chitosan coating which improved oral delivery while protecting carvedilol in an acidic environment (Venishetty *et al.*, 2012). In simulated gastric fluid, 5.2% of the drug was released by polymer-coated SLNs for 24 hours. The AUC of polymer-coated SLNs was higher than non-coated SLNs and free control. Anemia could be treated using iron supplements. However, in the GI system, these iron supplements that are commercially available can cause undesirable effects (Murioz *et al.*, 2011). Hence, a biphasic release behavior with a burst release followed by sustained release iron-loaded SLNs is exerted. There was about a 4-fold gain in oral iron bioavailability.

Oral raloxifene has been accepted in the treatment of postmenopausal osteoporosis. Due to its poor aqueous solubility and glucuronide conjugation, thus only 2% raloxifene is orally bioavailable (Gluck and Maricic, 2003).

Using Compritol 888 ATO as the lipid and poloxamer 188 as emulsifier SLNs for raloxifene delivery was prepared (Hu *et al.*, 2008). SLNs yielded a prolonged drug release for 24 hours, whereas control gave complete release within 4 hours. For the treatment of postmenopausal osteoporosis, a calcium-regulating peptide hormone called salmon calcitonin secreted from the ultimobranchial gland of salmon is employed (Cheng *et al.*, 2009). In a study, prepared SLNs exhibited effective *in vivo* hypercalcemic effect in rats than free calcitonin. The examination of the protective efficacy of SLNs on calcitonin opposed to pancreatin was studied. A major part of free calcitonin was broken down within 15 minutes, whereas in SLNs the rate of degradation was much slower.

SLNs were extensively used in treating infections, and they were utilized for loading antimicrobial agents to cure bacterial, parasitic, viral, and fungal infections. For example, antitubercular drug isoniazid proposed by the World Health Organization for treating all sorts of tuberculosis. A drug with a short half-life suggests the requirement for repeated dosing which leads to toxicity in the liver (Preziosi, 2007). SLNs loaded with isoniazid enhanced the bioavailability and extended circulation retention (Bhandari *et al.*, 2013). A three-phase design was observed from the *in vitro* release comprising a primary rapid release, followed by a hump and eventually subsided. Miconazole is a broad-spectrum antifungal drug with poor water solubility. A loading of miconazole in SLNs exhibited a two-phase drug release with a primary outburst followed by a delayed release (Aljaedi *et al.*, 2016). In the diffusion disk, the SLNs showed a better mortality.

Lopinavir was used in the antiretroviral treatment, a human immunodeficiency virus (HIV) protease inhibitor. Since the first-pass metabolism and P-gp efflux it, SLNs behave as a viable porter for lopinavir. Due to its particle size and release rate, the lopinavir-loaded SLNs were stable for 4 months at 4°C (Negi *et al.*, 2013). When compared with the solution form of lopinavir, the SLNs gave a higher oral bioavailability because of improved lymphatic delivery. Compritol 888 was utilized as the solid-lipid for formulating lopinavir-loaded SLNs (Negi *et al.*, 2014). Primaquine is exclusively used to prevent the relapsing form of malaria. Higher doses of primaquine conventionally lead to hematological- and GI-related toxicity (Baird, 2012). A good controllable release of the drug over 72 hours was observed by the entrapment of primaquine in SLNs (Omwoyo *et al.*, 2014). In these days, praziquantel is used for the treatment of parasitic disease, schistosomiasis. Due to the minimal effect on schistosomiasis, De souza *et al.* added praziquantel into SLNs to study the improvement of therapeutic efficiency (De Souza *et al.*, 2014). After a detailed study, it was noticed that SLNs were more efficient causing parasitic mortality in less duration when differentiated to free drug.

Enhanced permeation

The current research suggests the availability of abundant compounds obtained from natural resources for the treatment of cancer (Aljuffali *et al.*, 2016). The anti-inflammatory, antioxidant, anti-apoptotic, vasodilating, and antimicrobial potentials of these

products are responsible for their anticancer effects (Iriti *et al.*, 2009). An innate form of Vitamin E tocotrienol has a promising anticancer activity in breast malignancy. However, oral delivery of gamma-tocotrienol is less effective (9%) (Yap *et al.*, 2003). To improve the permeation in the intestine, SLNs were employed as the design for gamma-tocotrienol (Abuasal *et al.*, 2012). SLNs are used as targeted drug carriers for the cure of neoplasms. SLNs packed with drugs such as camptothecin and methotrexate have been used for targeting tumors (Ruckman *et al.*, 2006). An anticancer drug tamoxifen has been loaded in SLNs to improve the penetrability and retentivity and also for the sustained release of the drug following IV administration in breast cancer therapy (Murthy, 2005).

Enhanced cellular uptake

Hyperglycemia, a result of diabetes, is a serious pathological condition leading to nervous system-related and CV destruction. Through the oral route, the absorption of insulin is tough because of gastric pH (acidic), epithelial cells of the GI tract, and various digestive enzymes (Gundogdu and Yurdasiper, 2014). After many research experiments, SLNs were found as the conveyors to guard the proteins and peptides which are known for the sensitivity toward the environmental considerations (Almeida and Souto, 2007). SLNs enveloped with stearic acid-octarginine as a conveyor for insulin was outlined by Zhang *et al.* (2012). Octarginine is a cell-permeating protein chain, which induces cellular uptake of certain drugs (Golan *et al.*, 2016). This design expressed a remarkably enhanced hypoglycemic effect (3-fold) in rats when differentiated with nonenveloped SLNs. SLNs were designed consisting of Dynasan 114 as the lipid solid matrix for the case of insulin delivery through the oral route (Ansari *et al.*, 2016). SLNs also expressed a greater protection of insulin from the GI environment when discerned from the solution form. SLNs enclosed with polyethylene glycol (PEG) were designed to enhance the stability of glibenclamide in gastric solution. Oral SLNs showed a rapid decrease in glucose levels and further sustained for 8 hours after administration, whereas the administration of free glibenclamide through oral route (5 mg/kg) decreased glucose levels after 4 hours, and it retained to primary high levels in diabetic rats (Goncalves *et al.*, 2016).

Reduced toxicity

Metal nanoparticle has a cytotoxic impact on lung cells, and this is caused by the presence of metal nanoparticle in water, medicine, food, and cosmetic creams and lotions which we use on a daily basis. The size, concentration, and duration of exposure affect the level of cytotoxicity. These factors play a role in lung cancer and need to be controlled. The studies have been conducted for lung cancer therapy and diagnoses using nanoparticle. However, there has been a more extensive study with gold (Au) nanoparticle. Annihilation of A549 lung cancer cells could be achieved using hallow Au/silver (Ag) nanostructures with dendritic morphology (Hu *et al.*, 2008). Similarly, Au-based nanomaterials conjugated with an antibody for photothermal therapy of tumor cells have been developed. It was observed that Gold nanoparticles (Au-NPs) in conjugation

with methotrexate, an analog of folic acid, produced a cytotoxic effect. It was observed that conventional treatment for lung cancer is costly and failed to deliver the accurate results, and hence, a need for novel technique for the diagnosis of lung cancer from Au-NP-based diagnosis from breath sample was studied (Chen *et al.*, 2007). Principally volatile organic compound is altered in exhaled breath of person suffering from lung cancer compared to healthy individuals. Enzyme-linked immune solvent assay is less effective than hollow Au nanospheres in detecting lung cancer (Chon *et al.*, 2009). Neodymium used in treatment of cancer cell belongs to group of rare earth metals. Neodymium is observed to be cytotoxic against cancer cell neodymium oxide (nano Nd₂O₃), which was observed to induce vacuolization and extensive autophagy in cells by disturbing mitochondrial membrane and also arrest cycle in S phase (Chen *et al.*, 2005).

Diamonds measuring less than 1 μm are called nanodiamonds. These are carbon materials generated by events such as an explosion and meteoritic impacts. As it is not cytotoxic in lung cells, it remains harmless and biocompatible. It has numerous implementations such as tracing and tagging of cancer cells (Liu *et al.*, 2007). These nanoparticles associate with different molecules such as DNA, proteins, chemicals, and various anticancer drugs through covalent and noncovalent bonds. Superficially reorganized carboxylated nanometer-sized diamond was evaluated and detected. There was no reduction in cell viability and change in the protein expression profile in lung cells, but they stimulated cytotoxicity. In the case of lung cancer therapy, nanodiamonds are associated covalently with PTX. During experimentation, this combination when injected into xenograft of immunodeficiency mice restricted the growth of tumor and formation of cancer cells in the lungs by instigating apoptosis and mitotic arrest (Liu *et al.*, 2010).

Metals and their combinations have been used in the field of medicine from thousands of years. Arsenic, antimony, bismuth, gold, vanadium, iron, rhodium, titanium, gallium, and platinum are the ten most vital metals which show many anticancer activities. Transition metals can associate with many negatively charged atoms by presenting a varied number of oxidation states. For instance, a transition metal complex named cisplatin contains an ion of platinum metal in its center (Desoize, 2004). Cis-diamminedichloroplatinum (DDP, cis-platin), which is an anticancer drug, is useful for the treatment of varied types of tumors, but because of its poor cancer-specific targeting and its dangerous side effects, its use nowadays is limited. Then, in 2011, Peng *et al.* reported the production of biocompatible epidermal growth factor receptor (EGFR)-targeted heparin DDP nanoparticles by associating one chain variable fragment anti-EGFR antibody to it as the ligand of targeting for cancer in the lungs (Peng *et al.*, 2011). Newly, a new class of metal-established anticancer drugs of ruthenium has come out its efficiency in activity when compared to platinum and its less toxicity. Some of these drugs passed phase-1 trials (Vajpayee *et al.*, 2011).

Enhanced biocompatibility

Engineered nanomaterials have a distinctive size, shape, charge on the surface, crystallinity, solubility, and

surface coating. These features can trigger chemical state in cells to actuate a pro-oxidant condition within the cells, giving rise to disproportionate energy in the cells, causing the induct of inflammation path to the death of cells. For example, silver nanoparticles, which are round in shape, are mostly harmless to human alveolar epithelial cells, whereas wire-shaped nanoparticles exhibit vigorous cell toxicity (Stoehr *et al.*, 2011). The cell toxicity to varied cell lines has catalyzed necrosis and apoptosis techniques, which are one after the other stimulated by modifying the structure of the membrane (Carlson, 2008). The sole limitation that holds back the substantial implementation of Ag-NP is its deprived biocompatibility to the living conditions. Altering organically by covering the Ag-NP with latex from stems of *Euphorbia nivulia*, a medicinal plant showed a remarkable enhancement in the biocompatibility of silver nanoparticles. These nanoparticles are cytotoxic against human lung carcinoma cell (A549) condition on dose (Valodkar *et al.*, 2011). Latex-covered nanoparticles are produced from the terpenoid and peptide portions of the latex, which cross the membrane of the cell and can be employed as a biocompatible transporter for the NP.

Polymeric micelles are immensely confederated nanopatforms for targeting cancer, distribution of the drug, and cancer imaging. Supermagnetic iron oxide is extensively used as a contrasting agent, which enhances the visibility of blood vessels. A multifunctional micelle (MFM) system is converted into code along with a lung cancer-targeting peptide and enfolded with superparamagnetic iron oxide and doxorubicin for MR imaging and therapeutic delivery. When compared to a scrambled peptide-coded MFM, LCP-coded MFM exhibited remarkably upgraded alpha, beta-based cell targeting in H2009 lung cancer cells (Guthi *et al.*, 2010). An aqueous soluble and biocompatible theranostic anticancer drug transporter has been developed by conjoining fluorescent polymer chain and folic acid along with magnetic iron oxide or silica. Folic acid that is added helps for targeted drug delivery, and the fluorescent agent helps in imaging the target (Chen *et al.*, 2010).

Bionanoparticle approaches are the major research in metal-based nanotherapeutics, but in the case of *in-vivo* studies, their biocompatibility and toxicity are major concerns to be noted. Hence, to control the above-mentioned problems, the present researchers have diverted their concentration on the bionanotechnology-based therapeutic component. In this development, an already existing biological system is selected and is incorporated with therapeutic nanoparticles. This incorporation with biological components improved the stability and biocompatibility of the overall system. The examples for this type of systems are models with carrier molecules such as albumin nanoparticles or ABI-007 or hematoporphyrin-linked albumin nanoparticles with therapeutic components such as paclitaxel or gamma-emitting nuclides or carboplatin (Green *et al.*, 2006; Ibrahim *et al.*, 2002). Table 1 shows further research findings of SLN formulations reported by researchers. Tables 2 and 3 show the patents and clinical trials of various lipid systems in recent times, respectively.

Table 1. Research findings of SLNs formulations reported by researchers.

Therapeutic agent	Formulation components	Preparation methods	References
Chitosan-Shea butter SLNs (C-SLNs)	Curcumin, Phospholipids/ Tween 80 stabilised shea butter SLNs, Chitosan microparticles (CS-C-SLNs), Sodium tripolyphosphate (TPP)	High shear homogenization–ultrasonication	(Hassan <i>et al.</i> , 2018)
SLNs loaded with Simvastatin (SIM-SLNs)	Solid lipids glyceryl behenate, Glyceryl palmitostearate containing Tween 80 as surfactant	Nanotemplate engineering	(Rizvi <i>et al.</i> , 2019)
Piroxicam loaded SLNs	Piroxicam, Tripalmitin lipid, Polyvinyl alcohol (PVAL) stabilizer, Ethyl acetate solvent	Solvent emulsification/ Evaporation method	(Soliman <i>et al.</i> , 2018)
Ibuprofen loaded SLNs (Microparticles)	Ibuprofen with Glyceryl behenate, Tripalmitin, Beeswax	Emulsion congealing	(Long <i>et al.</i> , 2006)
Itraconazole (ITZ) (Intravenous formulation)	ITZ, Tristearin, Triolein, EggPC, Tween 80, DSPE-PEG 2000	HPH	(Jin <i>et al.</i> , 2010; Kang <i>et al.</i> , 2018)
Pterodon pubescens fruit oil NLCs	Precirol® ATO 5, 0.5% Phospholipon® 80H, PEG-40 hydrogenated castor oil/ sorbitan oleate	Melt emulsification	(Outuki <i>et al.</i> , 2018)
Candesartan Cilexetil-(CDC) SLNs	CDC, Stearic acid, Poloxamer 188, Dialysis membranes-70	Emulsification-Ultrasonication	(Arjun and Kishan, 2013)
[6]-shogaol- loaded liposomes (6-SRGO-LLPS)	Carrier 1,2-Dimyristoylsn- glycerol-3-phospho-rac- glycerol (used to produce liposomes), sodium salt, (DMPG-Na) lipid, 6-shogaol,	HPH	(Wang <i>et al.</i> , 2018)
Trehalose monooleate SLNs for Cyclosporin-A topic release	Dichloromethane (DCM), chloroform, n-hexane, concentrated sulfuric acid, 1-butanol and methanol, trehalose, Oleic acid, Dicyclohexylcarbodiimide, DCC, DMAP, Dimethylaminopyridine, Polyoxyethylene sorbital monolaurate(Tween 20), Biliary acid, Coumarin-6, Cyclosporin-A, Methylparaben, Propylparaben	Microemulsion	(Sonia <i>et al.</i> , 2019)
Glutathione loaded SLNs (GSH-SLNs)	Gelucire® 50/13, L-Glutathione reduced (GSH), Tween 85, acetic acid, 2,2-diphenyl-1-picrylhydrazyl (DPPH), cetyltrimethylammonium bromide, 3,3',5,5'- tetramethylbenzidine hydrochloride (TMB) phorbol myristate acetate (PMA), fluorescein isothiocyanate (FITC) and luminol, Penicillin and streptomycin, RPMI-1640 culture medium and foetal calf serum (FCS)	X-ray photoelectron spectroscopy analysis (XPS)	(Adriana <i>et al.</i> , 2018)
Clothronycin	Liquid matrix, Glyceryl behenate, Tripalmitin and stearic acid.	High speed homogenization technique.	(Alper <i>et al.</i> , 2019)
Seabuckthorn	Probiotic, Lactobacillus acidophilus, Bifidobacterium lactis, TTA.	Microwave extraction.	(Aynur <i>et al.</i> , 2016)
Clotrimazole loaded SLN and NLC	Cetostearyl alcohol, Cetyl esters wax, 2-octyldodecanol, polysorbate 60, Sorbitan monostearate, Benzyl alcohol, purified water.	Hot high-pressure homogenization technique.	(Souto <i>et al.</i> , 2004)
Cholesteryl butyrate SLN	Cholesterol, Cholesteryl, Acetonitrile, Chloroform, methanol (1:1:1 v/v)	Microemulsion formulation	(Elena <i>et al.</i> , 2001)
Polyhydroxy surfactants	Non-ionic ethylene oxide	Hot high-pressure homogenization	(Andjelka <i>et al.</i> , 2014)
Doxorubian	Adriamycin	Small angle neutron scattering (SANS), small angle X-ray scattering (SAXS).	(Fabiano <i>et al.</i> , 2018)
Lopinvir (Lo) SLN	Lopinavir and ritonavir	Hot homogenization, ultrasonication.	(Aji <i>et al.</i> , 2011)
Tretinain (TRE) SLN	Steric acid, Isopropyl, Myristate, Polyoxyl 40 stearate, Xanthan gum, Sorbic acid, Butylated Hydroxytoluene.	Simple emulsion solvent diffusion (ESD) technique	(Shah <i>et al.</i> , 2007)
Fenfitrate and Nabumetone SLN	Hypromellose, Polyethylene glycol, Polysorbate 80, SLS, Microcrystalline cellulose, Titanium dioxide.	Hot melt homogenization.	(Raj <i>et al.</i> , 2020)
Ascorbic acid	Vitamin C complex, Ascorbic acid, Volatile acid	Hot homogenization	(Gamze <i>et al.</i> , 2014)
Trans- Ferulic acid (TFA)	Ethyl oleate, Glyceryl behenate.	Microemulsion	(Zhang <i>et al.</i> , 2016)
Rivastigmine (RHT) SLN	Hydroxypropyl methylcellulose, Magnesium state, Microcrystalline cellulose, Silicon dioxide, Compritol 888 ATO, Poloxamer 188	Ultrasonication, Homogenization.	(Brijesh <i>et al.</i> , 2015)
α Bisabolol SLN	Sterols, Triterpenes, Volatiles, Polar and other constituents.	Hot homogenization	(Sethuraman <i>et al.</i> , 2018)

Table 2. List of patents published for various lipid systems.

Application number	Publication date	Title	Applicants
PCT/IB2018/001073	19.03.2020	Mucoadhesive dispersion nanoparticle system and method for production the same	Lead Biotherapeutics Ltd. [bg/bg]; bg
201833026370	17.01.2020	An improved acyclovir loaded solid lipid nanoparticulate gel formulation for topical application and method of formulating the same	Subhabtota, Majumdar, Samir kumar, Samanta, Suvalaxmi sarkar
201831016759	08.11.2019	Nanoparticle for targeted oral chemotherapy	Chakrabarti, gopal
201822045013	27.09.2019	Multilayer coating	Meril Life Sciences Pvt Ltd
PCT/IN2018/050300	26.09.2019	Drug-coated balloon	Meril Life Sciences Pvt Ltd [in/in]; bilakhia house muktanand marg, chala, vapi, gujarat vapi 396191, in
201910404515.0	06.08.2019	Preparation method of chlorogenic acid lipid nanoparticle solid dispersion	Bengbu University
16377032	01.08.2019	Compositions and methods for nanoparticle lyophile forms	Nitto Denko Corporation
PCT/IB2017/001582	20.06.2019	Solid lipid nanoparticle for intracellular release of active substances and method for production the same	Lead Biotherapeutics Ltd. [bg/bg]; bg
16263769	06.06.2019	Fluorescent solid lipid nanoparticles composition and preparation thereof	Bracco Imaging S.p.A.
201910182104.1	28.05.2019	Preparation method and application of resveratrol-solid solid lipid nanoparticle	Bengbu Medical College
1020170144092	09.05.2019	Composition for preventing or treating xeroderma containing phragmites communis root extract and serine-loaded solid lipid nanoparticles as active components	Erom Co., Ltd.
201811397576.0	09.04.2019	Ampelopsin grossedentata total flavonoid solid lipid nanoparticles and preparation method	Fujian University of Traditional Chinese Medicine
201811110809.4	08.03.2019	Construction method and application of nano drug loading system targeting cell endoplasmic reticulum	Zhejiang University
201711028760	01.03.2019	Topical nanoformulation of tetrahydrocurcumin (thc)	University Institute of Pharmaceutical Sciences
201810924463.5	04.01.2019	Carvacrol solid lipid nanoparticles dispersion liquid with bacteriostatic activity, preparation method and application thereof	Wuhan Polytechnic University
201721010354	28.09.2018	SLNs composition comprising metformin and pomegranate peel extract for the treatment of diabetes mellitus type II.	M.C.E.Society's Allana College of Pharmacy
201721010355	28.09.2018	SLNs composition comprising fenofibrate and pomegranate peel extract for the treatment of hyperlipidaemia.	M.C.E.Society's Allana College of Pharmacy
201810366608.4	21.09.2018	Local analgesic microneedle device for neuropathic pain and preparation method thereof	Sun Yat-sen University
201810266539.X	21.08.2018	Sports fatigue-resistant resveratrol solid lipid nanoparticles and preparation method thereof	Tongji University
201810042421.9	10.08.2018	Cyclosporin solid lipid nanoparticles with good storage physical stability and preparation method thereof	Nanchang University

WIPO - Search International and National Patent Collections (2020).

Table 3. List of clinical trials being carried in for lipid systems for various disease types.

Agent and trial no.	Trial type	Disease type	Title	Status	Phase	Study completion date
NCT03323398	Interventional (Clinical trial)	Advanced malignancies	Dose Escalation and Efficacy Study of mRNA 2416 for Intratumoral Injection Alone and in Combination with Durvalumab for Patients With Advanced Malignancies	Recruiting	Phase 2	March 2022
NCT04213937	Interventional (Clinical Trial)	Extensive Stage Small Cell lung cancer	The Efficacy and Safety of Nab-paclitaxel Versus Topotecan As Second-Line Treatment for Patients with Extensive Stage Small Cell Lung Cancer: A Multicentre, Randomized Controlled Study	Recruiting	Phase 2	January 31, 2022
NCT04183257	Interventional (Clinical Trial)	Vitamin D Deficient Type 2 Diabetes	Effect of Escalating Oral Vitamin D Replacement on HOMA-IR in Vitamin D Deficient Type 2 Diabetics	Completed	Phase 4	July 30, 2017
NCT03352843	Interventional (Clinical Trial)	Malaria	Single Low-dose Primaquine Efficacy and Safety for Treatment of Uncomplicated Plasmodium Falciparum Malaria Based on Cytochrome P450 2D6 Activity	Recruiting	Phase 4	November 30, 2020
NCT03314064	Interventional (Clinical Trial)	Infection, HIV	Long-term Safety of Subjects Continuing Dolutegravir After Participation in Clinical Studies of Dolutegravir in Russian Federation	Completed	Phase 4	October 1, 2018
NCT03199560	Interventional (Clinical Trial)	Sentinel lymph node biopsy	Tilmanocept vs. Sulfur colloid in Sentinel lymph node biopsy	Recruiting	Phase 4	August 22, 2019
NCT04186377	Interventional (Clinical Trial)	Diabetic Foot Ulcer Healing	A Study of the Effectiveness of Local S26E Extract Application for Diabetic Foot Ulcer Healing	Recruiting	Phase 2	November 29, 2021

Continued

Agent and trial no.	Trial type	Disease type	Title	Status	Phase	Study completion date
NCT04213170	Interventional (Clinical Trial)	Lung Cancer	Sintilimab Combined With Bevacizumab for Driving Gene-negative, Asymptomatic Brain Metastases From Non-small Cell Lung Cancer	Recruiting	Phase 2	December 2022
NCT04085419	Interventional (Clinical Trial)	Primary Hyperparathyroidism	Management of Osteoporosis in Patients With Primary Hyperparathyroidism	Recruiting	Phase 4	May 2022
NCT04206865	Interventional (Clinical Trial)	Decompensated Heart Failure and Low Cardiac Output	Comparison of ARNI to Alternate Oral Vasodilator Therapies to Determine the Hemodynamic Profile and Relative Tolerability of (ARNIs) in Patients with Decompensated Heart Failure and Low Cardiac Output	Recruiting	Phase 4	March 31, 2022

Home - ClinicalTrials.Gov (2009).

CONCLUSION

SLNs have radically gained the attention of several researchers with its exceptional properties and benefits over other conventional dosage forms, and other colloidal counterparts of SLN have proved to be a significant discovery in nanotechnology because of their effective performance and as a safe vehicle in pharmaceutical drug delivery. SLN as a colloidal drug carrier puts together the advantages of polymeric nanoparticles and fat-based emulsions. These systems abet various benefits such as easy incorporation of lipid- and water-soluble drugs, adequate physical stability, and available at low cost and easy to manufacture. Their inherent characteristics qualify SLNs as competent nanocarriers in the expansion of targeted delivery systems for the clinical trial investigations. Similarly, SLNs also favor sustained release besides effective drug targeting.

AUTHORS' CONTRIBUTION

All the authors were equally contributed to the data collection, information, writing, and critical review helped design for a framework of the document.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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