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FORMULATION TECHNIQUES OF LIPID BASED NANOPARTICLES: SLN/NLCS, ITS EVALUATION AND APPLICATIONS

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ABSTRACT

This review represents the usage of SLN and NLCs regarding their advantages, formulation methodology, characterization and applications. If suitably investigated, SLNs/NLCS may open new prospects in therapy of complex diseases. Solid lipid nanoparticles (SLN) were formulated at the emergence of the 1990s as a replaced carrier system to emulsions, liposomes and polymeric nanoparticles. SLN are aqueous colloidal dispersions, the matrix of which consists of solid biodegradable lipids. Nano structured lipid carriers (NLCs) are drug-delivery systems consists of both solid and liquid lipids as a core matrix. It was shown that NLCs has some advantages for drug therapy over conventional carriers, including higher solubility, the ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery. SLN and NLCs are manufactured by techniques like high pressure homogenization, solvent diffusion method ultrasonication, solvent emulsification etc. Both SLN/NLCs have applications in for parenteral, nasal, respiratory, ocular, rectal, and topical, in chemotherapy, etc.

Keywords: SLN, NLCs, colloidal drug carriers, homogenization, characterization, application.

1. INTRODUCTION

Now days, in pharmaceutical science, targeted delivery of drug moiety to particular organ position is highest demanding research field. Liposome, nanoparticles and micelles are other nano formulation for delivery of drug. Nanoparticles with their unique characteristics like size of nanoparticles, big surface area and the potential of altering surface properties have some benefits compared with other delivery systems. 10 to 1000 nm is suitable size range of nanoparticles. Dissolution and incorporation of drug are the active principles involve in the formulation of nanoparticles. In latest years, important effort has been dedicated to promote nano formulation for delivery of active drug. Drug having limited size range are transported by this approach.

Solid lipid particle are proposed in 1991 as surrogate to other traditionally available colloidal systems which involves other formulations like liposome, emulsions and polymeric nanoparticles. Solid lipid containing nano formulation is more attractive approach for delivery of drug intravenously. SLN are also called as submicron colloidal structure of limited size range from 50 to 100 nm containing physiological lipids Examples are triglycerides with different chain lengths (e.g. Dynasan series, Cremer Oleo, Germany), glyceryldibehenate (Compritol 888 ATO, Gattefossé, France), or carnauba wax and beeswax, and dissolve in aqueous phase containing surfactant. Particles having small diameter, big surface area, high loading capacity and high incorporation of drug are the most important characteristics of SLN. Oral

bioavailability is increases due to the use of solid lipid and fluctuation in plasma level of drug is minimized.
In SLN formulation the drawback associated with the lipid in liquid state and droplets of oils neglected by using lipid in solid state.
NLCs have been evolved as alternative drug carrier systems. NLC matrix is composed of mixture of spatially different lipid molecules, normally mixture of solid and liquid lipid, which makes more imperfection in the matrix to accommodate more drug molecules than SLN. Despite the presence of liquid lipid, NLC matrix is solid at room/body temperature. It is expected that the drug-loading capacity will be enhanced, drug expulsion during storage will be minimized due to the imperfect crystal lattice and drug release profile can be easily modulated by varying the lipid matrix composition(Figure 1).

1.1. Advantages of SLN

- ✓ Enhance the bioavailability of the molecule which is less soluble in water.
- ✓ SLN containing physiological lipid which minimize the risk of toxicity.
- ✓ Targeting the drug to specific area, improving diffusion of drug into skin by dermal route.
- ✓ Desirable biocompatibility.
- ✓ Great and increased drug content.
- ✓ Enhanced stability of pharmaceuticals.
- ✓ Control drug release.
- ✓ Excellent reproducibility with cost effective high pressure homogenization has been reported.
- ✓ There are many routes of administration are available for SLN such as intravenous, dermal, per oral and topical.
- ✓ High concentration of functional compound accomplish.

1.2. Disadvantages of SLN

- ✓ Of course the solubility of actives in solid lipids is lower than in liquid lipids, thus the SLN had a lower loading capacity than emulsions, NLCs.
- ✓ Relatively high water content of the dispersion.
- ✓ Uncertain gelatin tendency.
- ✓ Polymeric transitions is occurs.
- ✓ Particle growth.
- ✓ High possibility of high-pressure-induced drug degradation leading to poor product quality, and loss of loaded bioactive.

1.3. Advantages of NLCs

- ✓ Minimum drug leakage than SLN during storage.
- ✓ Physical stability is better than SLNs
- ✓ Drug loading is higher than SLNs
- ✓ Ease of production and scale up
- ✓ Entrapment efficiency is great for both lipophilic and hydrophilic drug
- ✓ Extended release of drug
- ✓ Controlled size of particle in formulation
- ✓ Hydration and elasticity of skin has been increased

1.4. Disadvantages of NLCs

- ✓ There is a irritation and sensitization due to use of some surfactant
- ✓ Application and efficiency in case of protein and peptide drugs and gene delivery systems still need to better exploited
- ✓ Lack of sufficient preclinical and clinical studies with these nanoparticles in case of bone repair, and cytotoxic effects related to the nature of matrix and concentration.

2. METHOD OF PREPARATION

2.1. High shear homogenization (HSH)

High shear homogenization is technique which uses the high pressure of 100-2000 bar. In this method, the liquid is forced at very high viscosity through small gap of few microns, which causes breaking of particles.5%-40% lipid concentration has been examined by this method. High pressure homogenization process is further differentiated into two methods namely: Hot high pressure homogenization and Cold high pressure homogenization.

2.2. Hot High Pressure Homogenization

The temperature required for hot high pressure homogenization technique is temperature above the melting point of the respected lipid. The process involves melting of the lipid and dissolving the drug in that melted lipid. Further hot aqueous surfactant solution is prepared and then dispersing this drug loaded lipid in prepared hot surfactant solution. Premixing is carried out via magnetic stirrer to form pre-emulsion. Then this pre-emulsion is passed through high pressure homogenizer, at temperature above the lipid melting point. Hot O/W nanoemulsion is formed then it is solidified by cooling down to room temperature, gives SLN.

2.3. Cold High Pressure Homogenization

Cold homogenization is necessary to avoid the problems occurring in hot homogenization techniques such as degradation of drug, loss of drug, crystallization complexity causes polymeric transition leads to modifications. The process involves melting of the lipid and dissolving the drug in that melted lipid. This

lipid containing drug is cooled rapidly by using liquid nitrogen and dry ice for drug distribution. The lipid containing drug is grinded to form micro particles by using ball mill or mortar mill (50-100 micron).Then the powder is dissolved in chilled surfactant solution. The resulting dispersion is passed through high pressure homogenizer at or below room temperature. Cold homogenization reduces the thermal liability of the sample, but it does not skip it because initial process of the melting of lipid/drug (Figure 2).

2.4. Ultrasonication or high speed homogenization

Sonication / high speed stirring can also be utilized for the production of SLN. Lab scale production of SLN is possible by this method because easy availability of such a simple equipment. This method is unfavorable because it gives wide range particles (micrometer range), it causes instability like particle growth on storage. Large amount of surfactant is necessary in this method. Ultrasonication causes high metal contamination. Mandal et al. used this method with polycaprolactone (PCL) as the polymer and hydrogenated soy phosphatidylcholine (HSPC) and DSPE-PEG2000 as the lipids to entrap erlotinib. (Fig. 2) Hot High Pressure Homogenization b) Cold High Pressure Homogenization (Figure 3).

2.5. Solvent Emulsification/Evaporation

The process involved dissolving the lipid in organic solvent (cyclohexane) which is insoluble in water and adding into the aqueous surfactant solution, stirring rapidly which forms the emulsion. Evaporation is carried out for the elimination of the solvent from the emulsion at low pressure. Evaporation causes lipid precipitation gives nanoparticles. The process does not involve any thermal energy but method depends on organic solvent which is disadvantageous (Figure 4).

2.6. Solvent Emulsification/Diffusion

The process involved dissolving the lipid matrix in organic solvent which is insoluble in water and adding into the aqueous phase to form the emulsion. . Evaporation is carried out for the elimination of the solvent from the emulsion at low pressure. Evaporation causes lipid precipitation gives nanoparticles. The size of particle based on the concentration of lipid used in organic solvent and type of surfactant. This method gives the particles between the range 30 -100 nm (Figure 5).

2.7. Double Emulsion

Initially the drug is added in aqueous phase and polymer/drug is added in lipid phase then both the phases are mixed and agitated which forms primary w/o emulsion. Next water is added to form w/o/w secondary emulsion. Further solvent is removed to form drug loaded SLN (Figure 6).

2.8. Spray drying

This is another method to convert aqueous formulation of SLN into dried drug product. This technique is profitable than Lyophilization and magnify the use of solid lipid having melting point greater than 70. This method creates aggregation of nanoparticles due to excessive heating shear forces and half way melting of the nanoparticles.

2.9. Solvent Injection technique

In this technique solid lipid is liquefy in organic solvent which is miscible in aqueous phase. The organic solvent consists of lipid added into aqueous phase with or without surfactant during stirring. lastly, the formulation filtered to remove extra lipid. Aqueous phase emulsion supports to form the small drops of lipid added and balance the SLN formulation up till the of solvent diffusion gets finished (Figure 7).

2.10. Supercritical fluid technique

This is different technique that newly applied for the SLN preparation. A fluid is called as supercritical while pressure and temperature of the fluid is go beyond appreciated critical values. The capability of fluid to liquefy the sample increases. This technology composes of a few steps of nanoparticles preparation such as supercritical solution expansion, supercritical fluid extraction of emulsion. The benefits of this technique contains lack of solvents, dry formulation depends upon minimum temperature and pressure condition (Figure 8).

2.11. Micro emulsion extrusion method

To prepare the formulations, we used an adaption of the micro emulsion method followed by extrusion through a 100-nm polycarbonate membrane (Millipore, Darmstadt, Germany) using an Avanti mini-extruder (Avanti Polar Lipids, Inc., Alabaster, AL). In brief, a solution of PLF68 (surfactant) and DOTAP (co-surfactant) (pre-heated above the melting temperature of the solid lipid used) was added to the melted lipid followed by homogenization using vigorous stirring. For some samples sonication was necessary to produce a homogeneous suspension before extrusion. Then, the hot emulsion was loaded into the donor syringe and extruded 15 times,

unless otherwise stated, through the double-syringe extruder, always finishing at the receiver syringe, to avoid contamination. A heating block, pre-heated above the melting temperature of the lipid, warmed the system during the whole process. Finally, the lipid nanoparticles were transferred to an ice bath and then stored at 4℃. A systematic study was performed to test different production parameters, such as the number of extrusion cycles (0, 5, 10, 15, 20, 25, and 30 times), and temperature (5, 10, or 15 °C above the melting point of the solid lipid, being 58–59℃ for GMS and 69.6 °C for SA, used in the formulation). Of note, to avoid extruder membrane disruption 10 mm was the maximum lipid concentration used in our studies. This concentration may vary when other lipid mixtures are used and also depends on the type of formulation (liposome's vs. SLN vs. NLC) that is produced. Second, to guarantee that the complete system has reached the same temperature, the heating block, the lipid, and the aqueous phases should be heated to the desired[15].

3. CHARACTERIZATION

3.1. Particle size

For the purpose of determination of particle size, Photon Correlation Spectroscopy is used. The PCS analysis gave the mean diameter of the particles (Z average) and the poly disparity index (PDI) as a measure of the width of the particle size distribution. It is equipped with a 5-mW helium neon laser with a wavelength output of 633 nm. Glassware was cleaned of dust by washing with detergent and rinsing twice with water for injections. Measurements were made at 25 °C at an angle of 90°. Data were interpreted using the "CONTIN" method. The principle on which PCS is based is dynamic light scattering. When the particle is moved, there is change occurs in the excitement of scattered light.PCS measures the fluctuated intensity. For the measurement of broader particle size, laser diffraction method is used. Diffraction angle on particle determines the particle size. Particle size of SLN/NLCs depends on the amount and type of lipids and surfactant used in the formulation process. More the surfactant, lesser will be the size obtained. The photon correlation technology determines the particles in range of 3 nm-3 µm and the laser diffraction method determines particles in range of 100 nm- 180 µm.

3.2. Zeta Potential

Stability of the SLN/NLCs during storage can be determined by measuring the zeta potential. When the particles are charged means with high zeta potential, there is low agglomeration of particles because of electrical repulsion. If the zeta potential is less then stability of the dispersion is also reduced. The requirement of the zeta potential for excellent stability is more than -60 mv and when ZP is more than -30 mv then there is good stability. The formulations containing stearic stabilizers do not obey the same rule because zeta potential will be decreases by shifting in the shear plane of particle due to the adsorption of Static stabilizers. By increasing the energies such as temperature and light, agglomeration and gelation of SLN/NLCs occurs which intern reduces the zeta potential. Crystalline modifications occur when such energies are employed. Autoclaving reduces the zeta potential of SLN.

For entering into the blood brain barrier, NLCs with positive charge is required. Because par cellular site of BBB is anionic. Sometimes negative charge is required to stabilize the system. Zeta meter is used for determination of the zeta potential. For the measurement, SLN or NLCs dispersion is diluted 50 folds. Higher value of ZP indicates disaggregation.

3.3. Electron microscopy

There are two ways for electron microscopy such as Scanning and transmission electron microscopy (SEM and TEM).This are most proffered way for direct observation of nanoparticles. For morphological analysis SEM is more desirable. TEM has certain limitations for size detection.SEM and TEM are used for the size and radius analysis of nanoparticles. SEM includes the transmission of electron from the surface of the nanoparticles while TEM utilize transmission of the electrons through the sample. For SEM sample preparation is easy and having high resolution. Freeze drying is necessary for sample detection by TEM.

3.4. Atomic Force Microscopy

In Atomic Force Microscopy, a topological map formation is depending on forces applied between probe tip and surface of sample. The probe tip having atomic scale is placed across the sample. The probe is either in contact with sample or not in contact with sample and its depending on the force employed. That more resolution is realizable with this technique for mapping the sample in relation to size, colloidal attraction or oppose to deformation, which makes AFM as more valuable. Structural features which are too small are measured by AFM. AFM based on principle of probe tip and not on the photons or any electrons. The technique of AFM is more advantageous such as minimum time for

sample preparation is required, better magnification at nano level

3.5. Dynamic Light Scattering (DLS)

DLS is quasi elastic light scattering method in which changed intensity of light which is scattered is determined by microsecond time scale. There is auto correction function system which quantifies changed intensity of light scattered of each particle in Brownian motion. Analysis speeds, no need to calibration, sensitivity of instrument are the advantages of technique.

3.6. Static Light Scattering (SLS)

Electromagnetic equation is utilized in SLS in which size is one variable. The way of scattered light is identified and then fitted to the equation. This method is fast but requires cleanliness as compared to DLS.

3.7. Differential Scanning Calorimetry

Melting enthalpy and recrystallization of solid lipid from SLN and NLCs is determined by DSC. Different lipid changes having different heat content and melting range. The ratio of NLC heat content to bulk lipid heat content is the degree of crystanallity of NLCs. Degree of crystanalline nature of NLCs is inversely proportional to the concentration of liquid lipid oil. So liquid lipid important factor in reducing crystalline. Due to the liquid oil, disturbance happens in structure which causes high drug entrapment.(1,16)

3.8. Nuclear Magnetic Resonance (NMR)

Qualitative nature and size of SLN/NLCs can be determined by using NMR. The physical and chemical nature of inside core is analyzed due to chemical shift. Movability of inner component of NLC is investigated through Proton NMR spectroscopy. The movability of the solid lipid and liquid lipid is associated width of signals half magnitude. Wide ranging signals and small scale magnitude are attributing of molecules with constricted movability and strong interactions. There is reaction takes place between liquid oil and solid lipid in NLCs when there is larger line width of NLC as compared to physical mixture of material. Incapacitation of NLC is stronger in relation to SLN with crystallized inner core.

3.9. Encapsulation Efficiency

Evaluation of drug loading efficiency is necessary as it has influence on release mechanism. The quantity of drug entrapment is principle signal of drug colloid system. As stated by mechanism of SLN amalgamation, the affecting of drug in lipid core includes, how much drug is soluble in lipid, liquid melt solubility, physicochemical nature of solid and liquid lipid, crystallization of lipids. The drug molecule which is lipophilic by nature is uniformly dispersed in lipid core or shell. For hydrophilic drug loading, aqueous and interfacial points are good positions. The precondition to accomplishing higher loading capacity is enough solubility of drug in lipids. The solubility must be high than demand since it declines when the lipid melt is cooling down and may lower in solid lipid. The percent drug entrapped in NLCs is hinge on dissociation of external and internal phase. For the dissociation purpose, various techniques for example gel filtration, ultra filtration, dialysis, ultracentrifugation are utilized. In comparisons with SLN, the entrapment of liquid lipid to solid lipid in NLCs causes imperfect matrix structure which creates maximum space for drug entrapment. So loading capacity and entrapment efficiency is better in NLC than SLN. The entrapment efficiency was determined by calculating the entrapped drug after removal of un-entrapped drug using a centrifugal filter

$$\%EE = \frac{W \text{ initial drug} - W \text{ free drug}}{W \text{ initial drug}}$$

Where "*W* initial drug" is the mass of initial drug used for the assay and the "*W* free drug" is the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

3.10. Drug release

By changing the structure of lipid, surfactant concentration, and temperature release character can be changed. From delayed release to the phenomenon of burst release, the release mechanism can shifted. The factors which influencing the mechanism of release are temperature, surfactant concentration, structure of lipid .When the SLN are produced by the method of HPH, then drug is diffuses from oil to aqueous phase, and when the temperature of the aqueous phase is increased or surfactant concentration is increased then it also increases the concentration of drug in aqueous phase. Higher solubility in aqueous phase is obtained by higher surfactant concentration and temperature.

By cooling the emulsion, temperature is lowered and so concentration of drug in aqueous phase is also declined, drug is reshuffle to oil phase. The central core of solid lipid is established at the temperature of lipid recrystallization. At that temperature some of the drug is incorporated in core, then at the

reduce temperature of dispersal phase, the aqueous phase drug solubility decreases; drug is dispersed in oil phase. The internal core restricts the new drug to inside because of this the drug saturates on the external shell of SLN. Then the drug which is present on the outer shell shows burst release and the drug present in inside core shows sustained release.

The controlled /sustained release from the drugs in NLCs can bring the extended half-life and delayed enzymatic breakthrough in systematic circulation. The drug release action from NLCs is based on the manufacturing temperature, emulsifier concentration, and percentage oil entrapped in lipid matrix. The concentration of drug in the external shell of the NLCs and on the surface is released in a burst mechanism, however the drug entrapped into the internal core is released in a extended way. The dialysis technique and the use of the Franz cell are the methods for determining *in vitro* drug release of nanoparticles. The elucidation of *in vitro* release of drug should examine the specific environment in the *in vivo* status.

4. APPLICATIONS OF SLN/NLC

4.1. SLN/NLC for Parenteral Application

SLN are hugely acceptable for systemic delivery as they composed of physiologically completely-tolerated constituent and they have fine storage potential after Lyophilization and/or sterilization. When they are injected intravenously, SLN are adequately tiny to disperse in the micro vascular system and stop macrophage intake in the event of deliquescent coating. Consequently, SLN have been proposed for viral non-viral gene delivery. Cationic SLN has been expressed to attach genes exactly through electrostatic reactions, and have possible advantages in targeted gene therapy in treatment of cancer. The charge of particles could be modified by the constitution, so permit binding of inversely charged molecules. Treatment of CNS diseases viz brain tumors, AIDS, neurological and psychiatric disorders is frequently constrained by the inability of drugs to pass blood brain barrier (BBB). Hydrophilic coating of drugs upgrade the transport of these through BBB and tissue distribution, prepared doxorubicin with stealth and non stealth SLN and observed that the stealth nanoparticles were available in blood at huge concentrations than non-stealth SLN after 24 h pursuing intravenous administration.

4.2. For Nasal Application

Nasal administration was a optimistic choice noninvasive route for drug administration owing to quick absorption and immediate onset of drug action, bypass degradation of reactive drugs (like peptides and proteins) in the GI tract and inadequate transport beyond epithelial cell layers. With regard to enhance drug absorption by the nasal mucosa, perspectives like formulation development and derivatization of pro drug have been hired. SLN has been suggested as substitute transmucosal delivery systems for macromolecular therapeutic ingredients and diagnostics by different research groups. In a current report, PEG coated polymeric nanoparticles gave hopeful results as vaccine carriers. The function of PEG coating polylactic acid nanoparticles in enhancing the transmucosal transport of the enclosed active molecule described to be fruitful. This approach can be convenient for solid lipid nanoparticles.

Inhalational drug delivery has several advantages over conventional (parenteral and oral) dosage forms such as non-invasiveness; negligible first-pass effects, and reduced systemic toxicity. Inhaled drugs may reach directly to the lung epithelium, enhancing local drug concentrations. Particles smaller than 500 nm may enhance pulmonary deposition due to an increased diffusional mobility.

4.3. For Respiratory Application

The lungs provide a giant surface for absorption of drug by bypassing first-pass metabolism. Quick drug absorption via aerosolization of drugs (1-3 µm) happens due to the alveolar wall in the lung are highly thin. Lymphatic discharge performs an important function in the intake of particulates in the respiratory tract. SLN can be recommended as vehicle of anti-cancer drugs for treatment of lung cancer to enhance bioavailability. Evaluation of inspired radio-labeled SLN distribution has been narrated and the data gives an essential and significant intake of the radio-labeled SLN into the lymphatic system after inhalation. In a current study, drugs used in tuberculosis (such as rifampicin, isonizide and pyrazinamide) were encapsulated into different formulations of solid lipid particles in size range 1.1–2.1 µm and formulations were atomized to guinea pigs through mouth for straight pulmonary delivery. Atomization of solid lipid particles consisting ant tubercular drugs was observed to be fruitful in enhancing drug bioavailability and decreasing the dosing frequency for good management of pulmonary tuberculosis.

4.4. For Ocular Application

Ocular drug delivery through SLN has been stated many times. Bio-compatibility and

mucoadhesive nature of SLN enhance their reaction with ocular mucosa and extend corneal residence time for the drug, with the objective of ocular drug targeting. It is evaluated that SLN as vehicles for ocular delivery of to bramycin in eyes of rabbit. Subsequently SLN can improve the drug availability in the blood in the aqueous humor. It is also studied that pilocarpine delivery through SLN, which usually used in treatment of glaucoma, earlier. They stated same results for the enhancement of the ocular bioavailability of drug.

4.5. For Rectal Application

A scarcely reports are accessible on the rectal administration of drug given by rectal route through SLN in the literature. Diazepam is encapsulated in SLN for the rectal administration for its fast action. They carried out the animal study on rabbits. They observed that lipid matrix, since it is solid in state at body temperature which is not a beneficial system for diazepam by rectal delivery. For that they decide to add lipids which melt at body temperature in the next experiments. This area appears very open to inspection, mainly when the advantages of rectal route are taken into deliberation. PEG coating appears to be a optimistic approach on rectal delivery and accordingly, increment of bioavailability.

4.6. For Topical application

SLN and NLC are extremely delightful colloidal carrier systems used for skin applications because of their different advantageous effects on skin apart from the typical characteristics colloidal systems. They are applicable for use on impaired or inflamed skin as they consists lipids which are non-irritant and non-toxic. Researchers have described actively on the topical use of SLN. In the past few years, SLN and NLC had been studied along with active compounds like Vitamin E, Tocopherol acetate, retinol, as corbylpalmitate, clotrimazole, triptolide, phodphyllotoxin and a nonsteroidalantiandrogen RU 58841 for their topical application. Recently SLN can be used in sun protecting creams.

Various drugs can be incorporated in SLN or NLC such as antifungal, anticancer, tropolide, imidazole, isotretinoin, ketoconazole, vitamin A, DNA, flurbiprofen and glucocorticoids for the purpose of topical application. Epidermal targeting can be done through incorporating the phodphyllotoxin into the SLN for the stratum corneum. Vitamin A containing nanoparticles can be prepared by using Glycerylbehenate. These methods are beneficial for the enhancement of penetration with controlled release. The lipid nanoparticle which contains isotretinoin was formulated for the usage of topical delivery. The lipid and surfactant such as soya bean lecithin and Twee 80 are used for this by hot homogenization method. The technique is beneficial because of the increase of uptake of isotretinoin through the skin. Higher tissue concentration of flurbiprofen can be achieved by incorporating it in SLN as gel for topical delivery which delivers the drug directly at the site of action. The ingredients used for the production of such type of SLN are Poly a crylamide, glycerol and water.

4.7. For Cancer chemotherapy

Many chemotherapeutic agents are incorporated into SLN and in-vitro, in-vivo effectiveness is estimated. For Breast cancer therapy, Tamoxifen is encapsulated in SLN for sustained release of Tamoxifen following I've. Administration. One of the applications of SLN in cancer therapy is tumor targeting such as methotrexate and camptothecin. For the treatment of breast cancer and lymph node metastases, metoxantrone is incorporated in SLN for local injections to decrease the toxicity and increase the bio efficacy and safety.

Yu et al. engineered paclitaxel (PTX)-loaded cationic SLN by solvent-emulsification and Sonication using cationic lipids, including 1,2-diphytanoyl-*sn*-glycero-3-phosphatidylethanolamine, 3β[*N*-(*N*',*N*' dimethylaminoethane)-carbamoyl]cholesterol(DC-Chol),1,2-dioleoyl-sn-glycero-3ethylphosphocholine, and methoxy-polyethylene glycol 2000-distearoyl phosphatidyl ethanolamine (mPEG-DSPE). MCL-1-specific small interfering (si)RNA was then conjugated to this preparation by polyelectrolyte complexation, resulting in an effective co-delivery system with improved in vitro and in vivo anticancer efficacy.(24)

4.8. Prospects for SLN and NLC in cancer therapy

A lot of work has been reported for improving the cancer treatment by multifunctional nanocarrier. The perfect multifunctional drug nanocarrier would furnish highly coherent and systematized system for the delivery of drugs, diagnostic agents, genes. This methodology would have independent functions acting in synchronized way, with a more optimized temporal spatial deposition and release pattern of the anticancer agents. Such promising multifunctional nanocarrier could possess many useful functions in the same carrier system such as (1) long-circulation (PEGylation), (2) co-loading of two or more drugs, (3) magnetic particles loaded into the

carrier together with the drug to allow for carrier sensitivity towards an external magnetic field and its use as a contrast agent for magnetic resonance imaging, (4) pH sensitivity to release drug in acidic areas of tumors, (5) ligands attached to the surface for active targeting (monoclonal antibody, peptides, proteins, small molecules, aptamers), (6) contrast agents for imaging purposes (heavy metals – 111In, 99mTc, Gd, Mn for gamma- or MR imaging application), (7) cell penetrating capacity (cell-penetrating peptide – CPP) for carrier-enhanced uptake, (8) a gene-carrying nanocarrier such as a lipoplex or polyplex (DNA or RNA complexed by the carrier via the carrier surface positive charge).All these functions have been addressed at least somewhat in this review and are summarized in Table 1. The nanoparticles described have each been developed with a few of the outlined functions mentioned. However, the combination of all functions would be very challenging. Much effort has been done with liposomes and polymeric nanoparticles to obtain multifunctional nanocarriers. However, the advantages of SLN and NLC over the others nanosystems qualify them as promising candidates in the development of combined therapeutic and diagnostic multifunctional pharmaceutical nanocarrier systems.

4.9. Oral SLN/NLC in antitubercular chemotherapy

Antitubercular drugs such as rifampsin, isoniazide, pyrazinamide-loaded SLN systems were able to reduce the dosing frequency and improve patient compliance. Antitubercular drugs loaded SLNs were prepared using solvent diffusion technique. The nebulization in animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.[11]

4.10. For potential agriculture application

Essential oil extracted from *Artemisia arboreseens*L when incorporated in SLN, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticide. The SLN were prepared here by using Compritol 888 ATO as lipid and poloxamer 188 or Miranol Ultra C32 as surfactant.[11]

4.11. SLNs/NLCs as gene vector carrier

Gene delivery is one of the most studied and promising application areas of SLN.[25] SLN can be used in the gene vector formulation. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acid. The lipid nuclic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nuclic 17 acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.(11)

4.12. SLNs as cosmeceuticals

The formulation of topical products is identical for both nanoparticles, SLN and NLC. There are basically three approaches to formulate products

1. Incorporation of SLN/NLC in existing products
2. Production of SLN/NLC containing gels by addition of viscosity enhancers to the aqueous phase of the dispersions
3. Direct production of the final product containing only nanoparticles in a one-step process using the production process of highly concentrated dispersion.[26]

SLN show a UV-blocking potential, i.e. they act as physical sunscreens on their own and can be combined with molecular sunscreens in order to achieve improved photoprotection.[17] The *in vivo* study reveals that skin hydration will be enhanced by 31% after 4 weeks by addition of 4% SLN to a conventional cream.SLN and NLCs have demonstrated to be controlled release innovative occlusive topicals. Better localization has been accomplish for vitamin A in upper layers of skin with glycerylbehenate SLNs compared to conventional formulations.[11] Many cosmetic products containing NLCs are currently available worldwide (e.g., in South Korea, Supervital products in the "IOPE" line from Amore Pacific)

4.13. Nanotechnology for oral drug delivery

Nanotechnology has revolutionized the field of drug delivery research. Various nanotechnologies that have been employed for improving oral drug delivery. Interestingly, nanotechnology- based oral formulations are available in the pharmaceutical market and few products are being evaluated in clinical trials[28].

5. CONCLUSION

SLN and NLCs as colloidal drug carrier merges the advantage of liposomes, polymeric nanoparticles and fat emulsions. SLNs and

NLCs are produced by hot and cold homogenization technique and by different advanced techniques. The site specific and sustained release result of drug can superior achieved by using SLNs and NLCs. A prime issue of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the development process, however NLCs having superior drug loading capacity. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix by using NLC drug loading can be improved and drug expulsion can be prevented. They are having vast applications in therapeutics. So in future research can be accomplish on formulation of NLC and LDC to achieve better drug loading, site specificity and low toxic effects.

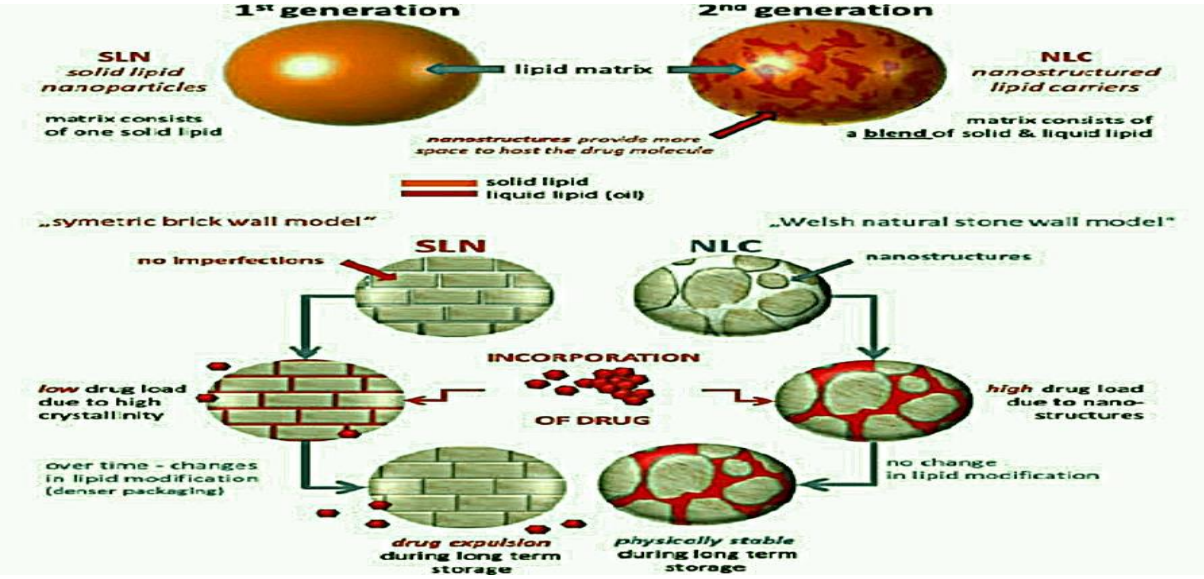

Fig. 1:

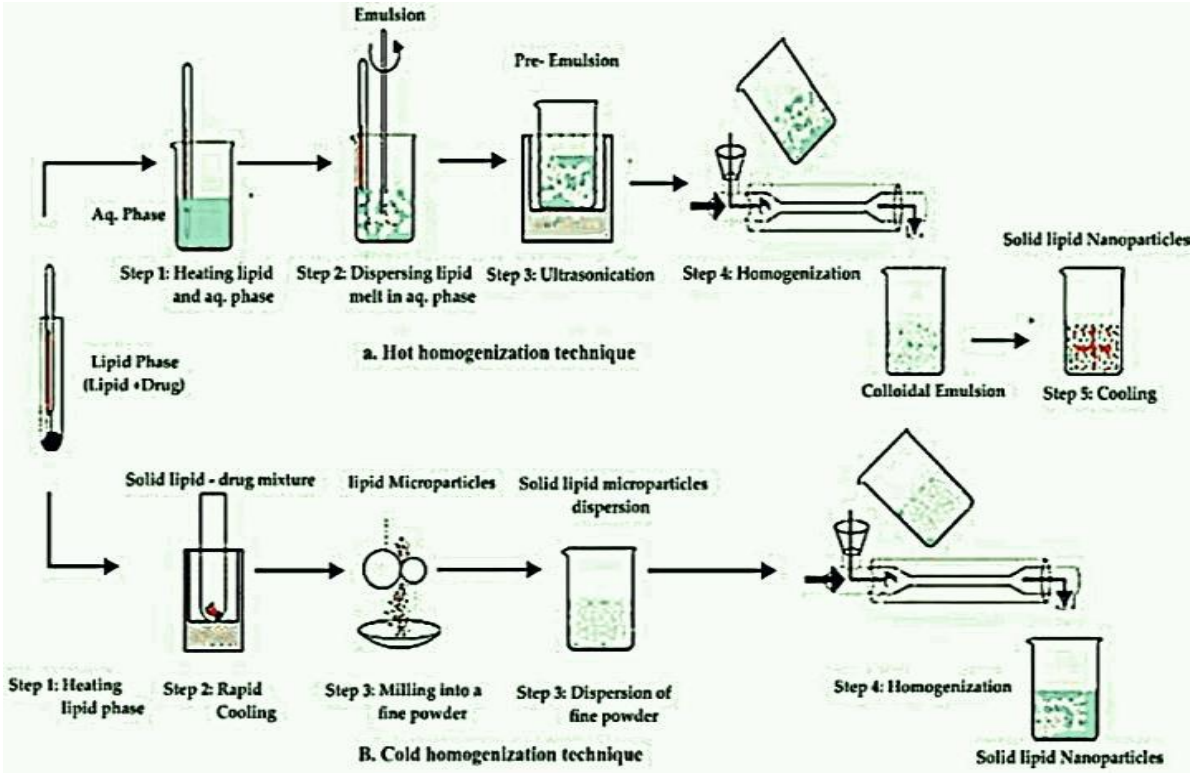

Fig. 2:

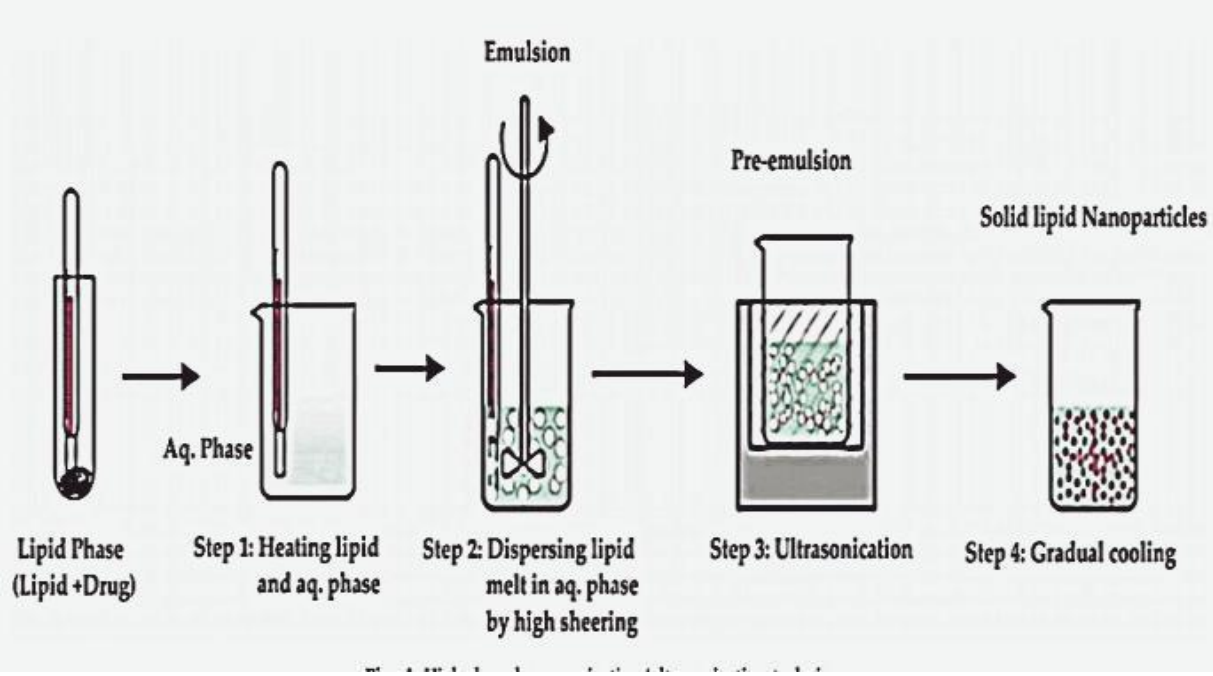

Fig. 3: Ultrasonication or high speed homogenization

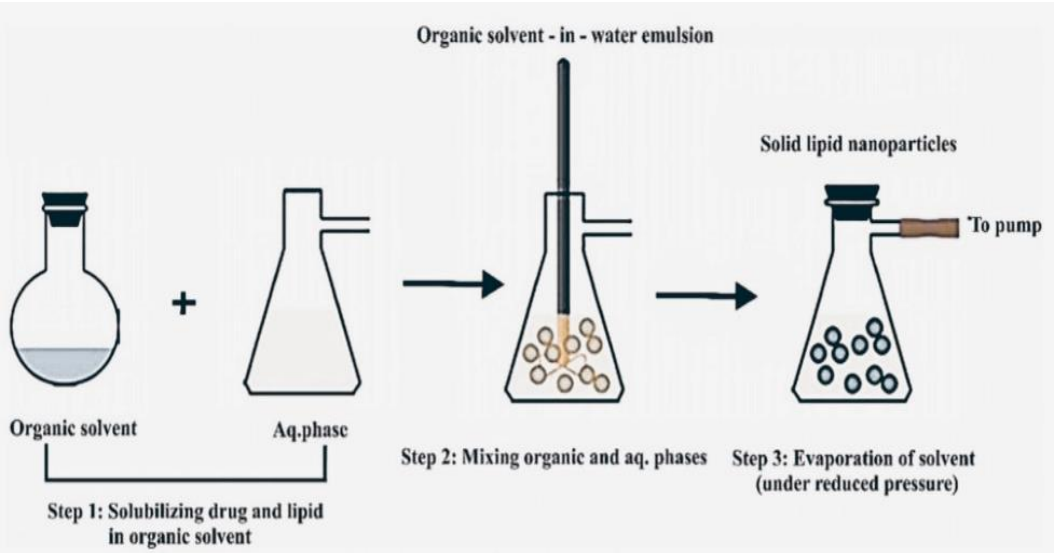

Fig. 4: Solvent Emulsification/Evaporation

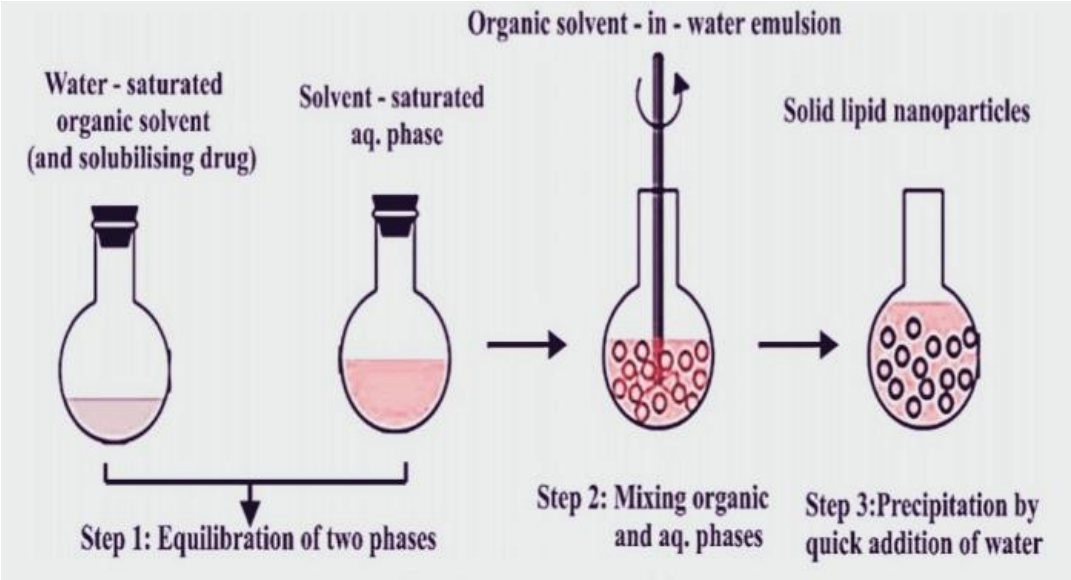

Fig. 5: Solvent Emulsification/Diffusion

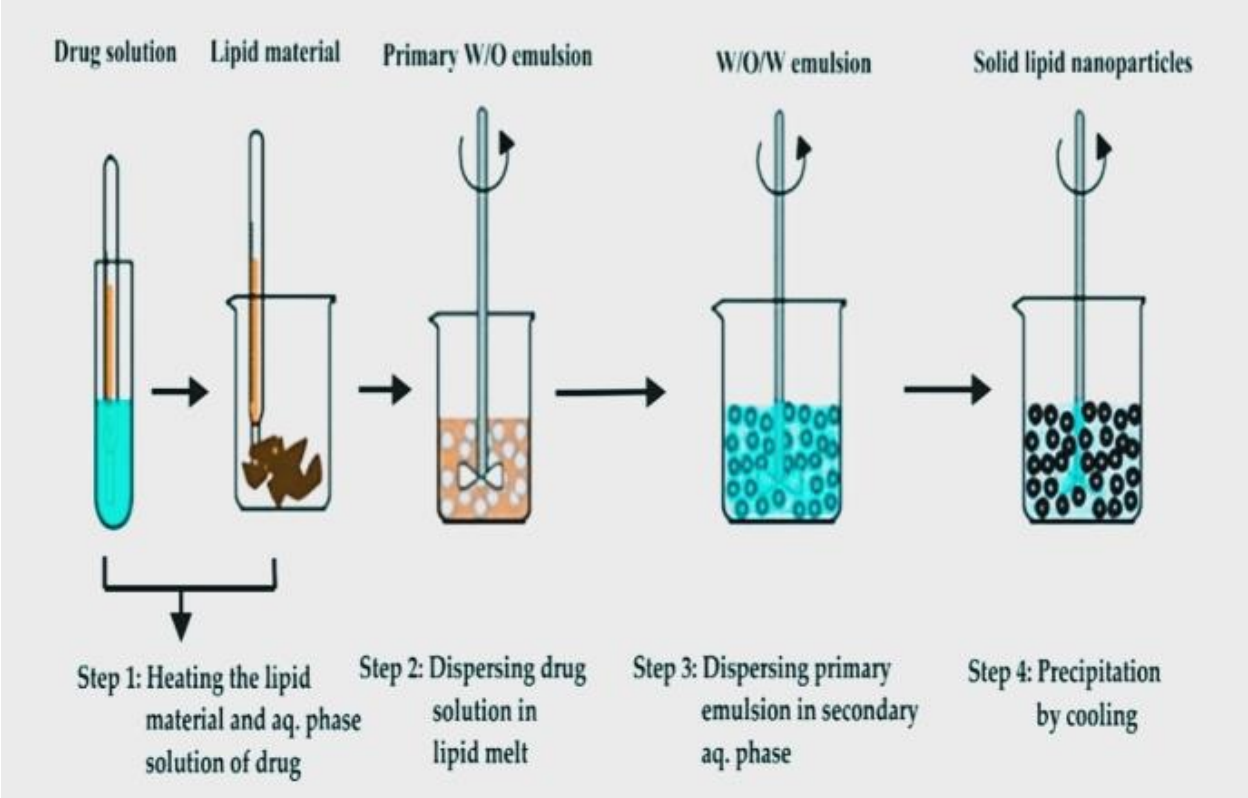

Fig. 6: Double Emulsion

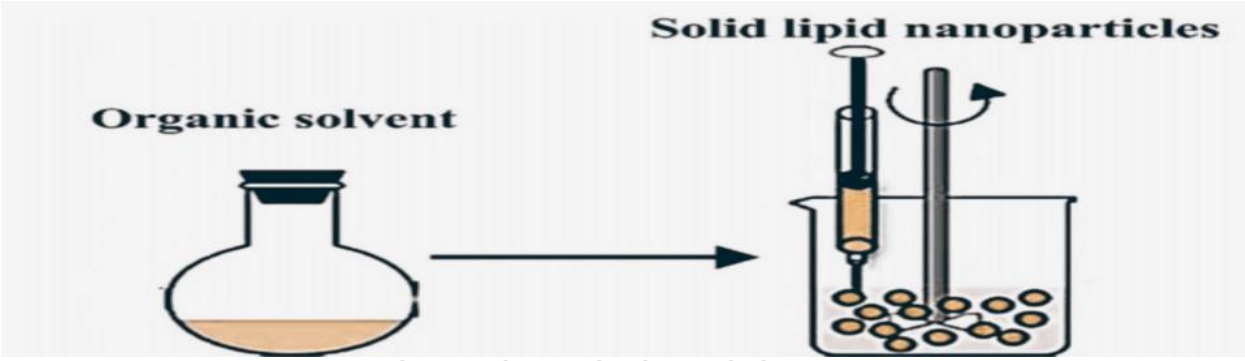

Fig. 7: Solvent Injection technique

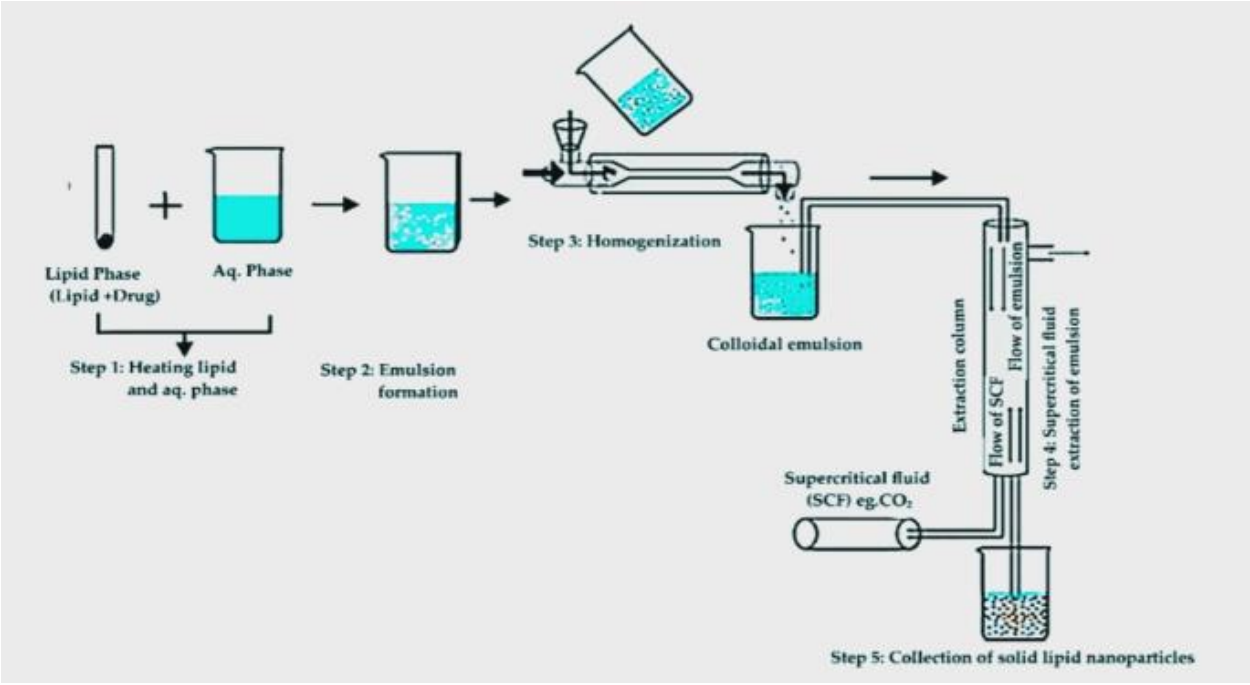

Fig. 8: Supercritical fluid technique

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