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A brief review on: methods of preparation of solid lipid nanoparticle.

Pallavi P Sambarkar, Priyanka P Thore.

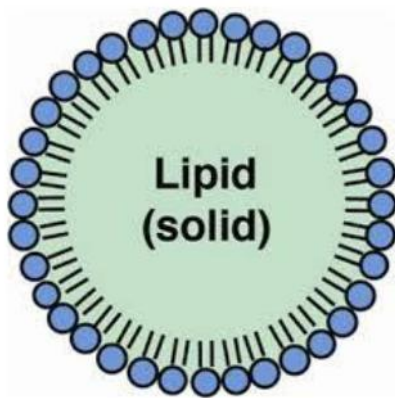
Sdmvm's Diploma In Pharmacy Institute, chh. Sambhajinagar

ABSTRACT Solid lipid nanoparticles (SLN) are at the front of the speedily emerging field of nanotechnology with several potential applications in drug delivery and research. Different invented nanoparticles and drugs retaining low solubility and poor pharmacokinetic profiles are the two major substances widely delivered to specific target sites. Solid lipid nanoparticles (SLN) has as a several potential applications in drug delivery and research. Due to their characteristic size dependent properties, solid lipid nanoparticles offer prospect to develop new therapeutics. The capacity to combine drugs into nanocarriers deals with new sample in drug delivery that could usage for drug directing. Therefore solid lipid nanoparticles hold excessive capacity for getting the goal of controlled and site specific drug delivery and therefore involved wide consideration of researchers. This review presents carriers and different methods of preparations of SLN.

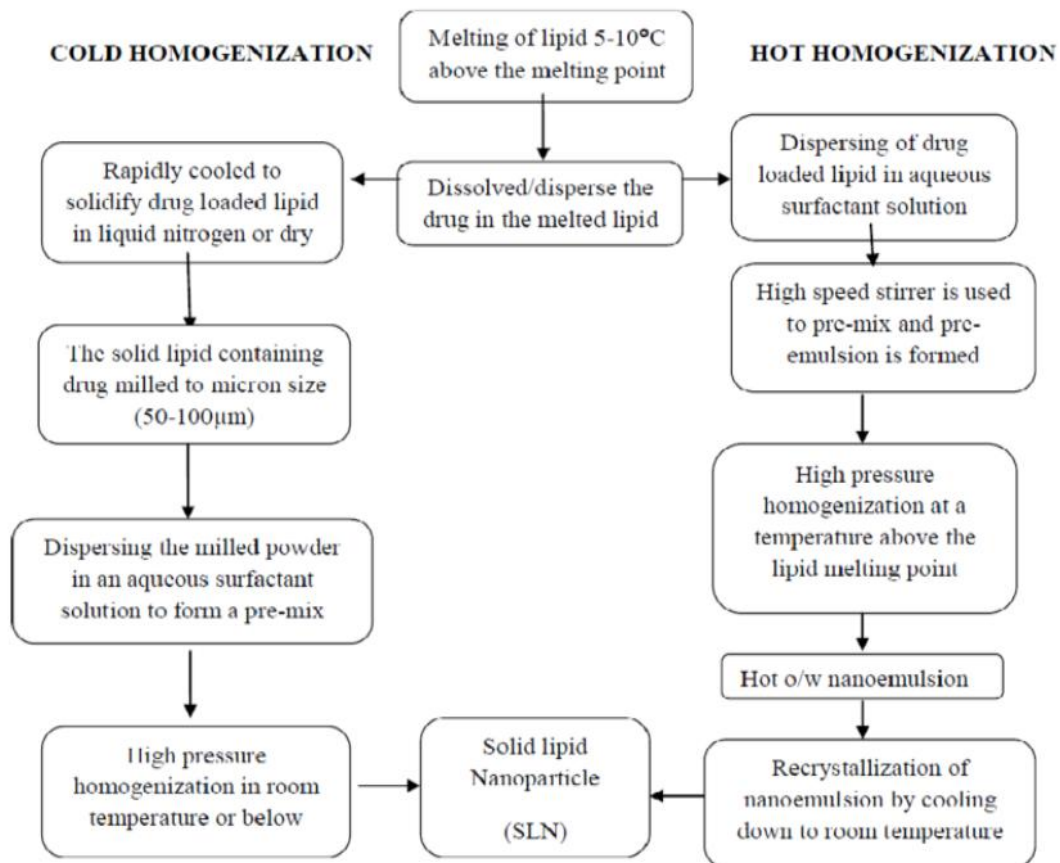
Key words: nanocarriers, Colloidal drug carriers, Homogenization, TEM, Biodistribution targeting.

INTRODUCTION The reduction in the particle size of materials at the nanometer scale increases their overall surface area by several orders of magnitude. Particles with a size in the range of 1 nm to 1000 nm are known as nanoparticles. Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to conventional colloidal carriers such as - emulsions, liposomes, and nanoparticles. Nanoparticles prepared from solid lipids are fascinating major attention as novel

colloidal drug carrier for intravenous use¹ as they have been proposed as another particulate carrier system. SLN offer distinctive properties such as small size, large surface area, high drug loading and the interaction of phases at the edge and are attractive for their potential to improve performance of pharmaceuticals^{2,5,6}. In order to overcome the drawbacks associated with the liquid state of the oil droplets, the liquid lipid was substituted by a solid lipid¹⁰ nanoparticles, which ultimately altered into solid lipid nanoparticles. Solid lipid nanoparticles are one of the distinctive potential colloidal carrier systems as substitute materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Fig. 1.



¹⁴
Fig. 1: A diagrammatic representation on SLN over emulsions and liposomes



The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs. SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes.

Advantages of SLN 1-4

- Control and target specific drug release.
- Excellent biocompatibility⁵.
- Improve stability of pharmaceuticals⁴.
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Enhanced control concluded release kinetics of encapsulated compounds.

- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- It is easier to manufacture than bio polymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable.
- Raw materials required is the same as in emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

Aims of solid lipid nanoparticles^{6,9}

- Possibility of controlled drug release.
- Increased drug stability.
- High drug content.
- No bio-toxicity of the carrier.
- Anticipation of organic solvents.
- Fusion of lipophilic and hydrophilic drugs.

Preparation of solid lipid nanoparticles^{1-4,6,2,43,52,56}

SLNs are also the potential carriers SLNs are prepared from lipid, emulsifier and water/solvent by using different methods, these methods are discussed here

Methods of preparation of solid lipid nanoparticles

1. High pressure homogenization
 - A. Hot homogenization
 - B. Cold homogenization
2. Ultra sonication/high speed homogenization
 - A. Probe ultrasonication
 - B. Bath ultrasonication
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion

1. High pressure homogenization (HPH)

It is a prevailing technique, which is used for the production of SLNs. High pressure homogenizers impulse a liquid by high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates at high velocity (over 1000 Km/h) over a very short distance. Because of Very high shear stress and force particles distribute down to the submicron range. Normally 5-10% lipid content is used but may increase up to 40%. Two general techniques of HPH are hot homogenization and cold homogenization, both are work on the same concept of mixing the drug in bulk of lipid melt.

A. Hot homogenization: this method is carried out at above the melting point of lipid and can hence it is known as the homogenization of an emulsion. Melting of pre-emulsion of the drug loaded lipid and the aq. emulsifier phase at same temperature is obtained by high-shear mixing device. HPH of the pre-emulsion is above melting point of lipid. Due to the decreased viscosity of the inner phase and higher temperatures result in lower particle sizes. Due to high temperatures may cause increase the degradation rate of the drug and the carrier. Increasing the number of cycles and homogenization pressure often results in an increase of the particle size due to high kinetic energy of the particles.

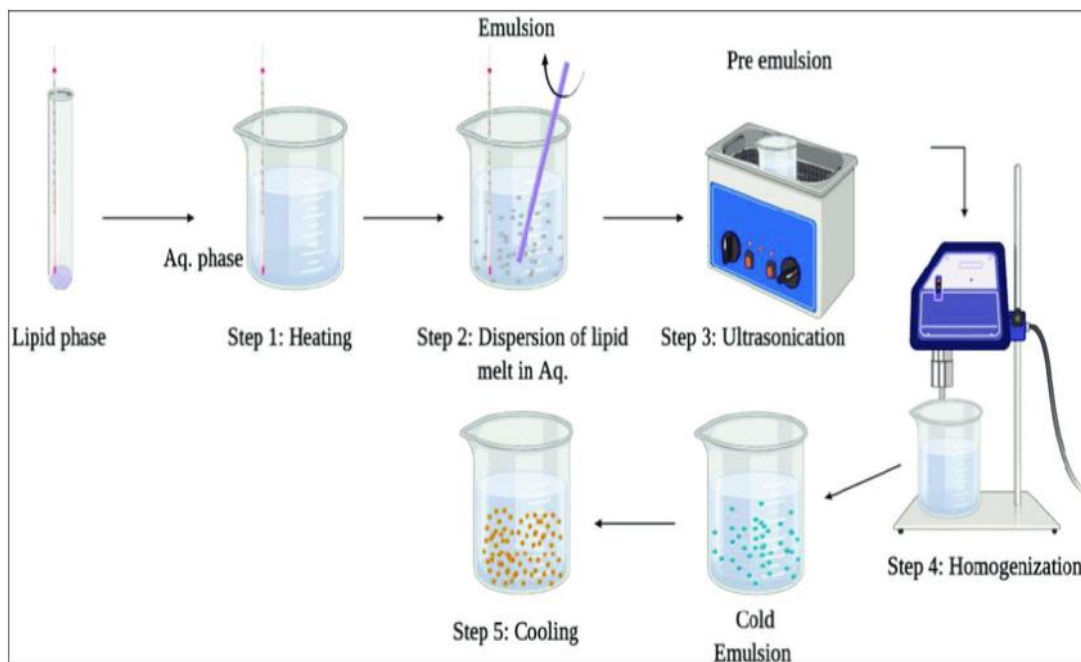


Fig. 3: hot homogenization method

B. Cold homogenization

Cold homogenization method is very useful to overcome the various problems in hot homogenization like Temperature-induced drug degradation, drug distribution into the aqueous phase, Complexion of the crystallization. This is a modified method in which drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

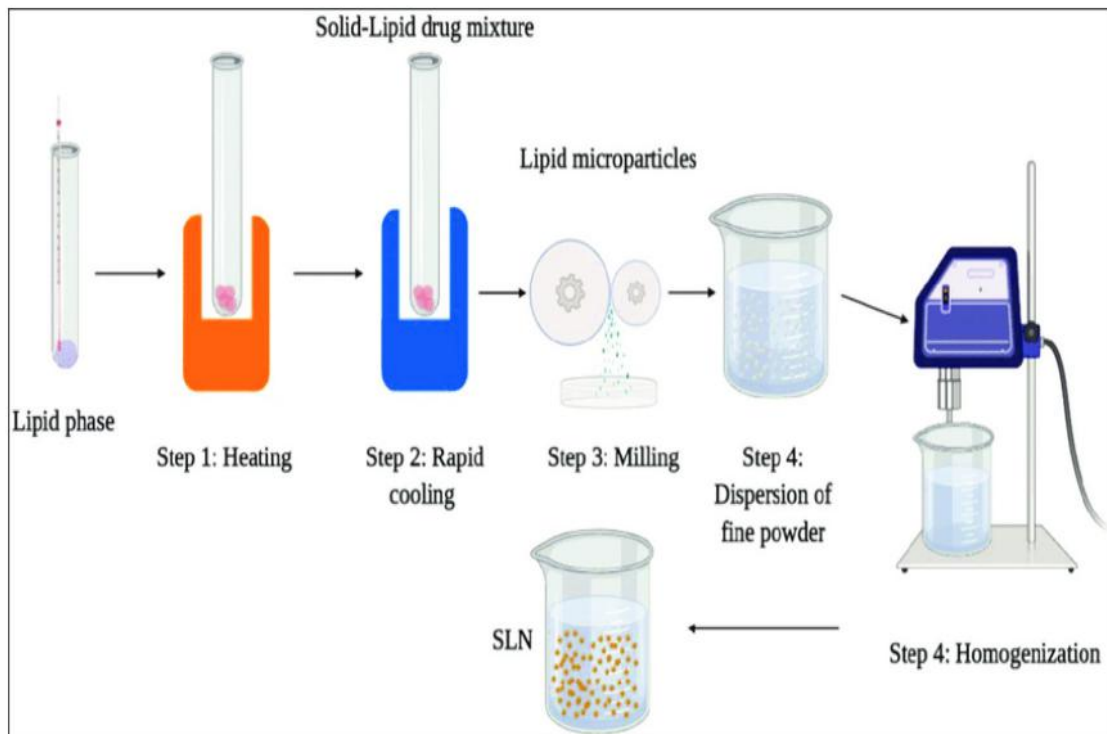


Fig. 4: cold homogenization process

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2. Ultrasonication/high speed homogenization

SLNs are also prepared by ultrasonication or high speed homogenization techniques. To reduced particle size both ultrasonication and high speed homogenization is required. Reduce shear stress is most important advantage.

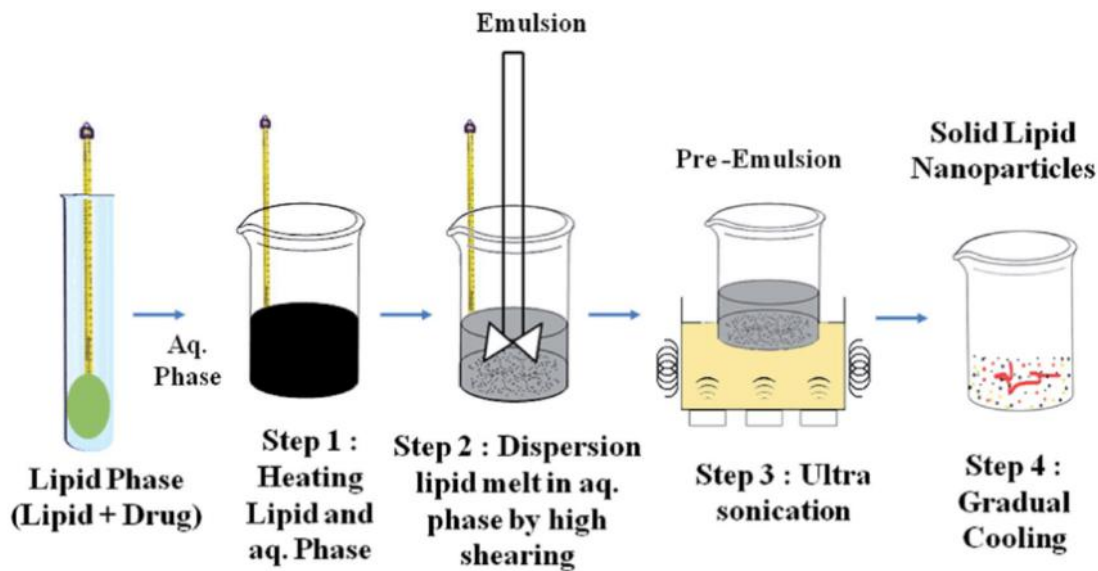


Fig.5: Ultrasonication/high speed homogenization process

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3. Solvent evaporation

SLNs can also be prepared by the solvent evaporation method. The material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) and is emulsified in an aqueous phase. By the evaporation of the solvent, a nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by formation of the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure (40–60 mbar). Solvent evaporation method is scalable, continuous, and commercially demonstrated.

4. Solvent emulsification-diffusion method

This method involves the emulsification of an organic solution of drug which is miscible with water and it also encloses stabilizers. The particles with normal diameters of 30-100 nm can be acquired by this method. Prevention of heat during the process is the most significant advantage of this technique.

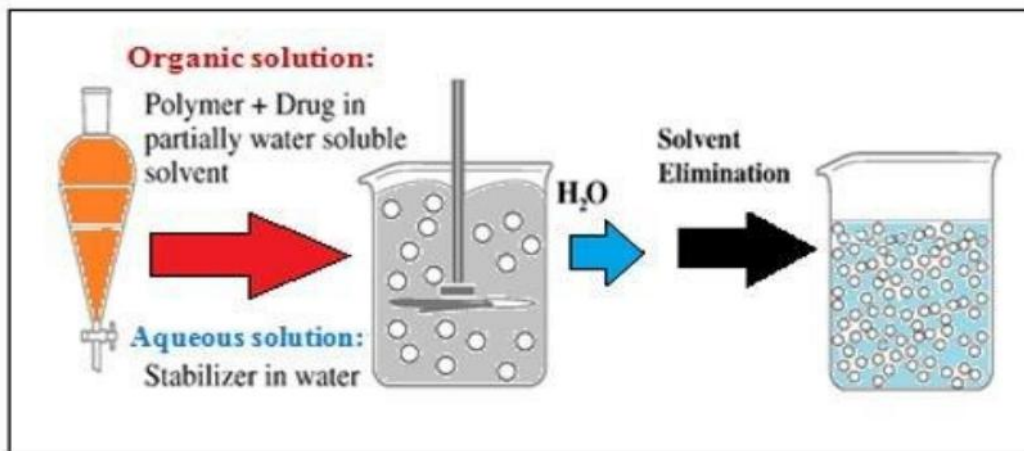


Fig. 5: Systematic representation for emulsification-diffusion method

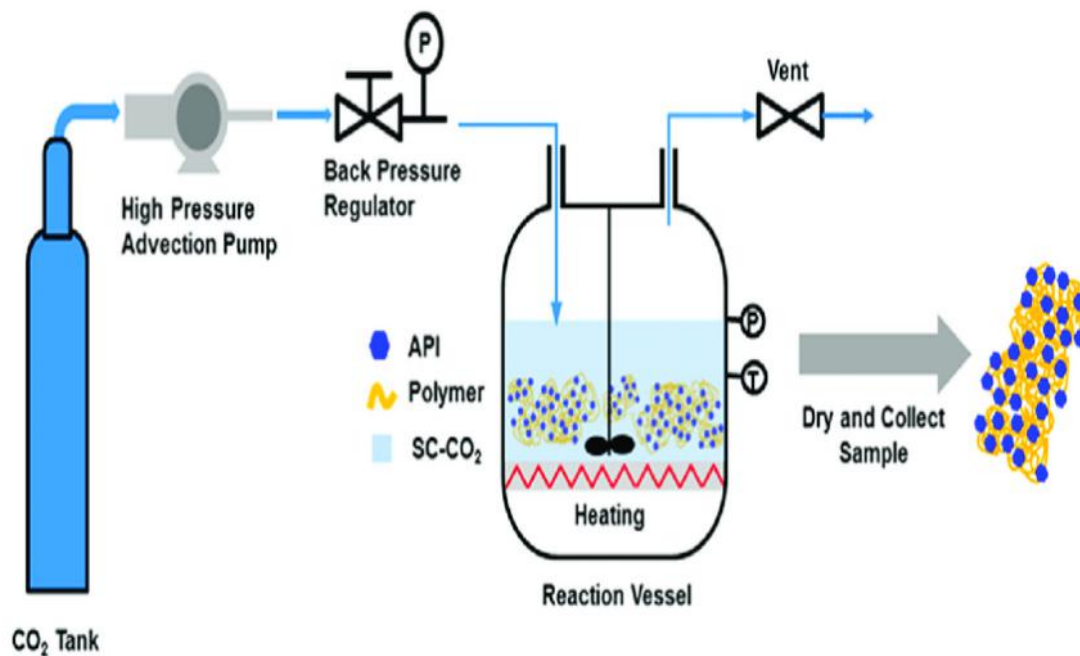
5. Supercritical fluid method

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS) this method is very useful for particle of dry powder and mild pressure temp condition.

this technique is the suitable to minimize the use of solvents.

The Particles are obtained in the form of dry powder.

Mild pressure and temperature conditions.



6. Microemulsion based method

This method is established on the dilution of microemulsions. This method is composed of micro-emulsions which are of two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. With continuous stirring the hot microemulsion is dispersed in cold water (2-3°C). SLN dispersion method can be used as granulation fluid for shifting in to solid product (tablets, pellets) by granulation method. High-temperature gradients help in rapid lipid crystallization and avoid aggregation.

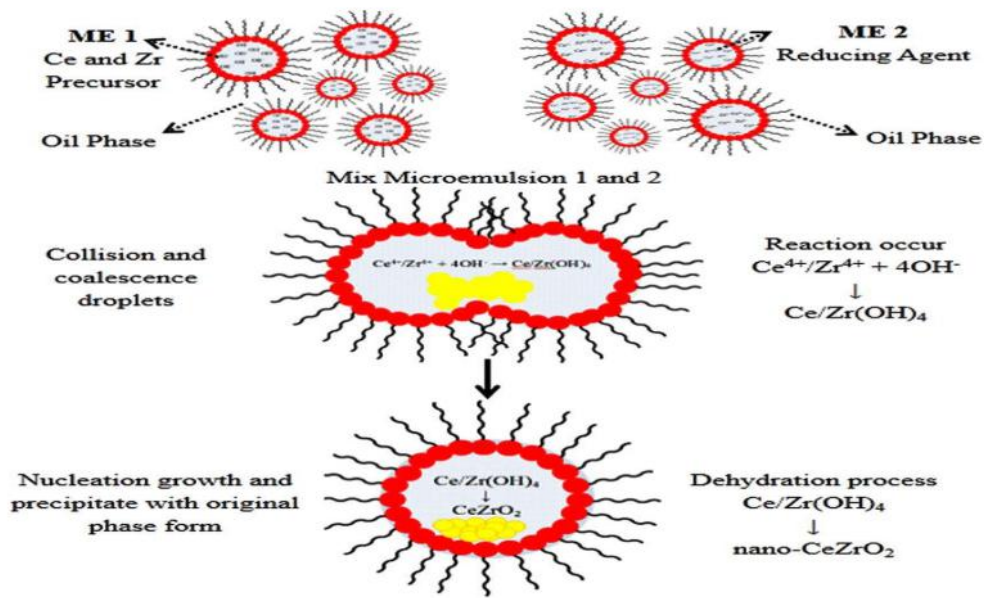


Fig. 6: Microemulsion method

7. Spray drying method

It is a substitute technique to the lyophilization method. This remarks the use of lipid with melting point more than 70°C. The best results were obtained with SLN concentration of 1% in a solution in water or 20 in ethanol-water mixture.

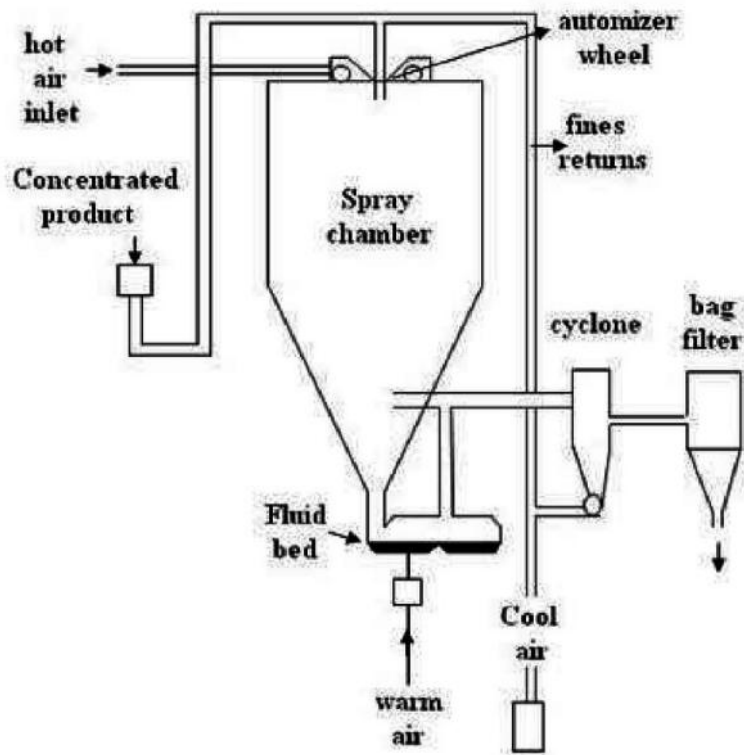
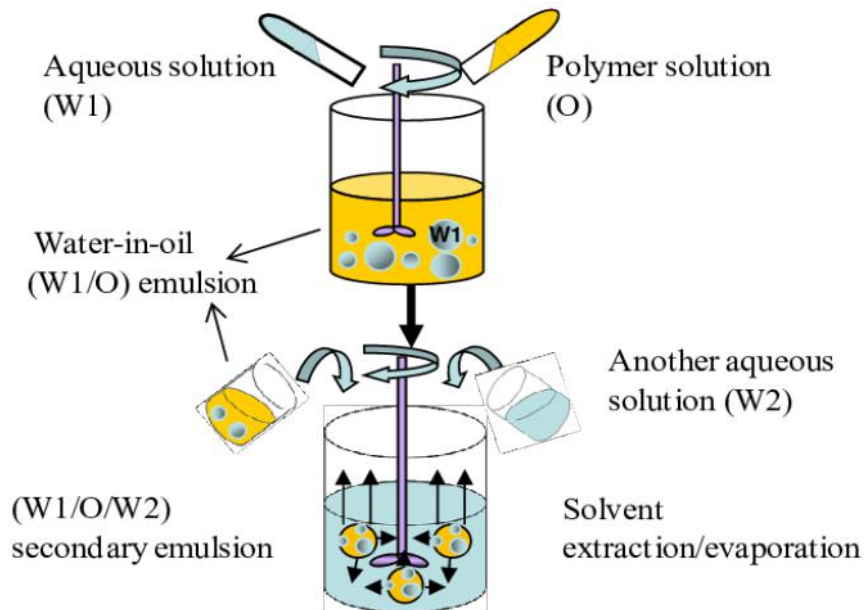


Fig 07-Spray drying method

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8. Double emulsion method

In this method the drug is encapsulated with a stabilizer to prevent the separating of drug in to external waterphase during solvent evaporation in the external water phase of w/o/w double emulsion.



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Fig 08-Double emulsion method

9. Precipitation method

The glycerides are liquefied in an organic solvent (e.g. chloroform) and the solution will form an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated and form nanoparticles. Chemical precipitation is the most common method used in removing dissolved (ionic) metals from solutions, such as process wastewaters containing toxic metals. The ionic metals are altered to an insoluble form (particle) by the chemical reaction between the soluble metal compounds and the

precipitating reagent. The particles made by this reaction are removed from solution by settling and/or filtration. The unit operations typically required in this technology includes neutralization, precipitation, coagulation/flocculation, solids/liquid separation, and dewatering.

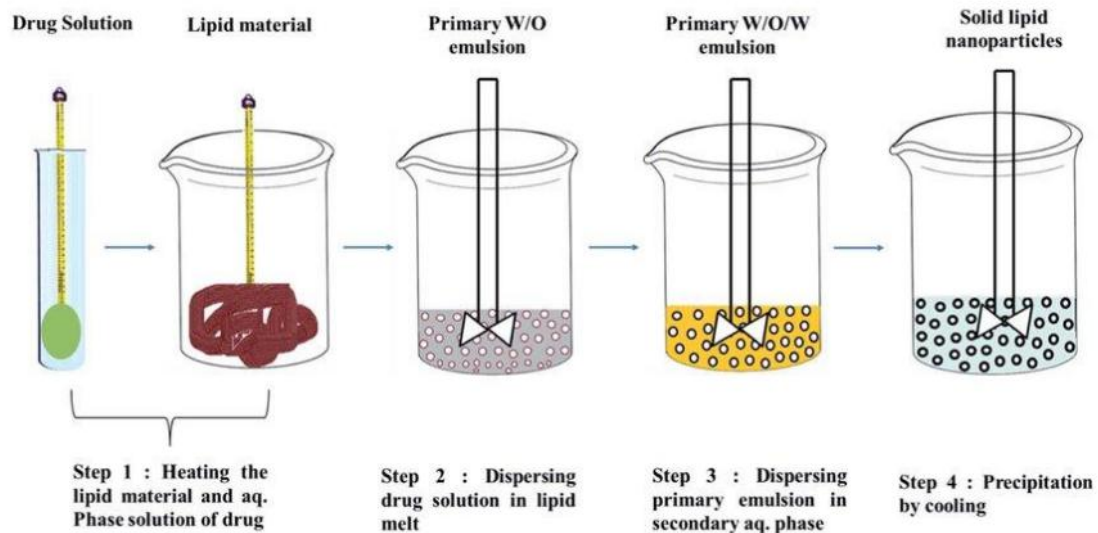


Fig 09-Precipitation method

10. Film-ultrasound dispersion

The solvent and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. By the ultrasound with the analysis to diffuser at last, the SLN with the slight and constant particle size is formed.

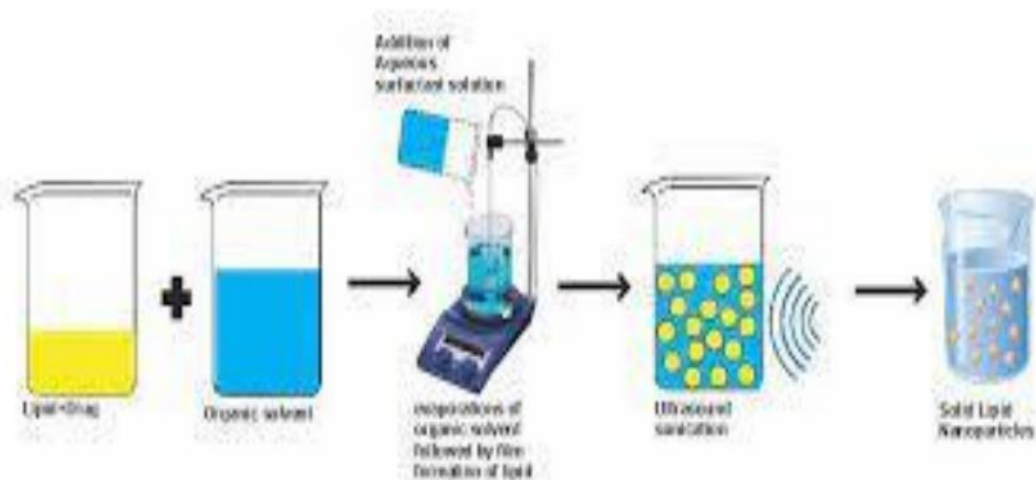


Figure 11: Film-ultrasound dispersion method

Conclusion- SLN provide a novel and unique drug-delivery system. The SLNs have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is aptly achieved with SLNs. Clear advantages of SLN include the composition (physiological compounds), the rapid and effective production process including the possibility of large scale production, the avoidance of organic solvents and the possibility to produce carriers with higher encapsulation efficiency. The appropriate characterization of the complex surfactant/lipid dispersions requires several analytical methods in addition to the determination of the particle size.

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