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Review Article

SOLID LIPID NANOPARTICLES: BUDDING FIELD OF LIPID NANOTECHNOLOGY

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Abstract

Solid lipid nanoparticles are at the forefront of the speedily developing field of nanotechnology with numerous potential applications in drug delivery, clinical medicine and research as well as in other diverse sciences. SLN combine advantages of the traditional systems but avoid some of their major disadvantages. Lipid nanoparticles offer the possibility to develop new therapeutics along with applicability for various routes such as oral, topical and parenteral. It acts as colloidal drug carriers for hydrophilic or lipophilic drugs. SLNs unite the advantages of polymeric nanoparticles, fat emulsions and liposomes. The ability to incorporate drugs into nanocarriers offers an innovative prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting.
Keywords: Solid Lipid Nanoparticles, Lipophilic, Hydrophilic, Nanotechnology.

INTRODUCTION:

The SLNs were first reported in1992 an alternative drug delivery system to traditional polymeric nanoparticles [1,2] . Over the past decade nanoscale size (<1000 nm) materials such as virus-like particles, liposomes, ISCOMs, polymeric, and non-degradable nanospheres have received attention as potential delivery vehicles for vaccine antigens which can both stabilize vaccine antigens and act as adjuvant[3,4].

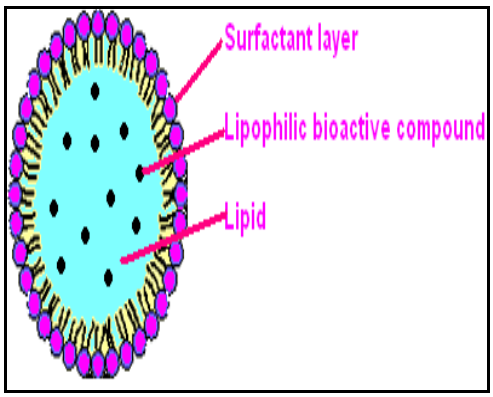

Fig.No.1: Structure of Solid Lipid Nanoparticles carrying a lipophilic bioactive compound

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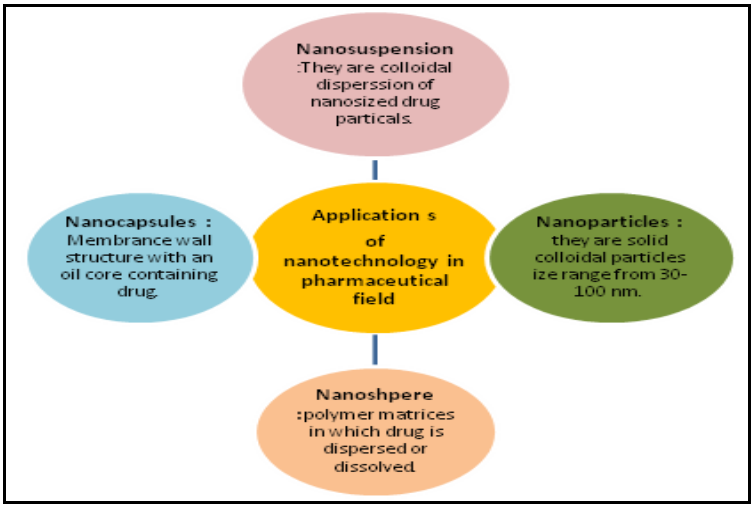

Fig.No.2: Application of nanotechnology in pharmaceutical field

SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in aqueous surfactant solution. SLN present unique properties such as small size, large surface area, high drug loading and are attractive for their potential to improve performance of pharmaceuticals [5,6].

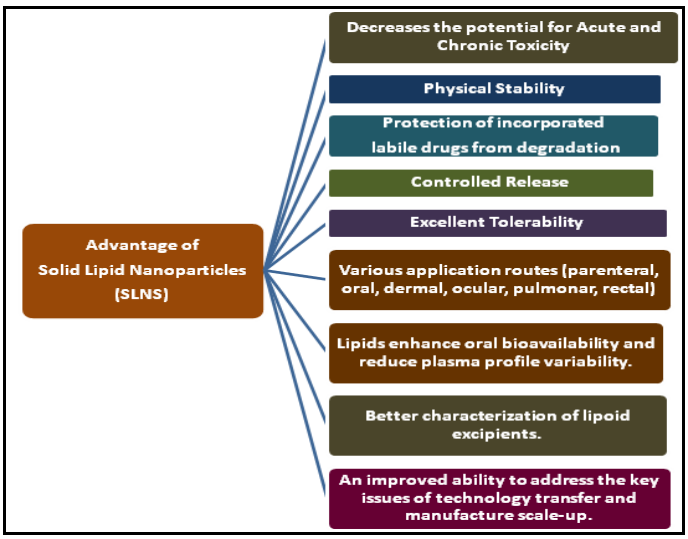

Fig.No.3: Advantages of SLNS

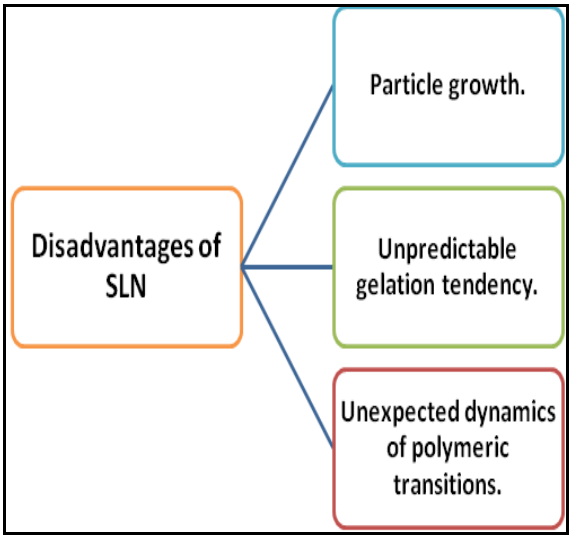

Fig No 4: Disadvantages of SLN

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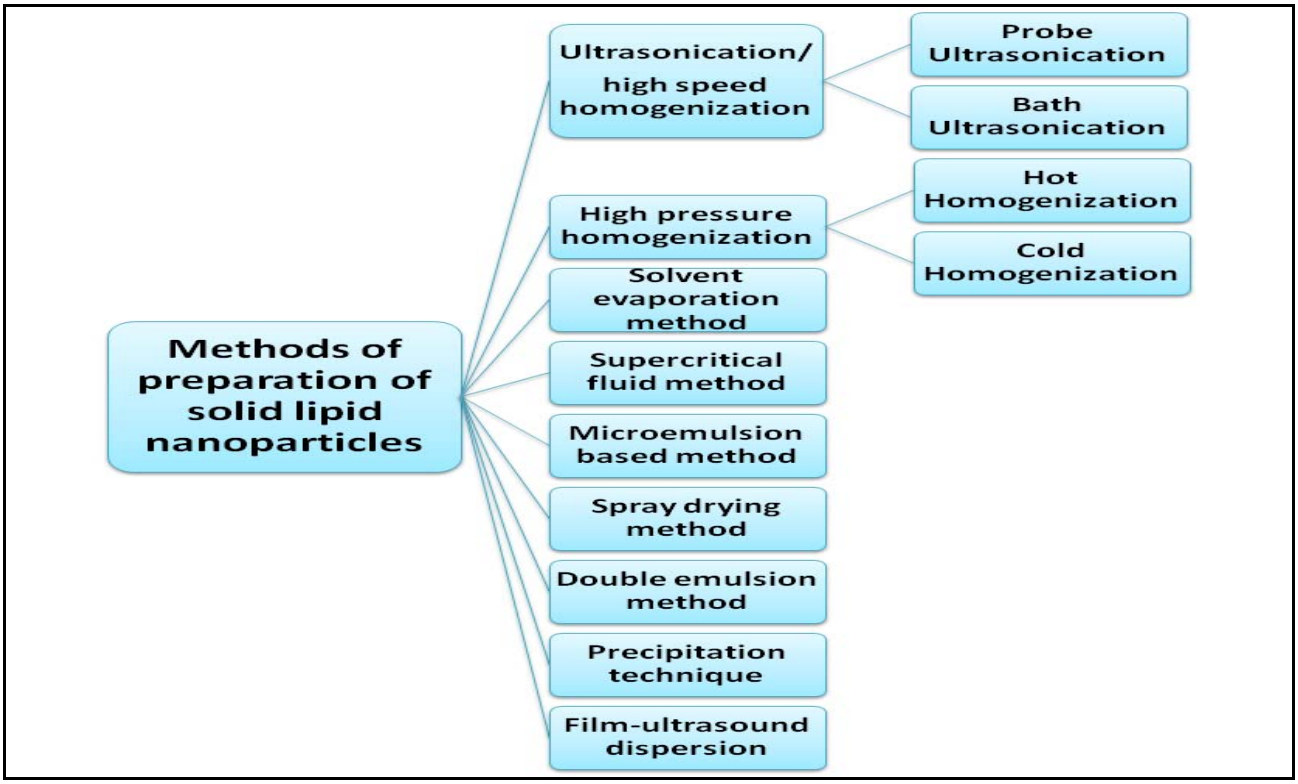

Fig No 5: Methods of preparation of solid lipid nanoparticles

1. Ultrasonication /High Speed Homogenization:

High speed stirring and ultrasonication are used in combination and performed at high temperature to make a stable formulation [7,8].

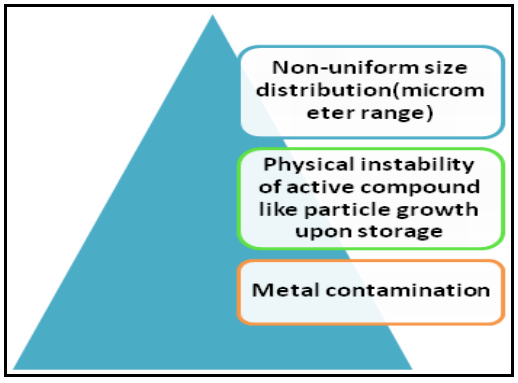

Fig No 6: Disadvantages of Ultrasonication /high speed homogenization

2. High Pressure Homogenization (HPH):

It involves high pressure homogenization which pushes the liquid with high pressure (100-2000 bar) through a narrow slit ranging a few microns. High-speed homogenization method is used to generate SLN by melt emulsification [9] .

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Influence of different process parameters on the particle size and zeta potential:

- Emulsification time
- Stirring Rate
- Cooling condition.

The fluid accelerates to a very short distance at very elevated viscosity of over 1000 km/h. Very high shear stress and cavitation forces disrupt the particles down to submicron range. Higher stirring rates did not considerably modify the particle size, but slightly enhanced the polydispersity/ heterogeneity index.

Two methods of HSH

a. Hot Homogenization
b. Cold Homogenization.

Both methods are suitable for processing lipid concentrations of up to 40% and normally yield very narrow particle size distributions [10] .

Hot Homogenization:

The hot homogenization is carried out at temperatures 5 to 10^0 C above the melting point of lipid, drug; combine with an aqueous surfactant solution at the identical temperature, which carry out homogenization of an emulsion. A pre-emulsion of the drug loaded lipid, melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (High Shear Mixer - Homogenizer ,Ultraturrax,). The quality of the pre-emulsion is very important for the final product quality. Mostly elevated temperature result in lower particle size due to the decrease of viscosity of the inner phase. The obtained pre-emulsion was then subjected to HPH. Three to five homogenization cycles at 10° at 500-1500 bar are adequate [11]. The produced hot O/W nanoemulsion is cooled to room temperature, the lipid recrystallizes and formation of solid lipid nanoparticles, NLC or LDC-nanoparticles [12].

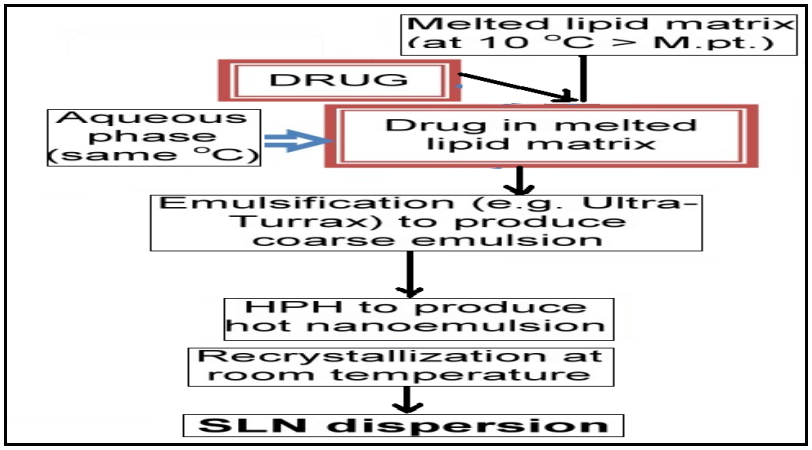

Fig No 7: Hot Homogenization

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Nagi A. ALHaj etal prepared SLNs containing tamoxifen, nonsteroidal antiestrogens have been loaded and to be used as breast cancer therapy by Hot homogenization method. Tamoxifen loaded SLN display significant cytotoxicity against MCF-7 cells and may be considered as an substitute formulation for this anti-estrogen drug. SLN was characterized by Differential Scanning Calorimetery (DSC), Transmission Electron Microscopy (TEM), Zeta Potential and

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Particle Size. The results of characterization studies support the prospective application of Tamoxifen-loaded SLNs as a carrier system[13] .

A.R. Gardouh etal carried out study on lipophilic drugs (Dibenzoyl peroxide, Erythromycin base and Triamcinolone acetonide) for preparation of SLN by high-shear hot homogenization technique. Drug release from prepared SLNs formulae was enhanced compared to commercially available formulae as obtained through in vitro release tests. The type of surfactant and also concentration of glycerol had a great influence on the physicochemical description and in vitro drug release. Formulation containing Tween 80 as a surfactant and the lipid matrix (10% Glyceryl monostearate and 5% Tween 80 with 1 % lecithin as co- surfactant) showed the best results according to the entrapment efficiency and in vitro drug release [14] .

Amornrat V etal had prepared Diazepam-glycerol behenate nanoparticles for parenteral delivery by the hot homogenization method using poloxamer 188 (P188), poloxamer 407 (P407), Phospholipon®80 (P80), Epikuron®200 (E200), tween 20 (T20) and tween 80 (T80). The formulation with T80 forms stable autoclaved SLN. The nanoparticles containing 5% lipid and 4% T80 yielded the smallest mean particle size of 118.4 and 122.0 nm before and after autoclaving. Loading diazepam into nanoparticles resulted in an increase in particle size. The release profiles of diazepam loaded SLN could be controlled for more than 60 hours [15].

Cold Homogenization :

The cold HPH is appropriate technique for heat-labile drugs or hydrophilic drugs. Lipid and drug are melted collectively and quickly ground under liquid nitrogen, forming solid lipid microparticles. A pre-suspension is produced by homogenisation of the particles in a cold surfactant solution. This pre-suspension is then homogenised in a HPH at or below room temperature at predetermined homogenisation conditions to produce SLN, NLC or LDC-nanoparticles which minimizes the thermal exposure of the sample [16,17,18].

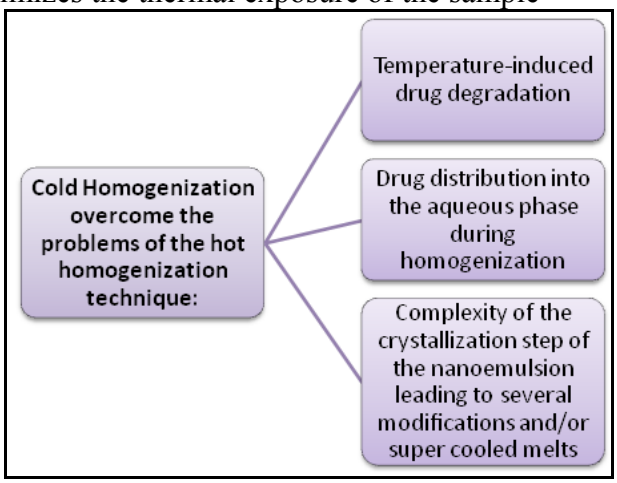

Fig No 8: Advantage of Cold Homogenization[19]

Jian You etal had prepared Vinorelbine Bitartrate (VB)-loaded solid lipid nanoparticles (SLNs) by cold homogenization technique. The mean particle size of the SLNs ranged from 150 to 350 nm. The drug entrapment efficiency (EE) improved with the increasing lecithin or oleic acid content in lipid matrix. The highest EE and drug loading capacity (DL) reached up to 80 and 6.6%, respectively. The physical stability experiment indicated that the SLNs were stable for 2

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months under room temperature. The cellular cytotoxicity of VB against MCF-7 cells could be improved by the entrapment of SLNs [20] .

Yang Y etal prepared chansu-loaded SLN by cold homogenization technique. Under the optimal conditions, the mean diameter, entrapment efficiency, drug loading of the Cs-SLN were 71.5 nm, 92.45% and 5.26% [21].

3. Solvent Evaporation :

Dispersions by precipitation in o/w emulsions, the lipophilic material is dissolved in water-immiscible organic solvent (eg: Cyclohexane, Dichloromethane, Toluene, Chloroform) which is emulsified in an aqueous phase using high speed homogenizer and immediately passed through the microfluidizer. The organic solvent then evaporated by mechanical stirring at room temperature and reduced pressure (e.g. Rotary Evaporator) leaving lipid precipitates of SLNs, Steps are shown in Fig No 9.The mean particle size depends on the concentration of lipid in organic phase[22] .

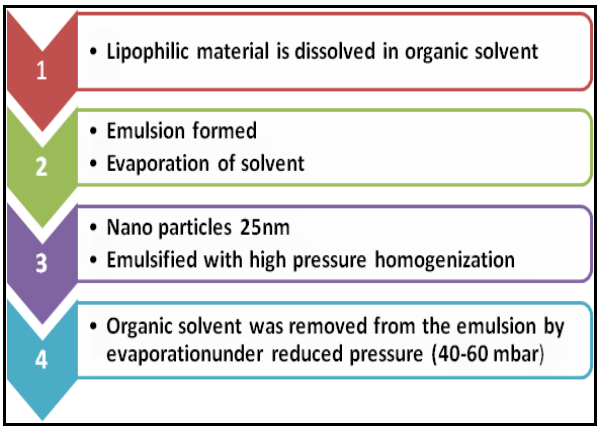

Fig No 9: Solid lipid nanoparticles preparation by solvent evaporation method

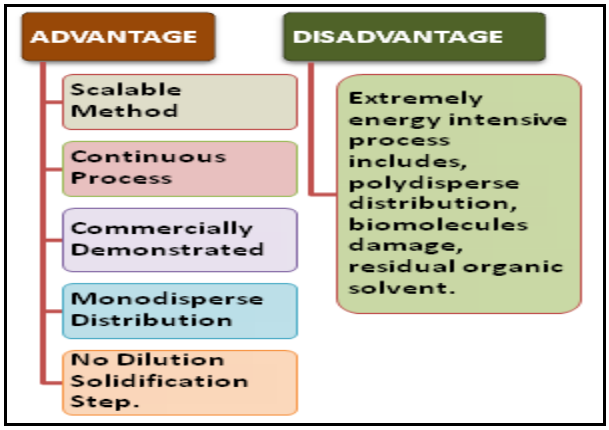

Fig No 10: Advantages and Disadvantages of Solvent evaporation

Dianrui Zhang had formed SLN delivery systems of Oridonin using stearic acid, soybean lecithin and pluronic F68. Stable SLN formulations of oridonin having a mean size range of 15–35 nm and mean zeta potential −45.07 mV.DSC and PXRD analysis showed oridonin is dispersed in SLNs in an amorphous state. The release pattern of the drug followed the Higuchi equations. In vivo studies demonstrated that oridonin-loaded SLNs increased the concentration of oridonin in liver, lung and spleen, while its distribution in heart and kidney decreased [23].

Shah M etal prepared of Ciprofloxacin Hydrochloride based solid lipid nanoparticles. The particle size of a solid lipid nanoparticle was in the range of 159-246 nm and drug encapsulation efficiencies were enhanced by choosing a binary mixture of physically incompatible solid lipids. Release of ciprofloxacin hydrochloride from SLNs was show Higuchi matrix model as the best fitted model [24] .

4. Supercritical fluid technology:

A fluid is qualified as supercritical when its pressure and temperature exceed their respective critical value. Above the critical temperature, it is not possible to liquefy a gas by rising the

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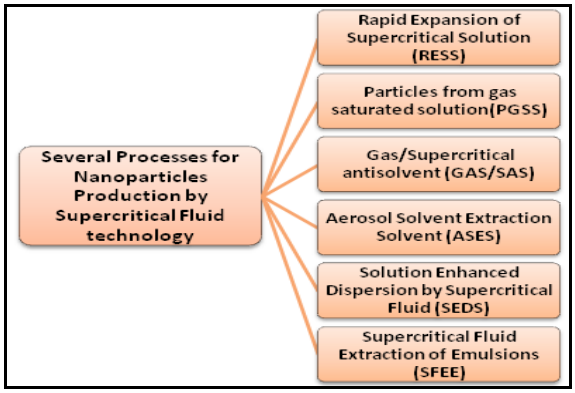
pressure. The supercritical fluid has distinctive thermo-physical properties. As the pressure is raised, the density of the gas increases without considerable increase in viscosity while the ability of the fluid to dissolve compounds also increases. As a result, its solvation power is altered by careful control of changes in temperature and pressure. The steps of Supercritical fluid technology shown in Fig No 11. Many gases like, CO2, ammonia, ethane, CHClF2 and CH2FCF3 were used and advantages of CO2 gas is explained in Fig No 12.



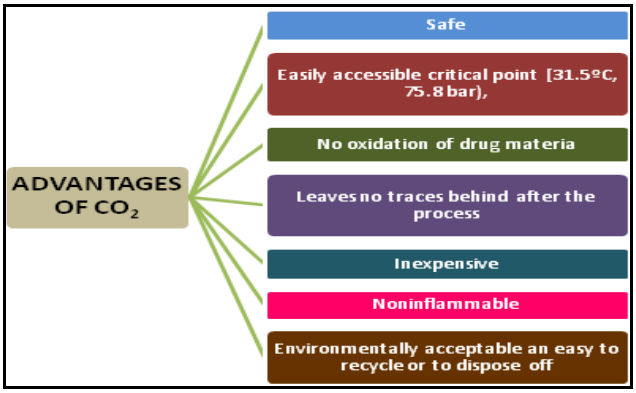


Fig No 11: Production methods by Supercritical Fluid technology

Fig No 12: Advantages of CO2

Chen YJ etal prepared SLN loaded with Xionggui powder- upercritical carbon dioxide fluid extraction (XG-CO2-SFE) using a hot dispersion- ultrasonic technique, establishing the best prescription of XG-CO2-SFE-SLN. The best prescription was: phospholipid: F-68: stearie acid glyceride = 5: 2 : 1, the entrapment efficiency of nanoparticles was 96.3%, with the mean size of 245.8 nm, the mean Zeta potential was -33.5 mV. In-vitro release meet to Weibull distribution in physiological brine and to single-index model in pH 7.4 phosphate liquid (40% EtOH) [25] .
Chattopadhyay P etal developed of a production method for nanoparticles of water-insoluble drugs in combination with lipids, with a volume mean diameter below 30 nm (D99% cumulative volume below 100 nm). Drug loading values between 10-20% w/w drug were obtained for model compounds ketoprofen and indomethacin in formulation with lipids such as tripalmitin, tristearin and Gelucire 50/13, typically used in these devices; i.e., greater than 90% of the aerosol mass resided in particles less than 3.5 mum aerodynamic diameter [26] .

5. Microemulsion technology:

As micro-emulsions are two-phase systems (inner and outer phase i.e: o/w microemulsions). Stirring an optically transparent mixture at 65-70°C, which typically contain low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50 , method is explained in Fig No 13.

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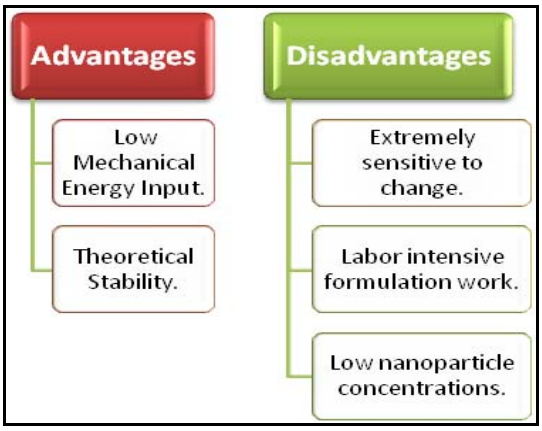

Fig No 13: Advantages and Disadvantages of Microemulsion technology

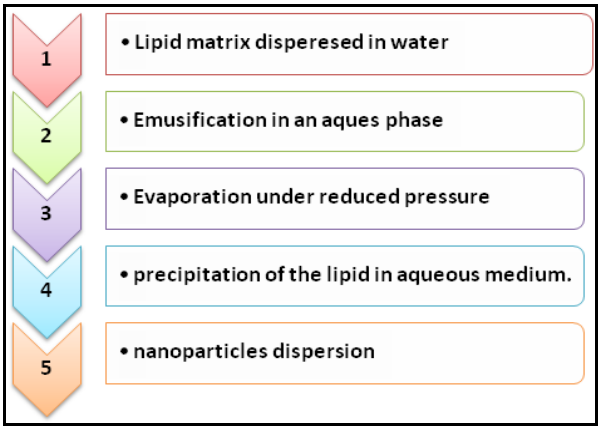

Fig No 14 : **Solid lipid nanoparticles preparation by solvent emulsification process**

Ruckman K. etal formulated by micro emulsification solidification method and characterized Methotrexate (MTX) SLN for intravenous administration. MTX-SLN particles (with MTX–Stearic acid–Soya lecithin—1:4:2) have an average size of 270 nm with 51.3% drug entrapment. The in-vitro release was attained up to 15th h. The pharmacokinetic study reveals that the half-life and MRT of SLNs were higher than MTX solution. The life span of EAC (Ehrlich Ascite Carcinoma) bearing mice was increased when treated with MTX-SLNs [27] .

Heni R etal developed SLN of Folic acid by microemulsion o/w technique with stearic acid 1.5%, Pluronic F127® 10%, ethanol (95%) 10%, and folic acid 0.015%. Emulsification rate at 500 rpm for 5 minutes at ±65°C and solidification process of microemulsion by dispersion microemulsion in water ±5°C for 10 minutes resulted in spherical particles in the range of 50-200 nm with the entrapment efficiency 12.82% [28] .

S. G. Padhye etal prepared Simvastatin SLN by hot melt emulsification process. Optimised formulations prepared from solid lipids glyceryl behenate and glyceryl palmitostearate containing Tween 80 as surfactant exhibited satisfactory entrapment efficiencies above 96% and mean particle size below 200 nm. Pharmacodynamic studies of simvastatin solid lipid nanoparticles revealed improved reduction in total cholesterol values as compared to pure drug powder indicating improved bioavailability[29] .

6. Solvent emulsification diffusion method :

The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most technique lipid is important advantage technique lipid this technique.

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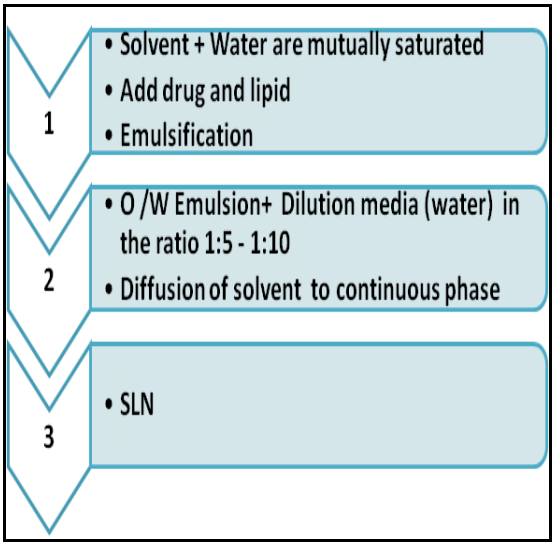

Fig No 15: Solvent emulsification-diffusion technique

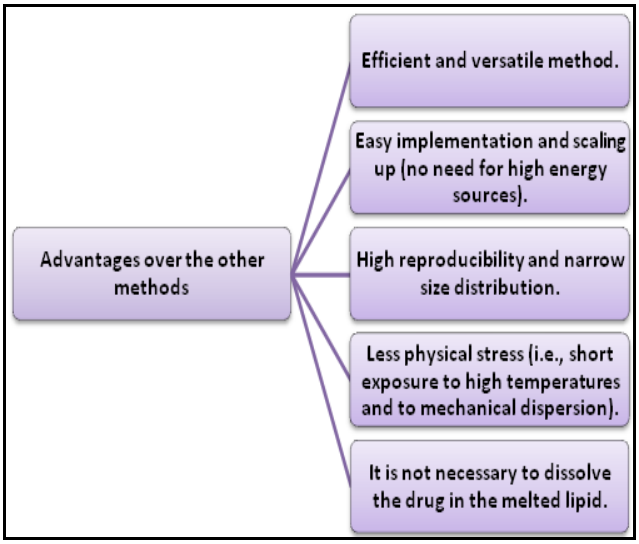

Fig No 16: Advantages of Solvent emulsification-diffusion technique

7. Spray drying method:

It's an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a drug product. This method cause particle aggregation due to high temperature, shear forces and partial melting of the particle. Most significant impact on redispersibility of spray dried particles. These optimized powders also showed significantly improved dissolution rates as compared to the micronized drug, or unoptimized nanosuspensions [30].

8. Double emulsion method:

For the preparation of hydrophilic loaded SLN, double emulsion method, a novel approach based on solvent emulsification-evaporation can be employed. Here, the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion [31].

9. Precipitation Technique:

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. [32]

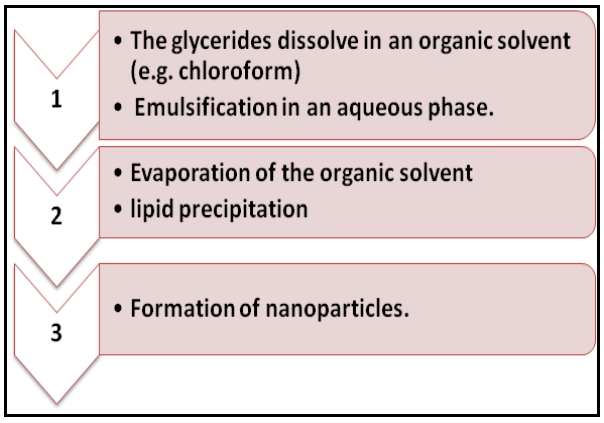

Fig No17: Precipitation technique

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10. Film ultrasound dispersion:

The lipid 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. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed.

11. Solvent injection technique:

It is based on lipid precipitation from the dissolved lipid in solution. In this technique the solid lipid was dissolved in water-miscible solvent (e.g. Ethanol, Isopropanol ,Acetone) or a water miscible solvent mixture. Then lipid solvent mixture was injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion then filtered to eliminate excess lipid. The emulsifier helps to construct lipid droplets at the spot of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent.

CONCLUSION:

Solid lipid nanoparticle drug delivery technology offers a highly versatile platform for improving medical therapeutics. Polymeric nanoparticles systems have some problems which overcome with help of SLN. Several research papers have been published for the improvement of drug delivery as explained above, but still there is necessitate stressing on its characterization and optimization. SLNs are easily manufactured nanoparticles made from economical, safe, stable, and eco-friendly materials and loaded with hydrophilic / lipophilic drugs for controlled delivery.

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