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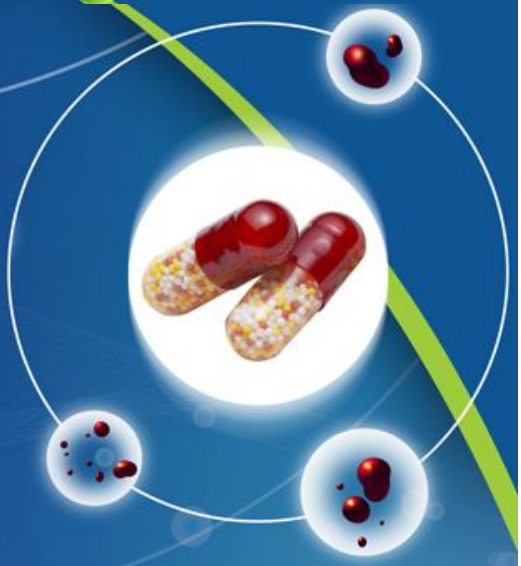

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Review Article

"SOLID LIPID NANOPARTICLE (SLN): A MODERN APPROACH FOR DRUG DELIVERY"

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ABSTRACT:

Lipid nanoparticles were developed in the last decade of the last century as alternative carrier system to emulsions, liposomes and polymeric nanoparticles. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are the two main types of lipid nanoparticles. The present review focuses on the utility of SLN in terms of their advantages, production methodology, characterization and applications. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers.

Keywords: *Solid Lipid Nanoparticle, SLN, Lipid Nanoparticle, Nanoparticle, Colloidal Drug Delivery*

INTRODUCTION:

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. [1,2] To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals.

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These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators world-wide. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and polymeric nanoparticles). They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve performance of pharmaceuticals, neutraceuticals and other materials.A solid lipid nanoparticle (SLN) is typically spherical with -an average diameter between 10 to 1000 nanometers. Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). The term lipid is used here in a broader sense and includes triglycerides (e.g. tristearin), diglycerides (e.g. glycerol

bahenate), monoglycerides (e.g. glycerol monostearate), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently. [3,4]In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. The reasons for the increasing interest in lipid based system are many fold and include. [4]

- Better control over release kinetics of encapsulated compound
  - Engineering via size and lipid composition.
  - Melting can serve as trigger.
- Enhanced bioavailability of entrapped bioactive.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvents required.
- Wider range of base materials (lipids).
- Conventional emulsion manufacturing methods applicable.
- Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility:
  - Can be subjected to commercial sterilization procedures.
  - Can be freeze-dried to produce powdered formulation. [4,5]

Definition of SLN:

Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles1. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals. [5] The SLN system can be easily explained. It is identical to an oil-in-water emulsion for parenteral nutrition (e.g., Intralipid, Lipofundin), but the liquid lipid (oil) of the emulsion has been replaced by a solid lipid, i.e., yielding solid lipid nano particles. SLN are particles made from solid lipid or lipid blends produced by high pressure homogenization. The mean photon correlation spectroscopy (PCS) diameter is typically between approximately 80nm to 1000nm. Particles below 80nm are more difficult to produce because very often they do not recrystallized8 The SLN are dispersed in an aqueous outer phase and stabilized by surfactants, e.g., Tween80, sodium dodecyl sulfate (SDS), lecithin. Alternatively, they can be produced surfactant free using steric stabilizers (e.g.poloxamer180) or an outer of increased viscosity (e.g. ethyl cellulose solution).SLN can also be produced in nonaqueous media, e.g., PEG-600 or oils like Miglyol 812. Production in PEG-600 gives a dispersion which can be directly filled into soft gelatin capsules.

Generally, they are made of solid hydrophobic core having a monolayer of phospholipids coating as shown in Fig.1. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipids are embedded in the fat matrix. They have potential to carry lipophilic or hydrophilic drugs or diagnostics. [4,6]

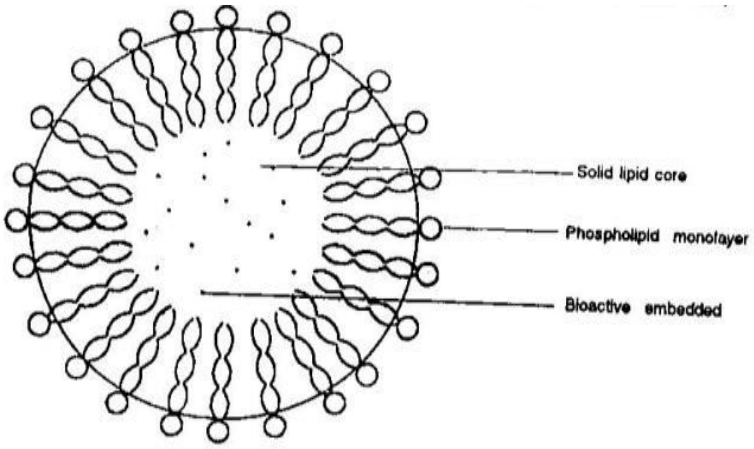

Figure-1: Proposed Structure of SLN

Advantages of SLN:[6,7]

- Control and/or target drug release.
- Excellent biocompatibility.
- Improve stability of pharmaceuticals.
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods applicable.
- Raw materials essential the same as in emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

Potential problems associated with SLN and its Production Technology [8]

The review by (Mehnert *et al*. 2001) high lights these aspects:

Pay-load for a number of drugs too low

Drug expulsion during storage

High water content of SLN dispersions

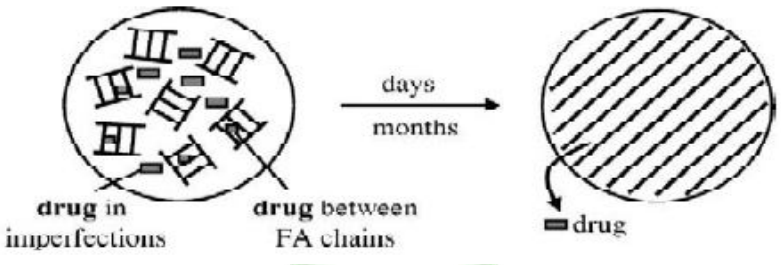

Figure-2: Mechanism of drug expulsion during storage of SLN dispersions, transition to highly ordered lipid crystal.

A potential problem in SLN is the formation of a perfect crystal, which can be compared to a dense 'brick wall'. Using different molecules, i.e. different 'stones' to build the matrix or 'wall' leaves enough imperfections to accommodate the drug. Drug load in SLN is limited due to the formation of the lipid crystal. Drug expulsion is caused by an ongoing crystallization process towards a perfect crystal.

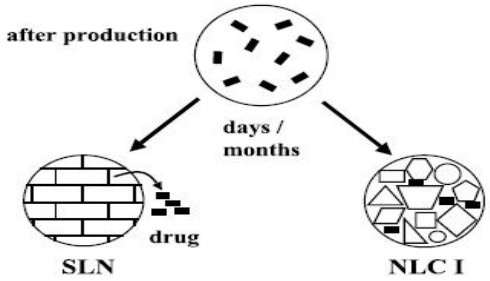

Figure-3: Crystallisation process during storage to perfect crystal in SLN (left) and unchanged remaining NLC I structure with imperfections.

Nanostructured lipid carriers (NLC) :

Although SLN have numerous advantages of controlled and targeted drug delivery increased stability of incorporated drug, there are some limitations too. During storage it was observed that drug was expelled out of SLN. The reason behind expulsion of drug was the highly ordered crystalline lipid matrix which was leaving very little space for drug molecules. To overcome the said problem nanostructured lipid carriers (NLC) were introduced, which are second generation SLN. [9] NLC show a higher loading capacity for active compounds by creating a less ordered solid lipid matrix, i.e. by blending a liquid lipid with the solid lipid, a higher particle drug loading can be achieved. Therefore, the NLC have an increased drug loading capacity in comparison to SLN and the possibility of drug expulsion during storage is less. [7]

Lipid drug conjugates (LDC):

A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this limitation, the so called LDC nanoparticles with drug loading capacities of up to 33% have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e.g. with a fatty acid) or by covalent linking (e.g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) to a nanoparticle formulation using high pressure homogenization (HPH). Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections. [2, 9]

Table: 1 Comparative properties of solid lipid nanoparticles, Polymeric nanoparticles, Liposomes, Lipid emulsions [10]

S.NO.	PROPERTY	SLN	POLYMER NANOPARTICLES	LIPOSOMES	LIPID EMULSIONS
1.	Systemic toxicity	Low	>or = to SLN	Low	Low
2.	Cytotoxicity	Low	>or = to SLN	Low	Low
3.	Residues from organic solvents	No	Yes	May or may not	No
4.	Large scale production	Yes	No	Yes	Yes
5.	Sterilization by autoclaving	Yes	No	No	Yes
6.	Sustained release	Yes	Yes	<or = to SLN	No
7.	Avoidance of RES	Depend on size and coating	No	Yes	Yes

Types of SLN: [11]

The type of SLNs depend on the chemical nature of the active ingredient and lipid, the solubility of actives in the melted lipid, nature and concentration of surfactants, type of production and the production temperature. Therefore 3 incorporation models have been proposed for study.

SLN, Type I or homogenous matrix model:

The SLN type I is derived from a solid solution of lipid and active ingredient.A solid solution can be obtained when SLN are produced by the cold homogenation method. A lipid blend can be produced containing the active in a molecularly dispersed form. After solidification of this blend it is ground in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

SLN, Type II or drug enriched shell model:

It is achieved when SLN are produced by the hot technique, and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w nanoemulsion the lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model is the incorporation of coenzyme Q10.

SLN, Type III or drug enriched core model:

Core model can take place when the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core.

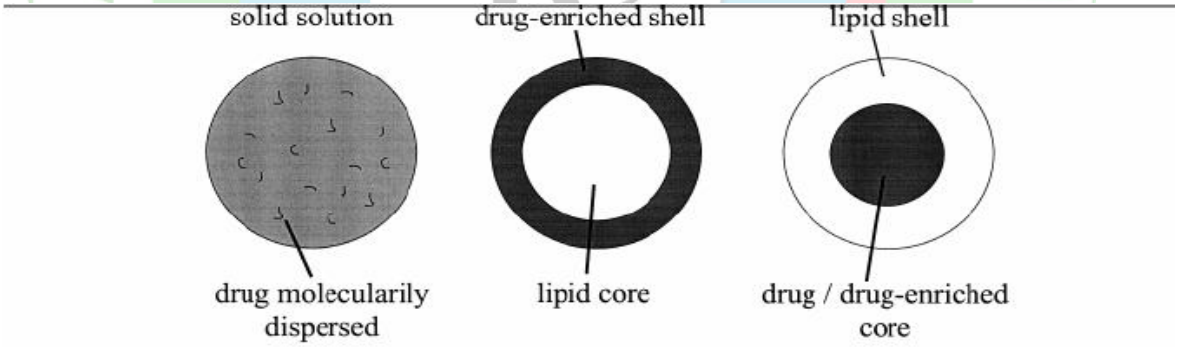

Figure-4 models of incorporation of active compounds into sln [10]

Preparation techniques for solid lipid nanoparticles:

SLNs are prepared from lipid, emulsifier and water/ solvent by using different methods and are discussed below

- High pressure homogenization
  Hot homogenization
  Cold homogenization
- Ultrasonication/high speed homogenization
- Solvent Emulsification Evaporation Technique
- Solvent emulsification-diffusion method
- Supercritical fluid method
- Microemulsion based method
- Spray drying method
- Double emulsion method
- Precipitation technique
- Solvent injection technique
- Membrane contractor technique
- Film-ultrasound dispersion

High Pressure Homogenization Technique: [8,12,13]

In high pressure homogenization technique, melted lipid solution is pushed with high pressure (100-200 bars) through a narrow gap of few micron ranges at high velocity with a rapid pressure drop causing cavitation. Subsequently, the mixture hits the solid surface causing further disruption and finally discharged as homogenized product. So, cavitation and shear stress are the forces which cause the disruption of particle to submicron range. Normally, the lipid contents are in the range of 5-10%, but even higher concentration (40%) of lipid can be homogenized to nanodispersion. Basically, there are two approaches for SLN production by high pressure homogenization namely hot- and cold homogenization techniques. In both the techniques as depicted in Fig. (5), the drug is dissolved or dispersed or solubilized in the lipid being melted at approximately 5-10oC above the melting point of lipid.

Hot Homogenization Technique

For the hot homogenization technique (HHT), the drug loaded in melted lipid is dispersed under high shear device (*e.g.* Ultra Turrax) in the aqueous surfactant solution of identical temperature. The hot pre-emulsion obtained is then processed in a temperature controlled high pressure homogenizer (*e.g.* piston gap homogenizer like Macron LAB 40 or Macron LAB 60 or APV-2000), generally a maximum of three cycles at 500 bars are sufficient. The resultant hot o/w nanoemulsion recrystallizes upon cooling down to room temperature to form SLNs. It is necessary to cool the nanoemulsion to lower temperature than room temperature to start recrystallization where the melting point of lipid is very close to room temperature and in the case of glycerides composed of short chain fatty acids (*e.g.* Dynasan-112) . In general, high temperature results in HHT, lowers the particle size due to the decreased viscosity of the inner phase and is also suitable for drugs showing temperature sensitivity to some extent because the exposure of drug to an increased temperature is relatively short. In addition, either medium scale or large scale production is possible for SLN by HHT. Furthermore, differently homogenizer from different manufacturers can be used for successful production of SLN by the above method.

The disadvantage associated with this technique is that at high temperature the rate of drug and carrier degradation is more and further due to small particle size and presence of emulsifier, lipid crystallization may be highly retarded and the sample remains as supercooled melt for several months . HHT is a poor technique for hydrophilic drug candidate because partitioning of drug into aqueous phase during homogenization and when cooled most of drug particle remained at the outer layer of the SLNs, which lead to burst release.[8,14]

Cold Homogenization Technique :

Cold homogenization technique is carried out with the solid lipid containing drug and therefore called as milling of a suspension. The first step of preparation is same as HHT, which includes dispersion or dissolving or solubilization of the drug in the melted lipid. Then, the drug lipid mixture is rapidly cooled either by means of liquid nitrogen or dry ice to convert it to solid state. The drug containing solid lipid is milled by means of mortar or ball mill to micron size (50-100 micron) and followed by the dispersion in chilled emulsifier solution to yield a pre-suspension. This pre-suspension is subjected to high pressure homogenization at room or below room temperature, where the cavitation force is strong enough to break the microparticles to SLNs. CHT avoids or minimizes the melting of lipid and thereby reducing the loss of hydrophilic drug to aqueous phase. Another way to minimize the loss of hydrophilic drug to aqueous phase is to replace water with other media (*e.g.* oil or PEG 600) with low solubility for the drug. In CHT, particle size and polydispersity index (less the polydispersity index more the stability of nanosuspension) are higher as compared to HHT. The cold homogenization only minimizes the thermal exposure of drug, but it does not avoid it completely due to melting of the lipid/drug mixture in the first step of

preparation. However, an effective temperature control is needed to ensure unmolten state of lipid as temperature increases during homogenization. [8]

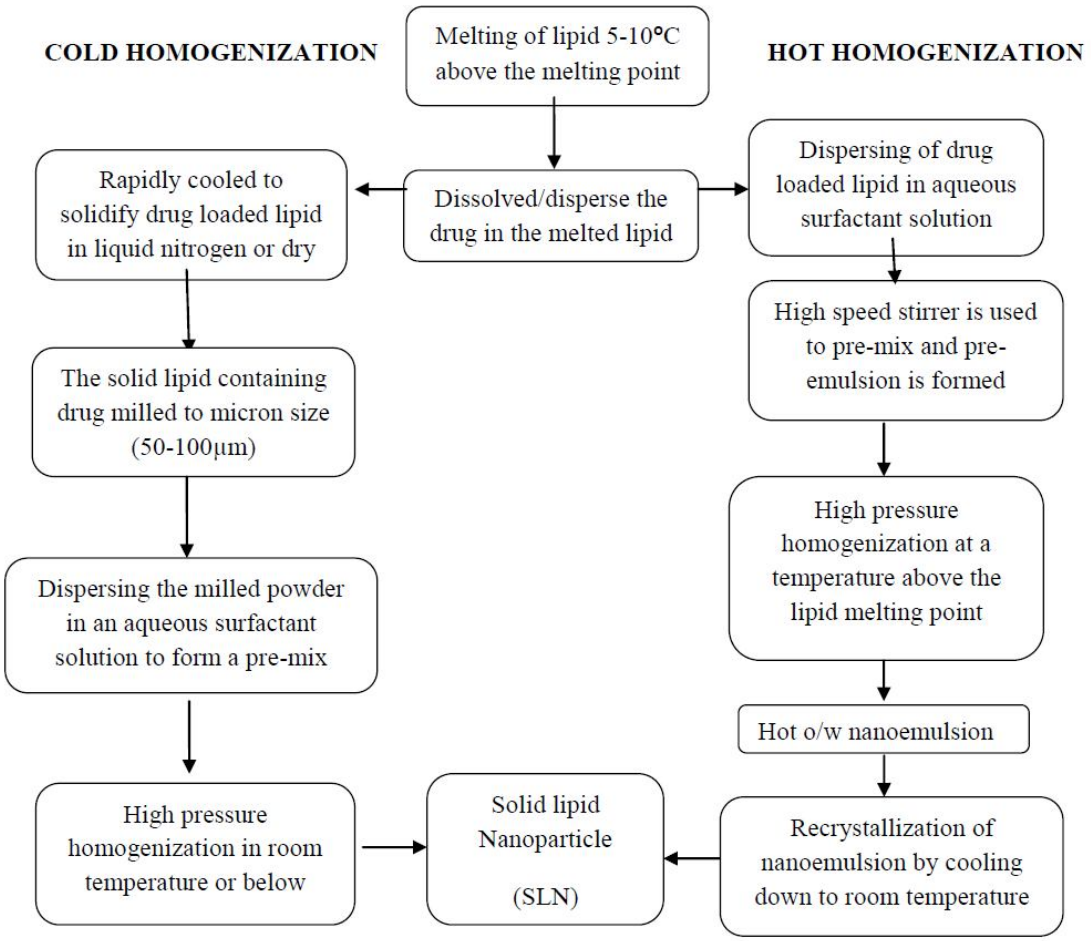

Figure-5. Schematic representation of SLN preparation by hot and cold homogenization.

Ultrasonication/high speed homogenization :

This ultrasonication technique is a dispersing technique, which was initially used for theproduction of solid lipid nanodispersion. Ultrasonication based on the mechanism ofcavitation. In first step, the drug was added to previously melt solid lipid. In second step, theheated aqueous phase (heated to same temperature) was added to the melted lipid and emulsifiedby probe sonication or by using high speed stirrer or aqueous phase added to lipid phase drop bydrop followed by magnetic stirring. The obtained pre-emulsion was ultrasonicated usingprobe sonicator with water bath (at 0ºC). In order to prevent recrystalization during the process,the production temperature kept at least 5ºC above the lipid melting point. The obtainednanoemulsion (o/w) was filtered through a 0.45µm membrane in order to remove impuritiescarried in during ultrasonication. Then they obtained SLN is stored at 4ºC. To increase thestability of the formulation, was lyophilized by a lyophilizer to obtain freeze-dried powder andsometime mannitol (5%) was added into SLNs as cryoprotector. [10]

Solvent Emulsification Evaporation Technique:

SLNs can also prepared by solvent evaporation method. Sjo¨stro¨m and Bergenst°ahl described a production method to

prepare nanoparticle dispersions by precipitation in o/w emulsions. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size.Siekmann and Westesen also preparedsolid lipid nanoparticles of 30 to 100 nm by dissolving tripalmitin in chloroform.This 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). [15]

Solvent emulsification-diffusion method:

SLNs can also be produced by solvent emulsifica-tion-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium. [16]

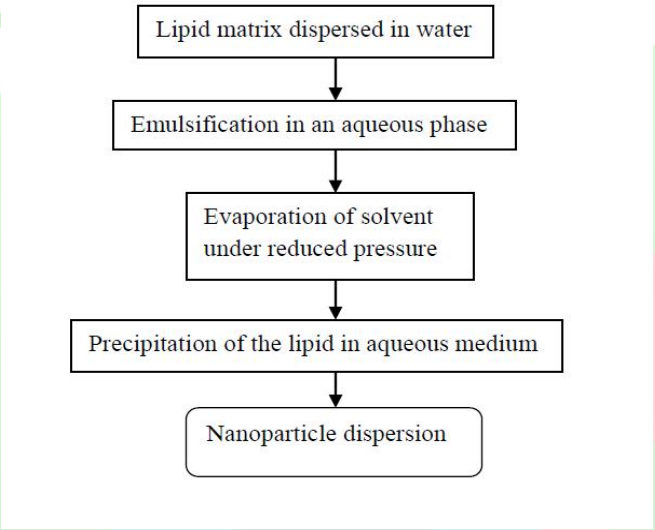

Figure-6 Systematic representation for emulsification-diffusion method [5]

Supercritical fluid technology:

This is a novel technique recently applied for the production of SLNs (Cavalli *et al.*, 1996). A fluid is termed supercritical when its pressure and temperature exceed their respective critical value. The ability of the fluid to dissolve compounds increases. This technology comprises of several processes for nanoparticle production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE). The advantages of this technique includes avoidance of the use of solvents, particles obtained as a dry powder, instead of suspensions, requires mild pressure and tempera-ture conditions. Carbon dioxide solution is the good choice as a solvent for this method. [16]

Micro emulsion based SLN preparations:

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions . They are made by stirring an optically transparent mixture at 65-70^0 which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-3^0) under stirring. Typical volume ratios of the