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Research Article

A REVIEW ON SOLID LIPID NANOPARTICLES

Yerikala Ramesh*[1], Chandra Sekhar K.B[2], Jayachandra Reddy P[3]

1. Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore (Dt) - 524346, Andhra Pradesh, India.
2. Department of Pharmaceutical Chemistry, JNTUA - Oil Technological Research Institute, Ananthapuramu - 515001, Andhra Pradesh, India.
3. Department of Pharmaceutical Analysis, Krishna Teja Pharmacy College, Chadalawada Nagar, Renigunta Road, Tirupathi-517506, Andhra Pradesh, India.

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E-mail: yramesh703@gmail.com

Abstract

The Solid lipid nanoparticles were developed in the early 1990s and up today they hfdave been considered as to be promising the drug delivery systems. The aim is to give a sustained release profile to corporated the active substances. The SLN are the submicron colloidal carriers ranging from 50 to 1000 nm it is composed of the physiological lipids dispersed in the water or in liquid surfactant solutions. SLNs combine with the advantages to avoid the drawbacks of several colloidal carriers, Potential disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage and relatively high water content of the dispersions have been observed. The main disadvantages are the limitation of lipid concentration in the organic solvent to form desirable particles and the use of organic solvents. The method is appropriate especially in the encapsulation of thermo sensitive APIs because of the absence of any thermal stress. The Essential oil extracted from *Artemisia arboreseens* when in corporated in solid lipid nanoparticles 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 pesticides.

Keywords: Nanoparticles, drug delivery system, Nanostructured lipid carriers, Hot & cold pressure homogenization

INTRODUCTION

The main Concept involved in nanotechnology has considered being a modern science has its history dating to 9th century [1]. Glittering effects of pots was generated by artisans of mesopotamia by preparing the nanoparticles from gold and silver. The ancient scientific description of the properties of nanoparticles was provided in year 1857 by Michael Faraday in his famous paper Experimental relations of gold (and other metals) to light. Biomimetics, two Learning from Nature In the year 1959, Richard Feynman gave a talk about molecular machines built with the atomic precision.

This was entitled as theres plenty of space at the bottom. The late 1950's and the early 1960's saw the world turning its focus towards the use of nanoparticles in the field of drug delivery system. The Peofessor Peter Paulspeiser was the one of the pioneer in this field. He and his research group at first investigated the Polyacrylic beads for oral administration, and then focused on microcapsules and in the late 1960s developed the first nanoparticles for drug delivery purposes and for the vaccines. It was followed by much advancement in the developing systems for drug delivery like by using nanoparticles the development of systems for the transport of drugs across the blood brain barrier [2]. After intraperitoneal injection of nano particles into Ehrlich Ascites Carcinoma-bearing mice an increase in life span of the mice is observed. In early 1980's with the first paper on nanotechnology being published in 1981 by K.Eric Drexler of space Systems Laboratory, Massachuetts Institute of Technology, the revolution of nano-revolution conceptually started. The Nanotechnology today has reached a stage where it is considered as the future to all technologies, with gradual advancements such as the invention of techniques like TEM, AFM, DLS etc. The solid lipid nanoparticles introduced in the year 1991 represented as an alternative carrier system to the tradition colloidal carriers like emulsions, liposomes

and polymeric micro and nanoparticles [3]. As they have been proposed as an alternative particulate carrier system, nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications. The SLN are the submicron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in the water or in liquid surfactant solutions. To improve the performance of pharmaceuticals, 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. SLN are nanoparticles made up of solid lipids with a Photon Correlation Spectroscopy mean diameter was approximately in between 50 and 1000 nm General ingredients include solid lipid(s), surfactant(s) and also water. Triglycerides, partial glycerides, fatty acids, steroids and waxes included under bord sence of lipids[4]. To stabilise the lipid dispersion all classes of surfactants have been used. SLN were developed in early 1990s and till today they have been considered as to be promising drug delivery systems and that too with the aim to give a sustained release profile to incorporated active substances. In fact, Drug mobility is really lower in solid lipids than in liquid oils when compared to liquid lipid formulations[5]. When compared to polymeric nanoparticles, they show better biocompatibility, because they are made of lipids similar to the physiological one, so the toxicity is reduced. However SLN are physicochemically stable and can be produced easily on a large scale, an draw material and production costs are relatively very low. The SLN have been equivalent composition to SLN, except higher particle size (>1000 nm), meaning that their application domains and administration routes are different.

Composition: The Solid lipid nanoparticles are composed of lipids and stabilizers in most cases surfactants, co surfactants and also coating materials. It is also used for Antioxidants, electrolytes, preservatives, viscosity enhancing agents, adhesives, absorption enhancers and other excipients. In most of the formulation ingredients are safe and under the Generally Recognized as Safe status issued by the Food and Drug Administration [6].

Lipids: In the next years SLN proved as a block buster in the nanotechnology because they believed that SLN offer many advantages of polymeric nanoparticles, fat emulsions and liposome's along with the possibility to successfully resolve problems related to drug physical and chemical stability drug carrieng and absorption [7]. Logical sequel was helps to development of Nanostructured Lipid Carriers which, still being solid at room and also body temperature, consist of both solid and liquid lipids. NLC have met the expectations and managed to resolve some problems related to the crystallinity and poor drug loading capacity. Lipids may be defined as the fatty or waxy organic compounds. Generally they are soluble in nonpolar and insoluble in polar solvents. Their typical constituents are free fatty acids, free fatty alcohols glycerol esters of fatty acids and waxes [8]. More complex structures as phospholipids, glycolipids and sphingophospholipids are also referred to this group. The lipid matrix itself determines the particles pharmaceutical properties as it is the structure that stores, transports and releases thedrug.

Advantages and problems of slns and other nanoparticles:

SLNs combine the advantages and avoid the drawbacks of several colloidal carriers, Potential disadvantages such as poor drug loading capacity, drug expulsion after polymeric transition during storage and relatively high water content of the dispersions (70-99.9%) have been observed [9]. The drug loading capacity of conventional SLN is limited by the solubility of drug in the lipid melt, the structure of the lipid matrix and the polymeric state of the lipid matrix. If the lipid matrix consists of especially similar molecules, a perfect crystal with few imperfections is formed. Since incorporated drugs are located between fatty acid chains, between the lipid layers and also in crystal imperfections, a highly ordered crystal lattice cannot accommodate large amounts of drug. Therefore, the use of more complex lipids is more sensible for higher drug loading [10].

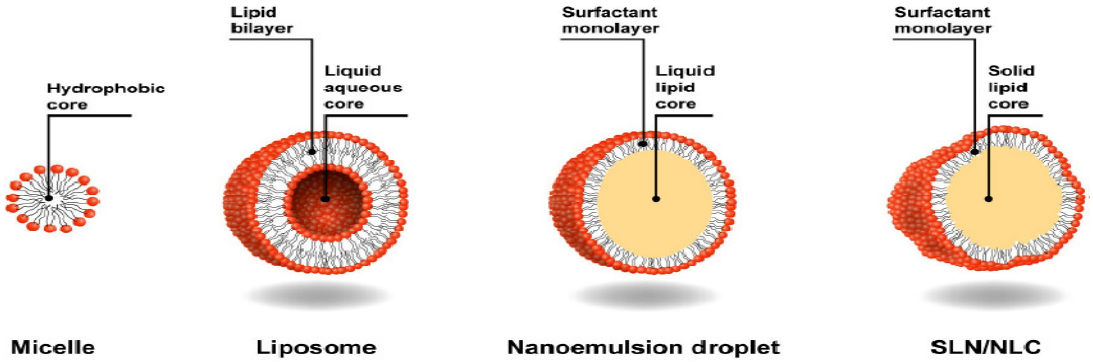

Figure-1: Comparison between micelles, liposomes, nanoemulsions and solid lipid nanoparticles.

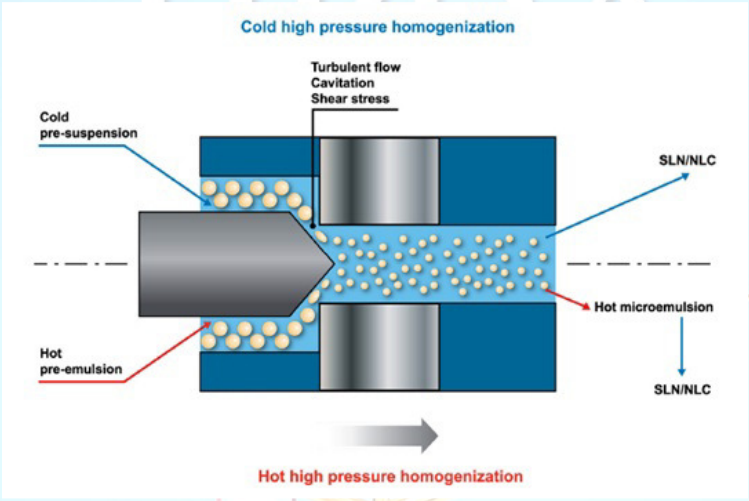

Figure-2: Mechanism of high pressure homogenization of cold pre suspension and hot pre emulsion respectively in the cold and hot technique

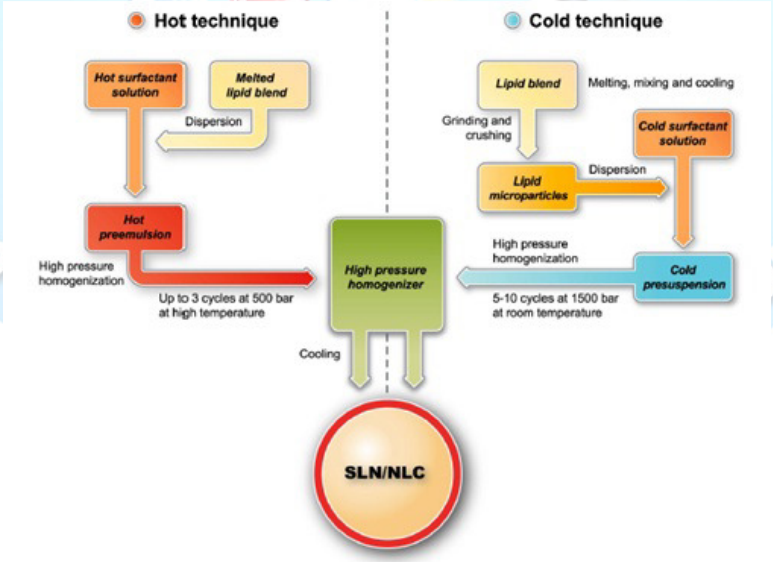

Figure-3: Hot & Cold high pressure homogenzation technique in the production of SLN/NLC

Nanostructured lipid carriers (NLC): The NLCs were introduced to overcome the potential difficulties with SLNs. The goal was to increase the drug loading and prevent drug expulsion. This could be visualized in three ways [11]. In the first model, spatially different lipids (like glycerides) composed of different fatty acids are mixed. The use of spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus provides more room for accommodation of guest molecules. The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils). This model is called imperfect type NLC. Drugs showing higher solubility in oils than in solid lipids can be dissolved in the oil and yet be protected from degradation by the surrounding solid lipids. These types of NLC are called multiple types NLC, and are analogous to w/o/w emulsions since it is an oil-in-solid lipid-in-water dispersion. Since drug expulsion is caused by on going crystallization or transformation of the solid lipid, this can be prevented by the formation of a third type, the amorphous type NLC. Here the particles are solid but crystallization upon cooling is avoided by mixing special lipids like hydroxyl octacosanyl, hydroxyl stearate and isopropyl myristate [12].

Lipid drug conjugates (LDC): A major problem involved in SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. The Only highly potent low dose hydrophilic drugs may be suitable incorporated in the solid lipid matrix. 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 protozoa infections [13].

Preparation: The techniques for SLN and NLC preparation can be grouped into three main branches high energy approaches, low energy approaches and methods employing organic solvents [14].

High-energy approaches:

High pressure homogenization: High pressure homogenization is one of the first techniques used in the preparation of SLN. Nowadays, it is well established in the production of nanoemulsions for parenteral foods, homogenization of milk, ice cream and others. In this technique, a liquid is pushed at high pressure through a narrow gap. Both the high pressure and the small size ofthe gap (in the range of few microns) cause a very high acceleration and pressure drop. As a resulta very high shear stress and cavitation forces disrupt particles/drops in the liquid. An increase in the temperature during the process is also possible due to the high acceleration and friction [15]. The method is easy accessible and scalable. Two approaches to produce SLN and NLC are utilized via this technique homogenization of hot pre emulsion and homogenization of cold pre-suspension.

In the "hot" method, the procedure is carried out at the temperature above the melting temperature of the lipid. A pre emulsion is formed usually with the help of high shear mixers. This emulsion is passed through a narrow orifice nozzle. Usually several cycles are applied to achieve submicron size with low polydispersity. The product obtained after the homogenization is a hot microemulsion [16]. The latter should be cooled fast so that the liquid lipid droplets can solidify and form the intrinsic structure of the SLN and NLC. The first stage of the cold homogenization approach is the formation of a hot lipid melt mixture of the substances that form the lipid matrix and the APIs. Then the melt is cooled down to a solidstate and grinded in powder mill to obtain particles in the size range of 50 to 100 micrometers. The obtained lipid powder is dispersed in aqueous solution of surfactant to form a pre-suspension. This pre-suspension is then passed through a homogenizer. Usually, more cycles and higher pressure required because the particles are more rigid and harder to break. The cold approach is desirable in formulations with drugs that are not stable at high temperatures or can distribute in the aqueous phase during the preparation.

High shear homogenization:

This is a simple and widely used technique in the production of aqueous dispersions. It is usually processed in chamber with a rotor-stator homogenizer. The procedure starts with placing the lipid ingredients and the water phase into the homoge-

nizer followed by applying high shear mixing (5000 – 25 000 rpm) at temperatures above the melting temperatures of the lipids as shown in figure.3. After homogenization, the formed hot micro emulsion is cooled to form SLN and NLC. Although it is very simple procedure to perform the properties of the final product are usually poor and particles in the micrometer range are detected [17]. Higher shearing rates can result in smaller droplets only until a certain critical value due to processes of coalescence. Although higher shearing rates cannot decrease particle size beyond that certain value they can reduce the polydispersity. The poor properties of the final product are the cause why this technique is preferably used as a pre homogenization step in high pressure homogenization and ultrasonication.

Ultrasonication: Ultrasonication is based on the cavitation in aqueous dispersions caused by powerful ultrasound with wave frequency usually around and above 20 kHz. In the reduction of SLN and NLC a mixture of pre-emulsion from melted lipid and hot surfactant solution is first prepared as shown in Figure. 4. Then the ultrasound is applied with a sonotrode that is in contact with the liquid. The cavitation causes disintegration of the lipid phase into smaller droplets. The obtained hot micro emulsion is then cooled to form the solid particles. Advantages of this technique, without doubt, are the possibility for scale up with flow cells, the low number of wetted and moving elements and the possibility to control the process by controlling the sound wave amplitude [18]. Main drawback, however, is the risk of metal contamination, which increases with longer sonication times.

Electro spray technique: In this relatively new technique an electrodynamics atomization is used to produce SLN directly in powder. The obtained particles by this method have narrow distribution and size below one micrometer [19]. However, the method is still under investigation for its applicability in theproduction of larger quantities of dispersions.

Low-energy approaches:

Micro emulsion method: Micro emulsion formation is used as a stage in the production of SLN and NLC since the early 90s. In this method the micro emulsion is spontaneously formed due to the high surfactants/lipid ratio. The proportions of the excipients are essential and in most cases pseudo ternary diagrams are used to study and describe the areas of micro emulsion formation. This method is simple and is performed by several common steps. Initially the lipids are melted and mixed with hot surfactant Solution [20]. Gentle stirring is applied until the micro emulsion is formed. In the second stage the hot microemulsion is dispersed in high volume of cold water (2-3 °C) under moderate stirring. This causes the liquid droplets to solidify. SLN or NLC obtained by this technique are spherical in shape and have Nar size distribution. This may require further concentration by ultra filtration, lyophylization or other method [21]. The high concentration of surfactants co-surfactants used is another major disadvantage of this technique.

Membrane contactor: Membrane contactor technique is a method which allows a gaseous and liquid phase to come indirect contact without dispersing one of the phases into the other and is used for purposes which require mass transfer between them. The two phases are separated by a hydrophobic membrane with typical pore size of 0,05 microns. This membrane doesn`t allow water to pass because of the high break through pressure needed [22]. In the production of SLN and NLC this technique is modified and the gaseous phase is replaced with a melted lipid blend. This blend is forced to pass through the membrane. Small droplets are formed spontaneously. On the other side of the membrane a hot surfactant solution is circulating and swapping away the droplets. The liquid lipid droplets are enveloped and stabilized by the surfactant molecules. Then, after cooling down the dispersion the droplets transform into solid particles. The method is scalable and the particle size can be tuned by using membranes with different pore size.

Phase inversion temperature (PIT) method: Phase inversion of O/W to W/O emulsions and *vice versa* induced by temperature change is a long known method to produce microemulsions stabilized with non-ionic surfactants. The technique is based on the change in the properties of polyoxy ethylated surfactants at different temperatures [23]. The hydrophillic-lipophillic balance (HLB) value of surfactants defined by Griffin is valid at 25°C. At this temperature the hydrophilic parts of the SAC molecules are hydrated to a certain extent. An increase in the temperature causes dehydration of the ethoxy groups. As a result, the lipophilicity of the molecules of the SAC rises with corresponding decrease in HLB val-

ue. At a certain point the affinity of the SAC to the aqueous and lipid phase is equal this temperature is defined as the phase inversion temperature. This particulate state is characterized by very low surface tension and presence of complex structures in the system. If the temperature is further increased the SAC's affinity to the lipid phase becomes higher enough to stabilize emulsions of W/O type.

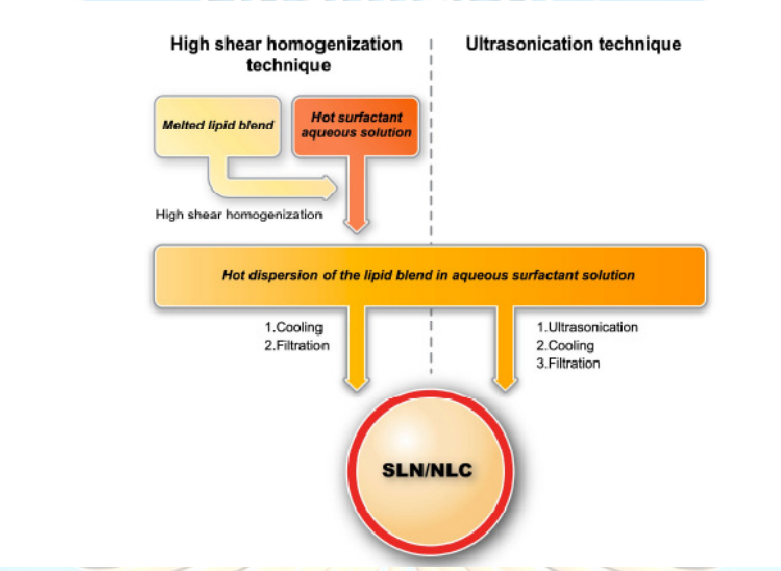

Figure:4 High shear homogenization and ultrasonication techniques in the production of SLN/NLC.

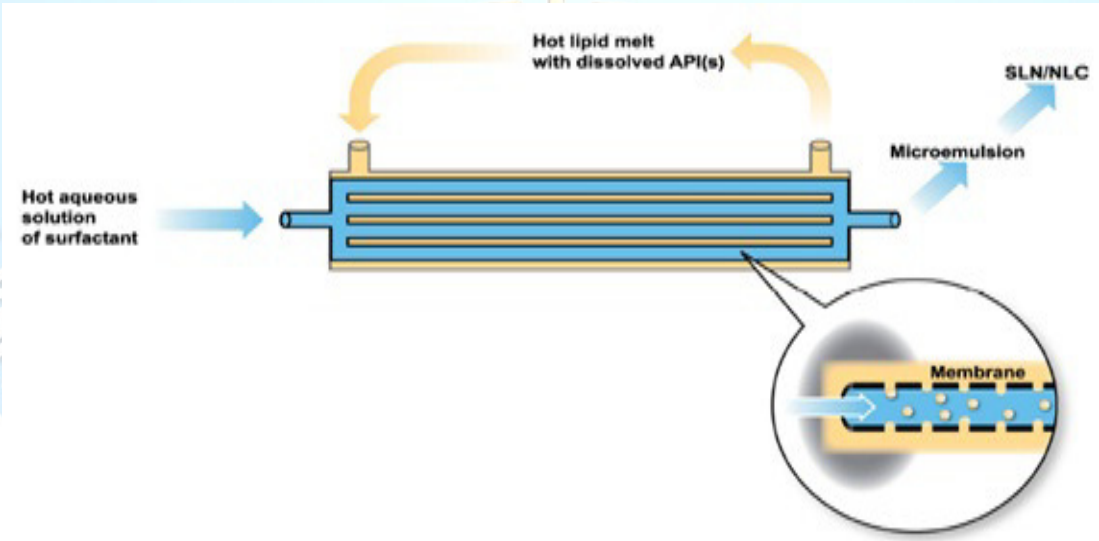

Figure: 5 Membrane contractor technique in preparation of SLN/NLC

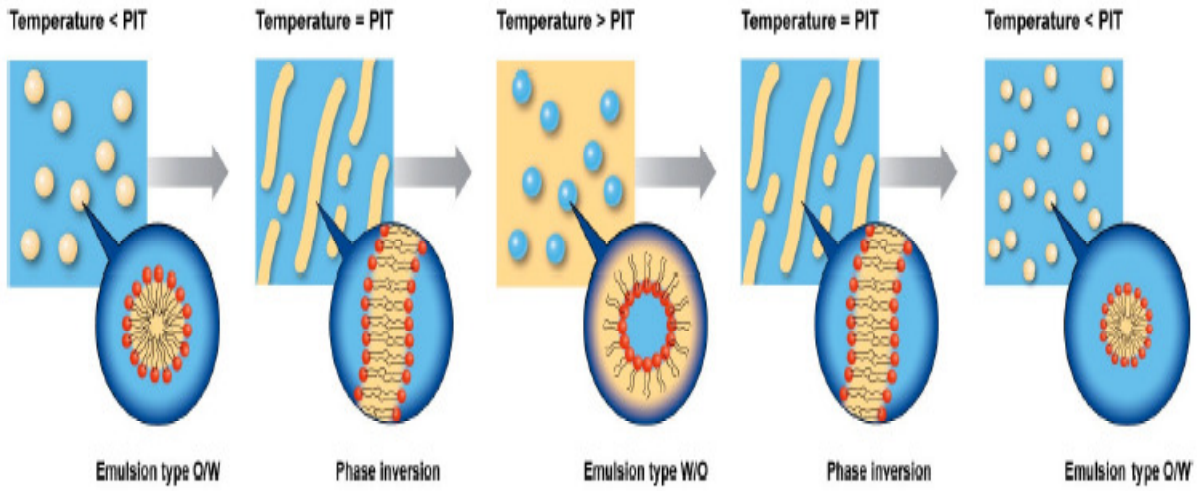

Figure: 6 Phase inversions of hot emulsion with variations of the temperature above and below PIT.

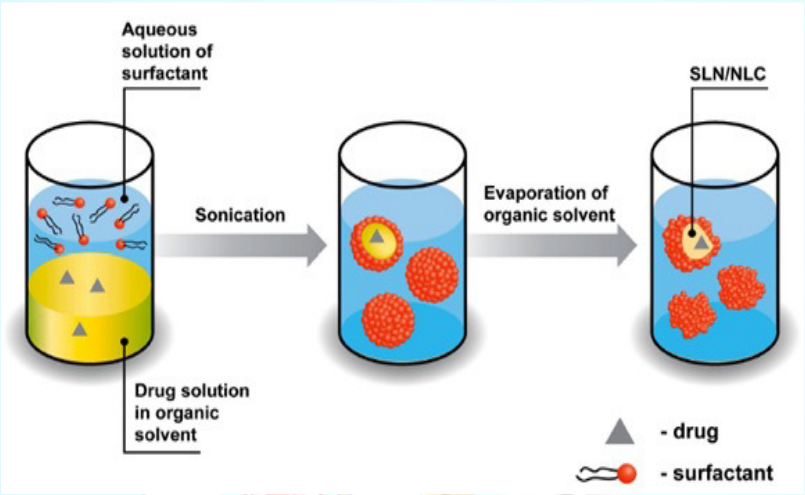

Figure: 7 Emulsification solvent evaporation technique in the preparation of SLN/NLC

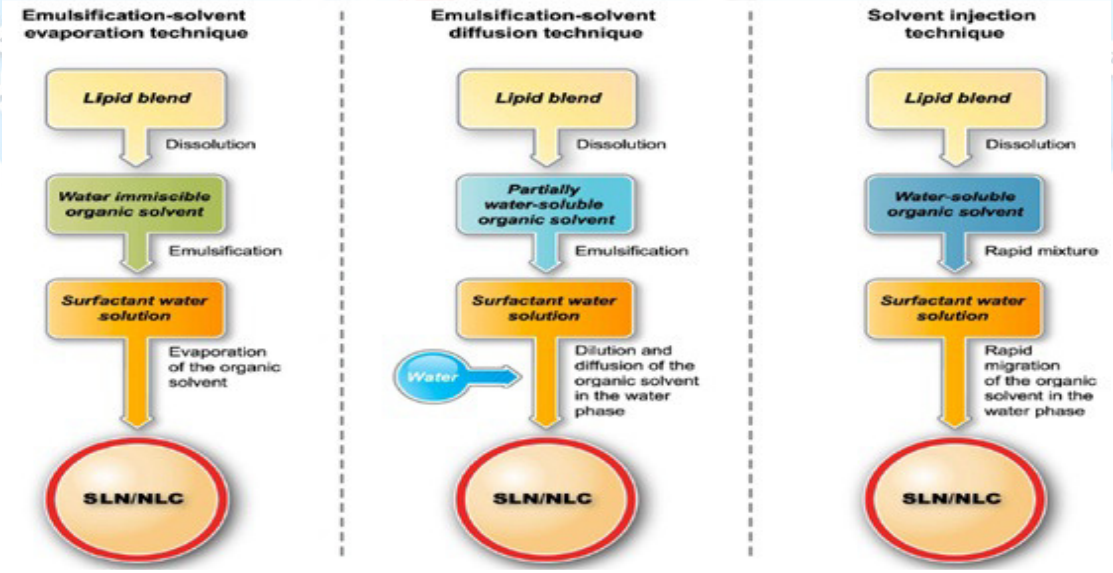

Figure: 8 Organic solvent based methods for preparation of SLN/NLC

If cooled down the system goes through the reverse process. Due to the specific properties of the system around the PIT very small particles are spontaneously formed just below that temperature [24]. If rapid cooling is applied at this point stable particles with desirable size and polydispersity can be obtained .In the last decade different groups report the feasibility of the method in the production of lipid nanocapsules, SLN and NLC. Several modifications to improve the final product are also developed e.g., cycling around the PIT to achieve better distribution of SAC at the phase interface and therefore smaller size and lower polydispersity.

Approaches with organic solvents:

Emulsification-solvent evaporation: This technique is based on precipitation of the lipids from O/W emulsions. The lipid material and drug are dissolved in organic water-immiscible solvent (e.g., chloroform). The organic solution is emulsified in an aqueous phase with the help of suitable surfactants to form O/W emulsion [25]. Then the organic solvent from this emulsion is evaporated at low pressure. This causes the lipid and API(s) to precipitate in the form of SLN or NLC. The particles obtained by this method have optimal properties small size (25-100 nm) and narrow size distribution. Main disadvantages are the limitation of lipid concentration in the organic solvent to form desirable particles and the use of organic solvents. The method is appropriate especially in the encapsulation of thermo sensitive APIs because of the absence of any thermal stress. It is not able that identical formulations don`t achieve the same results when they are processed by other technique.

Emulsification solvent diffusion: This method is based on the emulsification of partially water miscible solvent solution of a solid lipid in an aqueous solution of suitable surfactant. The aqueous phase of the obtained emulsion is saturated with the organic solvent and the excess of the solvent is in the form of emulsion droplets [26]. A dilution with fresh water causes the organic solvent, driven by the concentration gradient, to diffuse from the droplets to the water. As a result the solubility of the lipids decreases until they precipitate. The SLN and NLC below 100 nm with narrow size distribution can be produced by this technique. The solubility of the water miscible solvent in water and the solubility of the lipid in the organic solvent are crucial to the final results. However, the type and the concentration of the lipid, surfactant and organic solvent would require substantial optimization work. Note worthy advantage is the low processing temperature.

Solvent injection: The method is similar to the emulsification solvent diffusion method but the organic solvents used are selected from the group of the very miscible with water solvents thus eliminating the chance for emulsion to be formed [27]. Firstly, the lipid(s) and API(s) are dissolved in the organic solvent. Then the organic solution is injected in aqueous solution of surfactant under stirring. This causes a rapid migration of the organic solvent in the water and precipitation of the lipids. The obtained particle size depends strongly on the velocity of extraction respectively on the lipophilicity of the solvent. The more hydrophilic the solvent the smaller the particles but the less its capacity to dissolve lipids. The method offers advantages such as low processing temperatures and low shear stress.

Supercritical fluid (SCF) technique: A SCF is defined as a substance above its critical temperature (TC) and critical pressure (PC). The critical point represents the highest temperature and pressure at which the substance can exist as a vapor and liquid in equilibrium [28]. The supercritical fluid has unique thermo physical properties which can be finely tuned by small changes in the pressure. As the pressure raises the density and the ability of the fluid to dissolve compounds increases while the viscosity remains relevantly constant. Accordingly under high pressure and appropriate temperature in the supercritical range the fluid can act as an alternative to organic solvents and dissolve different APIs and lipids. SCF like carbon dioxide are safe, cheap, non irritable, relatively inert and has a low critical point. However, the method often yields particles in the micrometer range and is often combined with other homogenization technique like ultrasound.

APPLICATIONS:

Solid lipid Nanoparticles possesses a better stability and ease of up gradability to production scale as compared to liposome's. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which

are biodegradable and capable of being stored for at least one year. They can deliver drugs to the liver *in vivo* and *in vitro* to cells which are actively phagocytic [29]. There are several potential applications of SLNs some of which are given below:

1. **SLNs as gene vector carrier**: 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 [30]. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. The lipid nuclic acid nanoparticles were prepared from a liquid nano phase 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 nuclicacid 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.
2. **SLNs for topical use**: SLNs and NLCs have been used for topical application for various drugs such as tropolide, imidazole antifungals, anticancers, vitamin A, isotretinoin, ketoconazole, flurbiprofen and glucocorticoids [31]. The penetration of podophyllotoxin SLN into stratum corneum along with skin surface lead to the epidermal targeting. By using glycerylbehenate, vitamin A-loaded nanoparticles can be prepared. The methods are useful for the improvement of penetration with sustained release. The isotretinoin loaded lipid nanoparticles was formulated for topical delivery of drug. The soyabean lecithin and Tween 80 are used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin. Production of the flurbiprofen loaded SLN gel for topical application after a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Polyacrylamide, glycerol and water were used further preparation of this type of SLN gel.
3. **SLNs as cosmeceuticals**: The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The *in vivo* study showed that skin hydration will be increased by 31% after 4 weeks by addition of 4% SLN to a conventional cream [32]. SLN and NLCs have proved to be controlled release innovative occlusive topicals. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations.
4. **SLNs for potential agriculture application**: Essential oil extracted from *Artemisia arboreseens* when in corporated 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 pesticides[33]. The SLN were prepared here by using compritol 888 ATO as lipid and poloxamer 188 or Miranol Ultra C32 as surfactant.
5. **SLNs as a targeted carrier for anticancer drug to solid tumors**: SLNs have been reported to be useful as drug carriers to treat neoplasm's. Tamoxifen, an anticancer drug incorporated in SLN to prolong release of drug after i.v. administration in breast cancer and to enhance the permeability and retention effect. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin.
6. **SLNs in breast cancer and lymph node metastases**: Mitoxantrone loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug[34]. Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox loaded solid lipid nanoparticles. The system is enhanced its efficacy and reduced breast cancer cells.
7. **Oral SLNs in antitubercular chemotherapy**: Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance[35]. By using the emulsion solvent diffusion technique this anti tubercular drug loaded solid lipid nanoparticles are prepared The nebulization in animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug.

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Conclusions: In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept, the idea that drugs reach the right site in the body, at the right time, at right concentration. It should not exert side effects, neither on its way to the therapeutic target, nor at the target site, nor during the clearance process. The SLNs have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is achieved with SLNs. They are relatively young drug delivery systems, having received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of SLNs in the future.

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