SOLID LIPID NANOPARTICLES - A REVIEW

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ABSTRACT

Solid lipid nanoparticles were developed in early 1990s as an alternative to other traditional colloidal carriers like liposomes, polymeric nanoparticles and emulsions as they have advantages like controlled drug release and targeted drug delivery with increased stability. This paper gives an overview about the potential advantages and also the disadvantages of solid lipid nanoparticles, the excipients and all the different methods involved in their production including the membrane contractor method. Aspects of SLN stability and the influence of various excipients (used in SLN production) on stability with other secondary steps involved in their stabilization like freeze drying, spray drying etc. Problems associated with SLN production and instrumental techniques used in production are thoroughly discussed. Special attention is given to models of drug incorporation in SLN and the release pattern of SLN. Analytical methods involved in SLN evaluations are discussed in detail and the major applications of SLNs mainly targeted drug delivery are discussed.

Keywords: Colloidal drug carriers, Solid lipid nanoparticles, Solid lipid, Surfactants, Drug incorporation.

INTRODUCTION

The field of Novel Drug Delivery System is emerging at an exponential rate with the deep understanding gained in diversified fields of Biotechnology, Biomedical Engineering and Nanotechnology[1]. Many of the recent formulation approaches utilize Nanotechnology that is the preparation of Nanosized structures containing the API[2]. Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach[3]. Some of the important Drug Delivery System developed using Nanotechnology principles are: Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals[4]. In this article the main focus is on Solid Lipid Nanoparticles (SLNs). SLNs introduced in 1991 represent an alternative and better carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles[5].

Fig. 1: Shows structure of Solid Lipid Nanoparticles

Fig. 2: Shows a diagrammatic representation on SLN over emulsions and liposome[5].
SLNs are a colloidal carrier system composed of a high melting point lipid as a solid core coated by aqueous surfactant and the drugs used are of BCS Class II and IV[2]. In SLNs as compared to other colloidal carriers liquid lipid is replaced by solid lipid. The use of solid lipid as a matrix material for drug delivery is well known from lipid pellets for oral drug delivery (eg. Mucosolvan® retard capsules)[6]. The term lipid in a broad sense includes triglycerides, partial glycerides, fatty acids, hard fats & waxes. A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decreases the danger of acute and chronic toxicity[7]. The use of solid lipid instead of liquid lipid is beneficial as it has been shown to increase control over the release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients. These potentially beneficial effects are because of a number of physicochemical characteristics associated with the physical state of the lipid phase. Firstly, the mobility of reactive agents in a solid matrix is lower than in a liquid matrix and so the rate of chemical degradation reactions may be retarded. Secondly, microphase separations of the active ingredients and carrier lipid within individual liquid particles can be controlled, thereby preventing the accumulation of active compounds at the surface of lipid particles where chemical degradation reactions often occur. Thirdly, the absorption of poorly absorbed bioactive compounds has shown to be increased after incorporation into solid lipid nanoparticles. As a result of various research works it has also been shown that the use of a solid matrix instead of a liquid matrix can slow down lipid digestion thereby allowing for a more sustained release of the encapsulated compound. Other major excipients of SLNs are surfactants of aqueous type. They mainly act as emulsifier to form o/w type emulsion and stabilizer for SLNs dispersion and their choice depends on mainly the route of administration. They are generally made up of a solid hydrophobic core containing the drug dissolved or dispersed[8]. SLNs are mainly prepared by high pressure homogenization or micro emulsification. SLNs prepared by any technique are in dispersion form which on long term storage results in instability mainly because of hydrolysis reactions so to increase their stability they can be converted into solid dry reconstitutable powders through lyophilisation and a cheap and easy variant to lyophilisation is spray drying technique[9].

**Aims of solid lipid nanoparticles[10]**

It has been claimed that SLN combine the advantages and avoid the disadvantages of other colloidal carriers. Proposed advantages include:

- Possibility of controlled drug release and drug targeting.
- Increased drug stability
- High drug payload
- Incorporation of lipophilic and hydrophilic drugs
- No biotoxicity of the carrier
- Avoidance of organic solvents
- No problems with respect to large scale production and sterilization
- Increased Bioavailability of entrapped bioactive compounds

**Disadvantages of sln**

- Particle growth.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions
- Sometimes burst release

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<th>Lipids</th>
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**Solid lipid nanoparticles production procedure**

The major problem for the SLNs to be introduced to the market is the use of excipients having no accepted status. For topical SLN, all excipients used in current topical cosmetic and dermal...
pharmaceutical products can be used. For oral administration of SLN, all excipients can be employed that are frequently used in traditional oral dosage forms such as tablets, pellets, and capsules. Even surfactants with cell membrane-damaging potential, e.g. SDS, can be used. SDS is contained in many oral products and accepted as an excipient by the regulatory authorities. In addition substances with accepted Generally Recognized As Safe (GRAS) status can be used. The situation is different for Parenteral administration as solid lipids have not yet been administered parenterally before—in contrast to liquid lipids (o/w emulsions for iv administration, prolonged release oil-based injectables for im administration). However, the glycerides used for SLN production are composed of compounds (glycerol, fatty acids) which are also present in emulsions for Parenteral nutrition[11].

The general excipients used in any SLN formulation are solid lipids, emulsifiers, co-emulsifiers and water. The term lipid is used here in a broader sense and includes triglycerides (e.g.tristearin), partial glycerides (e.g. Inmivitor), 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[10].

Influence of various excipients used on product quality

Influence of the lipid

In hot homogenization it can be seen that average particle size of SLN dispersion is increasing with higher melting lipids and this is because of higher viscosity of dispersed phase. Some peculiar parameters are specific for every lipid like lipid crystallization, lipid hydrophilicity and shape of lipid crystals. Chemically most lipids are mixtures of various compounds so their composition can vary from different suppliers and also from batch to batch but these small differences affect the quality of SLNs to a great extent (e.g. by changing the zeta potential, retarding crystallization processes etc.). Increasing the lipid content over 5%-10% result in larger particles and broader particle size distribution in most cases[10,11].

Influence of emulsifier

Choice of emulsifier has a great impact on quality of SLN. Reduction in surface tension and particle partitioning during homogenization is facilitated by increasing the emulsifier concentration. Reduction in particle size leads to increased surface area.

During SLN preparation the primary dispersion must contain excessive emulsifier to rapidly cover the new surfaces formed during High Pressure Homogenization; otherwise it will lead to agglomeration of uncovered new lipid surfaces. The time taken for redistribution of emulsifier between new particle surfaces and micelles is different for different types of surfactants. It has been studied that Low Molecular Weight surfactants will take less time for redistribution and High Molecular Weight will take longer time for redistribution. The addition of some co-emulsifying agent like Sodium Glycocholate further decreases the particle size[10].

Methods of preparation of solid lipid nanoparticles[5,10]

1. High pressure homogenization
2. Cold homogenization
3. Ultrasonication / high speed homogenization
4. Probe ultrasonication
5. Bath ultrasonication
6. Solvent evaporation Method
7. Solvent emulsification-diffusion method
8. Super critical fluid method
9. Microemulsion based method
10. Precipitation technique
11. Film- ultrasound dispersion
12. Solvent Injection Technique
13. Using Membrane Contractor

1. High pressure homogenization (HPH)

It is a reliable and powerful technique, which is used for the first time for production of SLNs. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.

HPH is of two types—hot homogenization and cold homogenization. In both cases, a preparatory step involves the drug incorporation into the bulk lipid by dissolving or dispersing the drug in the lipid melt.

Hot Homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the 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 (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also accelerate the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. It should always be kept in mind, that high pressure homogenization increases the temperature of the sample (approximately 10°C for 500 bar). In most cases, 3–5 homogenization cycles at 500–1500 bar are sufficient. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result high kinetic energy of the particles. The primary product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months[3,5,6,10].

Cold Homogenization

In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the unmolten state of the lipid due to increase in temperature during homogenization. Cold homogenization has been developed to overcome the following three problems of the hot homogenization technique.

1. Temperature-induced drug degradation able equipment
2. Drug distribution into the aqueous phase during homogenization
3. Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts pressure.

The first step is same as in hot homogenization which includes the solubilization or dispersing of the drug in the melt of the bulk lipid. The drug containing melt is rapidly cooled which favours the homogeneous distribution of drug in the solid matrix. Low temperatures increase the fragility of the lipid and, therefore, particle comminution. The solid lipid micro particles are dispersed in a chilled emulsifier solution. The pre-suspension is subjected to high pressure homogenization at or below room temperature. In general, compared to hot homogenization, larger particle sizes and a broader
size distribution are observed in cold homogenized samples[3,5,6,10].

**Ultra sonication and high speed homogenisation**

SLNs are also prepared by ultrasonication or high speed homogenization techniques. For smaller particle size combination of both ultrasonication and high speed homogenization is required. It reduces shear stress but has some disadvantages like potential metal contamination, physical instability like particle growth upon storage. In this probe sonicator or bath sonicator is used[5,14].

**Solvent evaporation method**

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. 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)[5].

**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 important advantage of this technique. In this technique lipid is, are generally dissolved in the organic phase in water bath at 45°C and used an acidic aqueous phase in order to adjust the zeta potential to form coacervation of SLN, and then easy separation by centrifugation. The SLN suspension was quickly produced. The entire dispersed system can then be centrifuged and re-suspended in distilled water[5,15,16,17].

**Supercritical fluid method**

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. There are several variations in this platform technology for powder and nanoparticle preparation. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method[5].

**Microemulsion based method**

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions. By stirring at 65-70°C an optically transparent mixture is obtained which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers(sodium monooctylophosphate) 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. The dilution process is critically determined by the composition of the microemulsion. According to the literature, the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. Fessi produced polymer particles by dilution of polymer solutions in water. According to De Labouret et al., the particle size is critically determined by the velocity of the distribution processes. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic co-solvents of the microemulsion play a similar role in formation of lipid nanoparticles as acetone for formation of polymer nanoparticles[5,18,19].

**Double emulsion based method**

Warm w/o/w double microemulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In the second step, formed w/o microemulsion is added to a mixture of water, surfactant and co-surfactant to obtain a clear w/o/w system. SLNs can be obtained by dispersing the warm micro double emulsions in cold then washed with dispersion medium by ultra filtration system. Multiple emulsions have inherent instabilities due to coalescence of the internal aqueous droplets within the oil phase, coalescence of the oil droplets, and rupture of the layer on the surface of the internal droplets. In case of SLNs production, they have to be stable for few minutes, the time between the preparations of the clear double microemulsions and its quenching in cold aqueous medium, which is possible to achieve[5,20].

**Precipitation technique**

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles[5].

**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 disperse at last, the SLN with the little and uniform particle size is formed[5].

**Solvent injection technique**

It is a novel approach to prepare SLN, which has following advantages over other production methods like use of pharmaceutically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. 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, acetone, isopropanol) or a water miscible solvent mixture. Then this lipid solvent mixture was injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant dispersion was then filtered with a filter paper in order to remove any excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent[5,21,22,23].

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**Fig. 3:** Shows a Schematic diagram of Membrane Contractor for preparation of SLN[24]
Table 2: Shows comparison of different formulation methods[5].

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<tr>
<th>Formulation procedures</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<td>High pressure homogenisation</td>
<td>Low capital cost, Demonstrated at lab scale</td>
<td>Energy intensive process. Biomolecule damage</td>
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<td>Ultrasonic/ High speed homogenisation</td>
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<td>Solvent Evaporation Method</td>
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<td>Solvent Emulification Diffusion Method</td>
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<td>Super critical fluid method</td>
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<td>Micro emulsion based method</td>
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<tr>
<td>Membrane contractor method</td>
<td>Allow large scale production</td>
<td>Labor intensive formulation work</td>
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<td>Stability demonstrated</td>
<td>Low nanoparticle conc.</td>
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Whenever possible, a direct comparison between the different formulation procedures should be made by the same investigator, using the same ingredients, same storage conditions and the same equipment for particle sizing.

Membrane contractor method

The present study investigates a new process for the preparation of SLN using a membrane contactor, to allow large scale production. A schematic drawing of the process is shown in Fig. 3. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets. The aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLN are formed by the following cooling of the preparation to room temperature. The influence of process parameters (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) on the SLN size and on the lipid phase flux is investigated. Also, vitamin E loaded SLN are prepared, and their stability is demonstrated[24].

Secondary production steps

Sterilisation

Sterilization of the nanoparticles is desirable for parenteral administration and autoclaving which is applicable to formulations containing heat-resistant drugs. Effects of sterilization on particle size have been investigated and it was found to cause a distinct increase in particle size. Schwarz investigated the impact of different sterilization techniques (steam sterilization at 121°C (15 min) and 110°C (15min), g-sterilization) on SLN characteristics. The results indicate that particle aggregation might occur as a result of the treatment. Critical parameters include sterilization temperature and SLN composition. The correct choice of the emulsifier is of significant importance for the physical stability of the sample at high temperatures. Increased temperatures will affect the mobility and the hydrophilicity of all emulsifiers to a different extent. Steam sterilization will cause the formation of an o/w-emulsion due to the melting of the lipid particles. Solid particles are formed after recrystallization. Schwarz found that lecithin is a suitable surfactant for steam sterilization, because only a minor increase in particle size was observed. Experiments conducted by Freitas indicated that lowering of the lipid content (to 2%) and surface modification of the glass vials prevent the particle increase to a large extent and avoid gelation. Additionally, it was observed by Freitas that purging with nitrogen showed a protective effect during sterilization. That observation suggests that chemical reactions could contribute to particle de-stabilization. γ-irradiation could be an alternative method to steam sterilization for temperature sensitive samples[9,10].

Lyophilisation

Lyophilization is a promising way to increase the chemical and physical stability over extended periods of time. Lyophilization had been required to achieve long term stability for a product containing hydrolysable drugs or a suitable product for per-oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. In case of freeze drying of the product, all the lipid matrices used, form larger solid lipid nanoparticles with a wider size distribution due to presence of aggregates between the nanoparticles. The conditions of the freeze drying process and the removal of water promote the aggregation among SLNs. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process[9,10,25,26,27].

Spray drying

It is an alternative and cheaper technique to the lyophilization process. This recommends the use of lipid with melting point more than 70°C. The best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture. The addition of carbohydrates and low lipid content favor the preservation of the colloidal particle size in spray drying. The melting of the lipid can be minimized by using ethanol–water mixtures instead of pure water due to cooling leads to small and heterogeneous crystals, the lower inlet temperatures[5,10,28].

Problems associated with sln preparation

SLN offer several advantages compared to other systems (easy scaling up, avoidance of organic solvents, high content of nanoparticles) but some problems are also associated with its preparation process which are discussed below-

High pressure induced drug degradation

HPH has been shown to decrease the molecular weight of polymers. High shear stress has been assumed to be the major cause and evidence of free radical formation was reported. High molecular weight compounds and long chain molecules are more sensitive than low molecular weight compounds. For example, it was found that HPH causes degradation of DNA and albumin. According to the data in the literature, it can be stated that HPH-induced drug degradation will not be a serious problem for the majority of the drugs. However, HPH might be not suitable for the shear sensitive compounds (DNA, albumin, erythropoietin).
Lipid crystallisation and drug incorporation

Mainly X-ray and DSC studies are done to investigate lipid modifications. The following four key aspects should be considered in the discussion of drug incorporation into SLN:

1. The existence of supercooled melts.
2. The presence of several lipid modifications.
3. The shape of lipid nanoemulsions.
4. Gelation phenomenon

Supercooled Melts

The supercooled melts are formed in sln preparation when the lipid crystallization do not occur although the sample is stored at a temperature below the melting point of the lipid. Special attention should be paid to supercooled melts, because the potential advantages of SLN over nanoemulsions are linked to the solid state of the lipid. The main reason for their formation is the size dependence of crystallization process. In addition to size, crystallization can be affected by emulsifiers, incorporated drugs and other factors. NMR studies should be done to check the presence of supercooled melts.

Lipid Modifications

It is not sufficient to describe the physical state of the lipid as crystallized or non-crystallized, because the crystallized lipid may be present in several modifications of the crystal lattice. In general, lipid molecules have a higher mobility in thermodynamically unstable configurations. Therefore, these configurations have a lower density and ultimately, a higher capability to incorporate guest molecules (e.g. drugs). The advantage of higher incorporation rates in unstable modifications is paid off by an increased mobility of the drug. During storage, rearrangement of the crystal lattice might occur in favor of thermo-dynamically stable configurations and this is often connected with expulsion of the drug molecules. The performance of the SLN system will be determined to a large extent by the lipid modification, because this parameter triggers drug incorporation and drug release. Therefore, the utilization of the higher drug-loading capacity in unstable configurations requires the development of strategies to prevent modification during storage.

Further opportunities of modified drug release profiles will be open, if this problem will be solved. For example, Jennings has shown in vitro on skin that the evaporation of water leads to modification changes of SLN dispersions which cause drug expulsion from the lipid and result in increased penetration of the drug into the skin. DSC studies should be done to investigate lipid modifications.

Particle Shape

The shape of lipid crystal plays an important role in controlled release of drug from SLN. Lipids prefer to crystallize in platelet form and not spherical. Platelet shapes have much larger surface areas compared to spheres; therefore, higher amounts of surfactants are needed for stabilization. Particle sizes of 100 nm (measured by PCS or LD) translate into 20 lipid layers assuming a spherical shape. However, they translate into smaller values if a platelet structure exists. Therefore, a much higher amount of the drug will be localized directly on the surface of the particles, which is in conflict with the general aim of the SLN systems (drug protection and controlled release) due to the incorporation of the drug in the solid lipid. Cryo Transmission Electron Microscopy should be done to investigate particle shape.

Gelation phenomenon

When low viscosity SLN dispersion gets transformed into a viscous gel it is called Gelation phenomenon. It occurs very rapidly and it is very unpredictable. Gel formation leads to loss of colloidal particle size and are irreversible in most cases. Several mechanisms might be involved in the gelation process. All promoters of gelation (high temperature, light, shear stress) increase the kinetic energy of the particles and favor collision of the particles. The surfactant film might change his performance with temperature (especially PEG-surfactants!). Further aspects relate to the kinetics of crystallization and transformation between the lipids modifications which will be influenced by the factors mentioned above. Rapid crystallization of the lipid increases the gelation process. The presence of liquid phases promotes the crystallization in the stable form because unstable crystals may redissolve and crystallize in the stable modification. In this way, it is possible to accelerate the α→β transformation during storage at RT without melting of the Compritol. In most cases, triglycerides will crystallize in the α modification. The α→β transformation can be retarded by surfactants, e.g. poloxamer.

Coexistence of several colloidal species

The presence of several colloidal species is an important point to consider. Stabilizing agents are not localized exclusively on the lipid surface, but also in the aqueous phase. Therefore, micelle forming surfactant molecules (e.g. SDS) will be present in three different forms, namely: (i) on the lipid surface; (ii) as micelle; and (iii) as surfactant monomer. Only the detection of the presence of several colloidal species is not sufficient to describe the structure of colloidal lipid dispersions, because dynamic phenomena are very important for drug stability and drug release. Therefore, the kinetics of distribution processes has to be considered. Unstable drugs will hydrolyze rapidly in contact with water and, therefore, the distribution equilibrium of the drug between the different environments will be distorted. Carrier systems will be protective only if they prevent the redistribution of the drug. Increasing the matrix viscosity will decrease the diffusion coefficient of the drug inside the carrier and, therefore, SLN are expected to be superior to lipid nanoemulsions. However, drug stabilization is a very challenging task for colloidal drug carriers, because of the very high surface area and the short diffusion pathwys.[10]

Instrumental techniques for sln production

The IKA Ultra-Turrax T 18 rotorstator homogenizer

The lipid (lauric acid, stearic acid, trilaurin, or tristearin) was maintained at ~ 75 °C and allowed to melt completely. Separately, double distilled water was heated to 75 °C. Typically, surfactants were added to the water under magnetic stirring and allowed to equilibrate at 75 °C. Next, the water – surfactant solution was added to the melted lipid and once again allowed to equilibrate at 75 °C. If desired to create the emulsion (i.e., no spontaneous emulsification as in the case of micro emulsions), external mechanical energy then was added in the form of an IKA Ultra-Turrax T 18 rotor-stator homogenizer. The Ultra-Turrax T 18 homogenizer, equipped with the 19 mm dispersing tool, has a speed range of 6,000 – 30,000 rpm and an operational volume range of 10 – 2000 ml. The homogenizer motor produces 160 W of power. The homogenizer only was operated in a batch set-up.

The discontinuous Micron LAB 4018

Laboratory scale production of SLN and Disso Cubes is performed using a piston-gap homogenizer (Micron LAB 40, APV Homogenizer GmbH, Lubeck, Germany). Minimum batch size is 20 ml, maximum size is 40 ml. Pressure applied ranges from 100 bars to a maximum of 1500 bar. The aqueous dispersion is pressed by a piston through a small homogenization gap that is approximately 25 urns (at a pressure of 500 bars). The process is discontinuous, i.e., the system needs to be dismantled and the dispersion poured back into the central cylinder for the next homogenization cycle. It is more time consuming but the machine has the big advantage of an extremely low sample volume. This is of high interest for compounds that are expensive or of limited availability, but is very time consuming when performing a screening for optimized production parameters and optimized composition of the nanosuspension formulation. For example, screening of four production pressures (e.g., 100, 500, 1000, and 1500 bar) up to two homogenization cycles requires 40 homogenization steps. It gets even more complicated when different surfactants and surfactant mixtures at different concentrations in a nanosuspension need to be checked regarding optimized physical stability of the produced nanosuspension. For screening purposes, a continuous Micron LAB 40 is much more suitable.
The continuous LAB 4020

The continuous LAB 40 has a feeding vessel and a product vessel of a typical size of 0.5 L. It is only necessary to switch two tubes before running the next homogenization cycle. Product samples for size analysis can be drawn directly from the vessels between the homogenization cycles. This speeds up the screening procedure enormously but requires a sample volume of at least 200 mL. This minimum volume of suspension cannot be accepted in the case of very expensive drugs, e.g., paclitaxel (normal price for 1 g is approximately 10,000,- $ US). On the other hand the continuous LAB 40 provides the possibility of producing lab scale batches of up to 0.5—1 L (to fit larger vessels to the systems).

The Micron LAB 6022

The Micron LAB 60 is a homogenizer for continuous production with a production capacity of 60 L/h. It consists of two pumps yielding a product flow with minimized fluctuations in homogenization pressure. The dispersion is subsequently passed through two homogenization valves: a first main homogenization valve, and a secondary valve that creates a certain reverse pressure and is also in charge of dispersing coalesced droplets or aggregates in the case of solid suspensions. As a general rule, the homogenization pressure of the secondary valve should be about one-tenth of the pressure used in the first valve. The Micron LAB 60 was modified according to the needs of a Good Manufacturing Practices (GMP) production. The production unit with the LAB 60 requires a batch size of approximately 2 L (approximately 2 kg). It is not possible to run such a low volume in the discontinuous production mode because of the relatively large dead volume of the machine (0.5 L). About 25% of the suspension would remain in the machine without being homogenized prior to the next homogenization cycle. From this it is more sensible to run the unit in a continuous circulating mode, with the product feed back after having passed the homogenization tower directly to the feeding vessel.

Electro Hydrodynamic Aerosolisation [EHDA] as a novel approach for preparation of SLN

The limited commercial development of solid lipid nanoparticle technology indicates that more development is required to realize the technology’s theoretical potential. Solid lipid nanoparticle research has been plagued by an inability to produce particles of desired sizes, a lack of particle stability over time, polydisperse distributions, limited drug loading, burst release kinetics, and the lack of an economically viable production process. This research aimed to address these shortcomings by simultaneously investigating the chemical formulation and a novel production process based on electro hydrodynamic aerosolization (EHDA). EHDA utilizes electric charge to aerosolize liquids by overcoming the liquid’s surface tension. The liquid to be aerosolized is delivered to a nozzle, often a stainless steel capillary, maintained at high electrical potential. As the fluid passes through the nozzle, the electric field induces free charge at the liquids Surface. The free charge on the surface generates electric stress that causes the liquid to accelerate away from the nozzle, thereby producing a so-called Taylor cone and electric current at the liquid’s surface. At the cone apex where the free charge is highly concentrated, a liquid jet with high charge density is formed. At appropriate conditions, the jet will disintegrate into highly charged aerosol droplets. Three steps define EHDA: 1) acceleration of the liquid in the liquid cone and subsequent jet formation; 2) the jet disintegration into aerosol droplets; 3) droplet evolution after formation[29].

<table>
<thead>
<tr>
<th>Pharmacological category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer Drugs</td>
<td>Camptothecin, Etopside, Paclitaxel, Docetaxel, Vinorelbine, Doxorubicin, Idrabucin, Adriamycin, Mitoxantrone, Methotrexate, 5-Fluorouracil, Oxaliplatin, Tamoxifen, Ubidecarenone, Cholesteryl Butyrate, Chlorambucil, Temozolomide, β-elements, Podophyllotoxin, All trans retinoic acid.</td>
</tr>
<tr>
<td>Cardiovascular Drugs</td>
<td>Verapamil, Nifedipine, Nitrendipine, Hydrocortisone, Cortisone, Prednisolone, Deoxytocorticosterone, Progestosterone, Estradiol, Mifepristone, Betamethasone, Sildenafil Citrate, Insulin.</td>
</tr>
<tr>
<td>Antifungal Drugs</td>
<td>Ketoconazole, Miconazole, Itraconazole, Econazol, Terbinafine, Amphotericin.</td>
</tr>
<tr>
<td>Antibacterial Drugs</td>
<td>Ciprofloxacin, Tobramycin, Clotrimazole</td>
</tr>
<tr>
<td>Antitubercular Drugs</td>
<td>Rifampicin, Isoniazid, Pyrazinamide.</td>
</tr>
<tr>
<td>Antiviral Drugs</td>
<td>Aciclovir, Saquinavir, Penciclovir, Adefovir, Dipivoxil, Thymopentin, 3-Azida-3-deoxyuridine, Oxytetracycline, Quinine, Chloroquine.</td>
</tr>
<tr>
<td>Drugs acting on Nervous System</td>
<td>Diazepam, Oxazepam, Carbamazepine, Clobazam, Valproic Acid, Lamotrigine, Gabapentin.</td>
</tr>
<tr>
<td>Anxiety and Epilepsy</td>
<td>Clozapin, Olanzapin, Piribedil.</td>
</tr>
<tr>
<td>Antipsychotic Drugs</td>
<td>Cyclesporin, Tacrolimus.</td>
</tr>
<tr>
<td>Parkinson’s disease Drugs</td>
<td>Timolol, Pilocarpine, Tetracaine.</td>
</tr>
<tr>
<td>Immuno suppressant Drugs</td>
<td>Lovastatin, Simvastatin, Fluvastatin, Pravastatin, Rosuvastatin.</td>
</tr>
<tr>
<td>Miscellaneous Drugs</td>
<td>Etomide, Avertin.</td>
</tr>
<tr>
<td>Glaucoma Drugs</td>
<td>Actarit, Reserpine, Domperidone.</td>
</tr>
<tr>
<td>Hypolipidaemic Drugs</td>
<td>Praziquantel, Sodium Cromoglycate, Clobetasol Propionate, Repaglinide.</td>
</tr>
<tr>
<td>Anaesthetic drugs</td>
<td>Diminazene, Gamma Oryzanol, Calixarene, Reseratrol, Taspine, Apolipoprotein P, Tashione.</td>
</tr>
</tbody>
</table>
Models for incorporation of active compounds into slns-

There are basically three different models for the incorporation of active ingredients into SLN. (I) Homogeneous matrix model (II) Drug-enriched shell model (III) Drug-enriched core model. The structure obtained is a function of the formulation composition (lipid, active compound, surfactant) and of the production conditions (hot vs. cold homogenisation). A homogeneous matrix with molecularly dispersed drug or drug being present in amorphous clusters is thought to be mainly obtained when applying the cold homogenisation method and when incorporating very lipophilic drugs in SLN with the hot homogenisation method. In the cold homogenisation method, the bulk lipid contains the dissolved drug in molecularly dispersed form, mechanical breaking by high pressure homogenisation leads to nanoparticles having the homogeneous matrix structure. The same will happen when the oil droplet produced by the hot homogenisation method is being cooled, crystallise and no phase separation between lipid and drug occurs during this cooling process. This model is assumed to be valid for incorporation of, e.g. the drug Prednisolone, which can show release from 1 day up to weeks.

An outer shell enriched with active compound can be obtained when phase separation occurs during the cooling process from the liquid on droplet to the formation of a solid lipid nanoparticle. According to the TX diagram, the lipid can precipitate first forming a practically compound-free lipid core. At the same time, the concentration of active compound in the remaining liquid lipid increases continuously during the forming process of the lipid core. Finally, the compound-enriched shell crystallises comparable to the eutecticum in the TX diagram. This model is assumed, for example, for coenzyme Q10 the enrichment leads to a very fast release. A fast release can be highly desired when application of SLN to the skin should increase the drug penetration, especially when using the occlusive effect of SLN at the same time. A core enriched with active compound can be formed when the opposite occurs, which means the active compound starts precipitating first and the shell will have distinctly less drug. This leads to a membrane controlled release governed by the Fick law of diffusion. The structure of SLN formed clearly depends on the chemical nature of active compound and excipients and the interaction thereof. In addition, the structure can be influenced or determined by the production conditions.[11,34]

Release of active compound from sln

The effect of formulation parameters and production conditions on the release profile from SLN was intensively investigated by Mehnert, Müller and zur Mühlen. For example, they investigated the release profile as a function of production temperature. It can be summarised that the release profiles were often biphasic—an initial burst release was followed by a prolonged release. The burst release often occurs when hot homogenisation is used and very high temperatures are applied. It is almost non existent when cold homogenisation is used. The extent of burst release also depends on the amount of surfactant used. High surfactant concentration leads to high burst release and vice versa. This was explained by redistribution effects of the active compound between the lipid and the water phase during the heating up process and subsequently the cooling down process after production of the hot oil in water emulsion during the hot homogenization process. Heating the lipid /water mixture leads to an increased solubility of the active compound in the water phase, the compound partitions from the melted lipid droplet to the water phase. After homogenization, the oil in water emulsion is cooled, the lipid core starts crystallizing with still a relatively high amount of active compound in the water phase.

Further cooling leads to super saturation of the compound in the water phase, the compounds tries to partition back into the lipid phase; a solid core has already started forming leaving only the liquid outer shell for compound accumulation. From this discussion it is clear that higher the solubility in water phase higher the burst effect. The solubility increases when increased temperature and increased surfactant concentrations are used. Consequently, when low production temperatures and low surfactant concentrations are used little or no burst effect occurs.[11,34]

Storage stability of sln

The physical properties of SLN’s during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be of primary importance for long term stability. The zeta potential should be in general, remain higher than -60mV for a dispersion to remain physically stable.

4°C - Most favorable storage temperature.
20°C - Long term storage did not result in drug loaded SLN aggregation or loss of drug.
50°C - A rapid growth of particle size was observed.

Characterization of slns-

Analytical characterization of SLN

An adequate characterization of the SLNs is necessary for the control of the quality of the product. Several parameters have to be considered which have direct impact on the stability and release kinetics:

- Particle size and zeta potential.
- Degree of crystallinity and lipid modification.
- Co - existence of additional structures and dynamic phenomena.

Measurement of particle size and zeta potential-

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion.[35,36]

Dynamic light scattering (DLS)

DLS also known as PCS records the variation in the intensity of the scattered light on the microsecond timescale.

Static light scattering (SLS)/Fraunhofer diffraction

SLS is an ensemble method in which the light scattered from a solution of particles is collected and fit into fundamental primary variable.

Acoustic methods

It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations.

Nuclear magnetic resonance (NMR)

NMR can be used to determine both the size and qualitative nature of nanoparticles.

Electron microscopy

Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) are the direct method to measure nanoparticles, physical characterization of nanoparticles with the former method being used for morphological examination. TEM has a smaller size limit of detection.
Measurement of crystallinity and lipid modifications

**Powder X-ray diffraction and differential scanning calorimetry (DSC)**

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature. Thermodynamic stability, lipid packing density and quantification are a serious challenge due to the increase, while drug incorporation rates decrease in the following order:

- Super cooled melt < α-modification < β9-modification < β-modification.

Due to the small size of the particles and the presence of emulsifiers, lipid crystallization modification changes might be highly retarded. Differential scanning calorimetry (DSC) and X-ray scattering are widely used to investigate the status of the lipid. Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids. Their potential to characterize SLN dispersions has yet to be explored[37].

**Co-existence of additional structures**

The magnetic resonance techniques, nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are powerful tools to investigate dynamic phenomena and the nano-compartments in the colloidal lipid dispersions. Dilution of the original SLN dispersion with water might cause the removal of the surfactant molecules from the particle surface and induce further changes such as crystallization changes of the lipid modification[5].

**Parameter Method of analysis**

- Molecular weight Gel chromatography
- X-ray photoelectron spectroscopy
- Laser Doppler anemometry

**Determination of incorporated drug (Loading Efficiency and Entrapment Efficiency)**

It is of prime importance to measure the amount of drug incorporated in SLNs, since it influences the release characteristics. The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium. This separation can be carried out using centrifugation, filtration or gel permeation chromatography. Centrifugation filtration the filters such as U'ltrafree→MC (Milipore) or Utrasart→ 10 (Sartorius) are used along with classical centrifugation techniques. The degree of encapsulation can be assessed indirectly by determining in the supernatant after centrifugation filtration / ultracentrifugation of SLN suspension or alternatively by dissolution of the sediment in an appropriate solvent and subsequent analysis.

**Limitation of analytical techniques**

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-appropriated for very polydisperse populations</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Great influence of aggregates or larger particles</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>High amount of sample required</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Time consuming</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Influence of the preparation sample</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Non-automated</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Complexity of the set up</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Image treatment</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Subjective</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Complex Data Processing</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Difficult to handle</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Optimization needed for each kind of particles</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Long steps of optimization</td>
<td>Light Interaction</td>
</tr>
<tr>
<td>Time consuming</td>
<td>Light Interaction</td>
</tr>
</tbody>
</table>

**Table 3: Shows main characteristics of particle size measurement methods[35].**

<table>
<thead>
<tr>
<th>Method</th>
<th>Principle</th>
<th>Measured size</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS</td>
<td>Light Interaction</td>
<td>50nm-1µm</td>
<td>Non-appropriated for very polydisperse populations</td>
</tr>
<tr>
<td>LLD</td>
<td>Light Interaction</td>
<td>1-1000µm</td>
<td>High amount of sample required</td>
</tr>
<tr>
<td>SEM, TEM</td>
<td>Microscopy</td>
<td>50nm-100µm</td>
<td>Indirect method</td>
</tr>
<tr>
<td>AFM</td>
<td>Microscopy</td>
<td>10nm-1µm</td>
<td>Time consuming</td>
</tr>
<tr>
<td>ANUC</td>
<td>Centrifugation</td>
<td>20nm-1µm</td>
<td>Complex Data Processing</td>
</tr>
<tr>
<td>FFF</td>
<td>Elution</td>
<td>20nm-1µm</td>
<td>Difficult to handle</td>
</tr>
<tr>
<td>CE</td>
<td>Electrophoresis</td>
<td>20-500nm</td>
<td>Optimization needed for each kind of particles</td>
</tr>
<tr>
<td>PCH, SEC</td>
<td>Chromatography</td>
<td>&lt;100nm</td>
<td>Complexity of the set up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time consuming</td>
</tr>
</tbody>
</table>

LS, light light diffraction; LLD, laser light diffraction; SEM, scanning electron microscopy; TEM, transmission electron microscopy; AFM, atomic force microscopy; ANUC, analytical ultracentrifugation; FFF, field flow fractionation; CE, capillary electrophoresis; PCH, packed column hydrodynamic; SEC, size exclusion chromatography.
• Agitation followed by ultracentrifugation or centrifugal ultrafiltration[25].

**In vitro drug release**

**Dialysis tubing**

*In vitro* drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre-washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

**Reverse dialysis**

In this technique a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.

**Ex vivo model for determining permeability across the gut**

Ahlin et al. demonstrated the passage of enalaprilat SLN's across rat jejunum. In short the rat jejunum (20–30 cm distal from the pyloric sphincter) was excised from the rats after sacrificing the animal used for the study. Qing Zhi Lu et al. excised 10 cm long segments of duodenum (1 cm distal to pyloric sphincter), jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum) and colon (2 cm distal to cecum) were immediately cannulated and ligated on both sides used for their permeability studies[40].

**Applications of SLN**

**Per oral administration**

Per oral administration forms of SLN may include aqueous dispersions or SLN loaded traditional dos-age forms, e.g., tablets, pellets or capsules. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It can be expected, that food will have a large impact on SLN performance. The plasma levels and body distribution were determined after administration of CA–SLN suspension versus a CA solution (CA-SOL). Two plasma peaks were observed after administration of CA–SLN. The first peak was attributed to the presence of free drug, the second peak can be attributed to controlled release or potentially gut uptake of SLN. These two peaks were also found in the total CA concentration-time profiles of all measured organs. It was also found that the incorporation into SLN protected CA from hydrolysis. The conclusion from this study was that SLN are a promising sustained release system for CA and other lipophilic drugs after oral administration. Increased bioavailability and prolonged plasma levels have been described after per oral administration of cyclosporine containing lipid nanodispersions to animals[5].

**Parenteral administration**

SLN have been administered intravenously to animals. Pharmacokinetic studies of donrubricin incorporated into SLN showed higher blood levels in comparison to a commercial drug solution after i.v. injection in rats. Concerning the body distribution, SLN were found to cause higher drug concentrations in lung, spleen and brain, while the solution led to a distribution more into liver and kidneys. Parenteral administration is a very wide field for SLN. Subcutaneous injection of drug loaded SLN can be employed for commercial aspect, e.g., erythropoietin (EPO), interferon-β. Other routes are intraperitoneal and also intra-articular. Intraperitoneal application of drug-loaded SLN will prolong the release because of the application area. In addition, incorporation of the drug into SLN might reduce irritation compared to injecting drug micro particles[5].

**Transdermal application**

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal ad-ministration. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content. An increase of the solid lipid content of the SLN dispersion results in semisolid, gel-like systems, which might be acceptable for direct application on the skin[41].

**Topical application**

Regarding the regularity aspect, topical application is relatively unproblematic. The major advantages for topical products are the protective properties of SLN for chemically labile drugs against degradation and the occlusion effect due to film formation on the skin. Especially in the area of cosmetics there are many compounds such as retinol or vitamin C which cannot be incorporated because of the lack of chemical stability. Incorporation of retinol is only possible when applying certain protective measures during production (e.g. noble gasing) and using special packing materials (e.g. aluminium)[42].

**Ophthalmic administration**

Many investigations have been made to use nanoparticles for prolonged release of drugs to the eye. The basic problem of ophthalmologic formulation is the fast removal from the eye, which implies clearance of the applied drug through the nose. It could be shown for nanoparticles that an increased adhesiveness is available leading to higher drug levels at desired site of action. However, the basic problem was that the nanoparticles are of limited toxicological acceptance. It was shown by Gasco that SLN have a prolonged retention time at the eye. This was confirmed by using radiolabeled formulations and γ-scintigraphy. The lipids of SLN are easy to metabolize and open a new ways for ophthalmological drug delivery without impairing vision[43].

**Pulmonary administration**

A very interesting application appears to be the pulmonary administration of SLN. SLN powders cannot be administered to the lung because the particle size is too small and they will be exhaled. A very simple approach is the aerosolization of aqueous SLN dispersions. The important point is that the SLN should not aggregate during the aerosolization. The aerosol droplets were collected by collision of aerosol with a glass wall of a beaker. This basically demonstrates that SLN are suitable for lung delivery. After localization into the bronchial tube and in the alveoli, the drug can be released in a controlled way from the lipid particles[5].

**REFERENCES**