International Journal of Pharmacy and Industrial Research (IJPIR)

ISSN:2231-6567

IJPIR |Volume 12 | Issue 4 | Oct - Dec - 2022
Available online at: www.ijpir.com

Review article ***SLNs***

Solid lipid nanoparticles (SLNs). A Comprehensive review

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ABSTRACT

Solid lipid nanoparticles (SLNs) have become a highly effective nanocolloidal drug delivery method. This review provides up-to-date information on a number of SLN-related topics, including their morphology, structural characteristics, preparation techniques, and characterizations. The potential for surface modification, improved penetration across different biological barriers, resistance to chemical degradation, and the capacity to encapsulate two or more therapeutic compounds at once have all drawn interest to SLNs. This study highlights current research developments related to this carrier system at the same time. Solid lipid nanoparticles (SLNs), a novel technique of medication delivery, are better soluble and bioavailable. Solid lipid nanoparticles, or SLNs, are at the forefront of the quickly expanding field of nanotechnology and have a number of potential uses in research and medicine delivery. Solid lipid nanoparticles (SLN) consist of a monolayer phospholipid shell surrounding a solid lipid core. Lipid nanoparticles present a chance to create novel treatments because of their special size-dependent characteristics. Drug targeting may be made possible by the novel drug delivery concept made possible by the capacity to put medications into nanocarriers. The development of lipid nanoparticles, their preparation process, subsequent production processes, characterisation, applications, and future were the main topics of this review. This review discusses the benefits and drawbacks of solid lipid nanoparticles in a comprehensive manner.

***Keywords*:** Solid-lipid nanoparticle, Nano formulations, Nano vehicles

INTRODUCTION

Solid Lipid Nanoparticles (SLNs) provide a flexible platform for drug delivery systems, marking a significant advancement in the field of nanomedicine. With SLNs, active medicinal components are delivered with enhanced stability, controlled release, and targeted distribution, bridging the gap between polymeric nanoparticles and conventional colloidal carriers. Their special makeup, which usually consists of lipids that degrade biodegradably, guarantees compatibility and lower toxicity. SLNs have gained popularity due to their ability to improve the bioavailability of medications, especially those with low solubility.[1]

Solid lipid nanoparticles (SLNs), a medication that dissolves in water, are recommended as a useful carrier method for correcting effective treatment. Colloidal molecules have diameters that range from 10 to 1000 nm, which define nanoparticles. These are

designed to improve medicine administration and reduce mortality; they are made of unique, synthetic polymers.1.
They have developed a versatile substitute for lipid nanoparticles in the delivery of pharmaceuticals. Since they are made of synthetic or unique polymers, they are perfectly suited to maximise sedate delivery and minimise lethality.2.

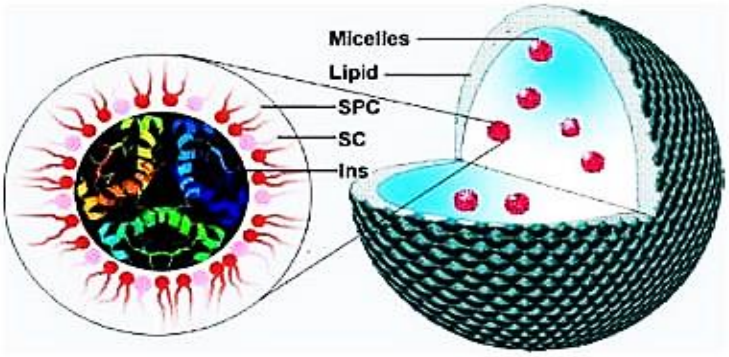

Fig 1: Structure of Solid Lipid Nanoparticles

SLN feature intriguing properties such as tiny size, large surface zone, high medication mounting, and stages interacting at the interface that make them appealing due to their potential to improve the application of medicines.3.

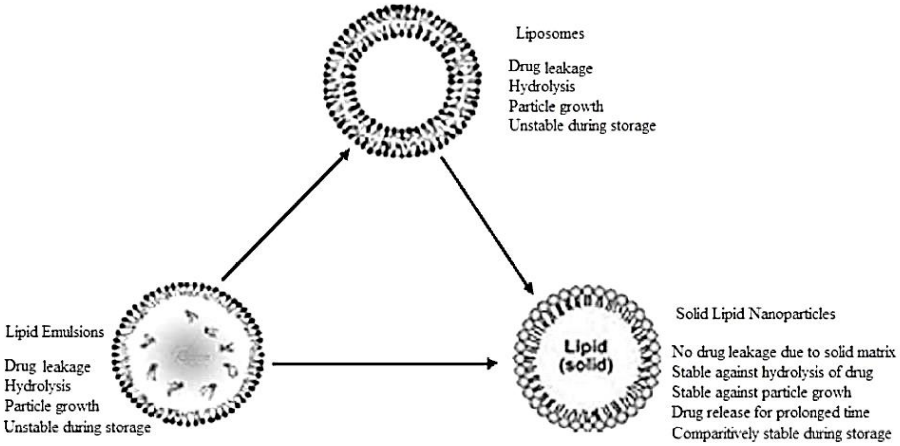

Fig 2: Diagrammatic representation on SLN over emulsions and liposome

For parenteral distribution, SLNs are a state-of-the-art colloidal carrier technology that can replace an oil-in-water emulsion. It is an SLNs that has replaced the liquid lipid in the emulsion.4.

Solid Lipid Nanoparticles (SLNs) offer several advantages in drug delivery:[2,3]

- **Enhanced Bioavailability**: SLNs improve the solubility and bioavailability of poorly soluble drugs.
- **Controlled Release**: They enable controlled and sustained release of drugs, enhancing therapeutic efficacy.
- **Targeted Delivery**: SLNs can be targeted to specific tissues or cells, reducing side effects.
- **Biocompatibility**: Made from physiological lipids, they are biocompatible and less toxic.
- **Physical Stability**: SLNs offer better stability than liquid formulations.
- **Protection of Sensitive Drugs**: They protect labile drugs from degradation.
- **Scalability:** Their production processes can be scaled up for industrial manufacturing.
- **Versatility:** SLNs are suitable for multiple routes of administration, including oral, intravenous, and topical.
- **Reduced Drug Toxicity:** They can reduce the systemic toxicity of encapsulated drugs.
- **Flexibility in Drug Release:** SLNs can be engineered to release drugs at a specific site or rate, enhancing therapeutic outcomes.

- **Improved Pharmacokinetic Properties:** SLNs can modify the pharmacokinetics of drugs, leading to better distribution and prolonged circulation time.
- **Patient Compliance:** Due to their improved efficacy and reduced side effects, SLNs can enhance patient compliance.
- **Environmental Sustainability:** The use of biodegradable lipids makes SLNs more environmentally friendly.
- **Co-encapsulation Capability:** They can encapsulate multiple drugs simultaneously, allowing for combination therapies.
- **Barrier against Oxidation and Degradation:** SLNs can protect encapsulated drugs from oxidation and degradation.
- **Feasibility for Lyophilization:** They are amenable to freeze-drying, which facilitates long-term storage and stability.
- **Potential for Personalized Medicine:** SLNs can be customized for individual patient needs, aligning with the principles of personalized medicine.
- Powdered detailing may be shaped after being stop dry.
- Dynamic medicine can be introduced gradually over a lengthy period of time.
- Outstanding biocompatibility
- Enhance medications' stability.
- Excellent repeatability using as the readiness process a clever high-weight homogenization procedure.
- Significantly increased drug content.
- The possibility of combining drugs that are both hydrophilic and hydrophobic.
- The biodegradable nature of the transporter lipids provides protection.
- Staying away from natural solvents atoms that are only partially soluble in water have increased bioavailability.
- Strategies for avoiding natural solvents are in place.
- Possibility of mass production and clean-up.

Disadvantages of SLN

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

PREPARATION OF SLN4

1. Hot Homogenization

- **Variations in Heating**: The temperature to which the lipid is heated can vary. It's typically above the melting point of the lipid but not too high to avoid drug degradation.
- **Controlled Cooling**: After homogenization, the hot o/w (oil-in-water) nanoemulsion is cooled at a controlled rate, leading to the crystallization of the lipid and formation of SLNs.

2. Cold Homogenization

- **Particle Size Reduction**: The grinding or milling of the solid lipid to micron size is crucial for stability and uniformity of particle size in the final product.
- **Importance of Temperature**: Maintaining low temperatures during homogenization is critical to prevent melting of the lipid.

3. Solvent Evaporation/Emulsification Method

- **Choice of Solvent**: The solvent choice is crucial as it should adequately dissolve the lipid and the drug but be miscible with water to allow for its complete removal.
- **Solvent Removal Techniques**: Techniques like rotary evaporation or reduced pressure evaporation are commonly used to remove the solvent without degrading the drug.

4. Microemulsion-Based Method

- **Thermal Cycling**: In some variations, thermal cycling (repeated heating and cooling) is used to improve the crystallinity and stability of the nanoparticles.
- **Dilution Techniques**: The method of dilution can influence the size and distribution of the nanoparticles.

5. Ultrasonication or High-Speed Homogenization

- **Ultrasonication Duration and Intensity**: These parameters must be optimized to prevent drug degradation while ensuring effective size reduction.
- **High-Speed Homogenization Parameters**: Speed and duration of homogenization can significantly affect the particle size and distribution.

6. Supercritical Fluid Method

- **Parameters of Supercritical CO2**: Pressure and temperature conditions for the supercritical CO2 must be finely tuned for optimal solubility of the lipid and drug.
- **Rapid Expansion Techniques**: Various techniques like Rapid Expansion of Supercritical Solutions (RESS) or Supercritical Anti-solvent (SAS) are employed.

Additional Considerations

- **Sterilization**: For pharmaceutical applications, the sterilization of SLNs is a critical step. Methods like autoclaving, filtration, or gamma irradiation may be used.
- **Characterization**: Post-preparation, SLNs are characterized for particle size, zeta potential, drug loading, encapsulation efficiency, and in vitro drug release behavior.

- **Stability Studies**: Long-term stability studies are essential to ensure the SLNs maintain their integrity and effectiveness over time.

Tailoring Methods to Specific Needs5

- **Drug Characteristics**: The solubility, stability, and molecular weight of the drug can dictate the choice of method.
- **Lipid Composition**: Different lipids have different melting points and biocompatibility profiles, influencing the choice of method.
- **Targeted Delivery**: Modifications in the preparation method can be made for targeted delivery, like attaching targeting ligands to the surface of SLNs.

1. High pressure homogenization (HPH)6

It is a reliable and powerful technique, which is used for the 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.

Two general approaches of HPH are hot homogenization and cold homogenization, work on the same concept of mixing the drug in bulk of lipid melt.

A. 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. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.

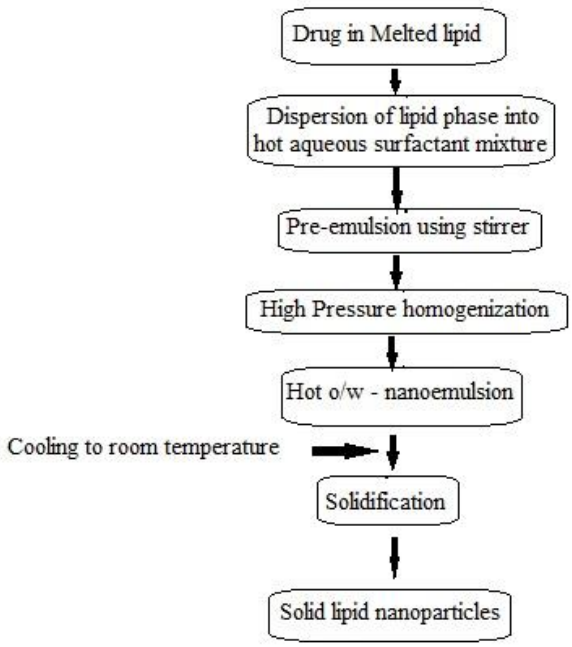

Fig 3: Solid lipid nanoparticles preparation by hot homogenization process

B. Cold homogenization

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.

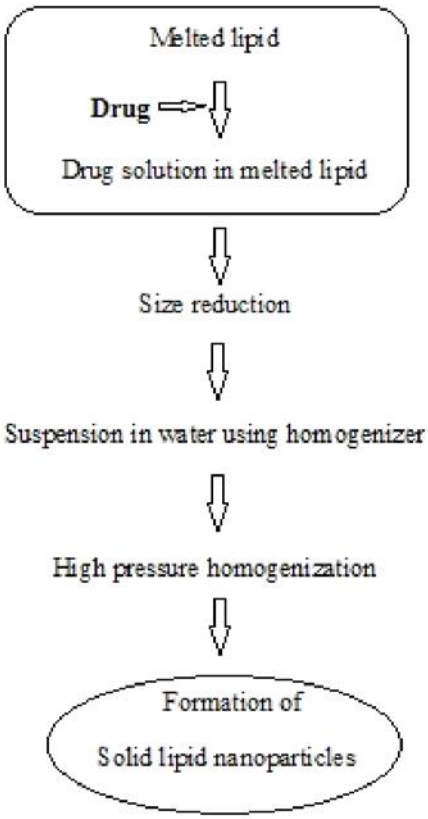

Fig 4: Solid lipid nanoparticles preparation by cold homogenization process

Advantages
Low capital cost.
Demonstrated at lab scale.

Disadvantages
Energy intensive process.
Demonstrated at lab scale Biomolecule damage.
Polydisperse distributions.
Unproven scalability.

2.Ultrasonication/high speed homogenization

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.

Advantages
Reduced shear stress.

Disadvantages
Potential metal contamination.
Physical instability like particle growth upon storage.

3. Solvent evaporation

SLNs can also prepared by 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).

Advantages
Scalable.
Mature technology.
Continuous process.
Commercially demonstrated.

Disadvantages
Extremely energy intensive process.
Polydisperse distributions.
Biomolecule damage.

4. 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.

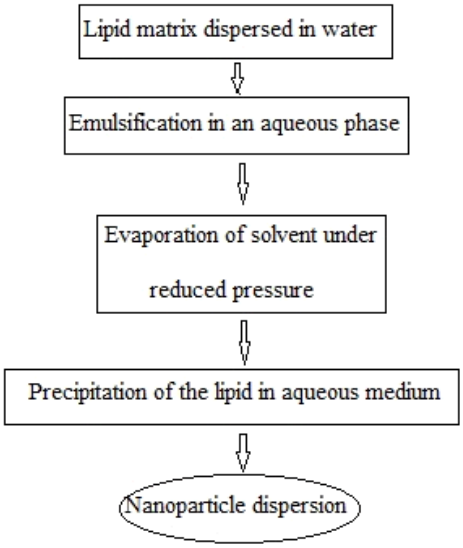

Fig 5: Systematic representation for emulsification-diffusion method

5. Supercritical fluid method

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS).

Advantages

- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions.
- Carbon dioxide solution is the good choice as a solvent for this method.

6. Microemulsion based method

This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. o/w microemulsions). They are made by stirring an optically transparent mixture at 65-70°C, which typically composed of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2-3°C) under stirring. SLN dispersion can be used as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process, but in case of low particle content too much of water needs to be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.

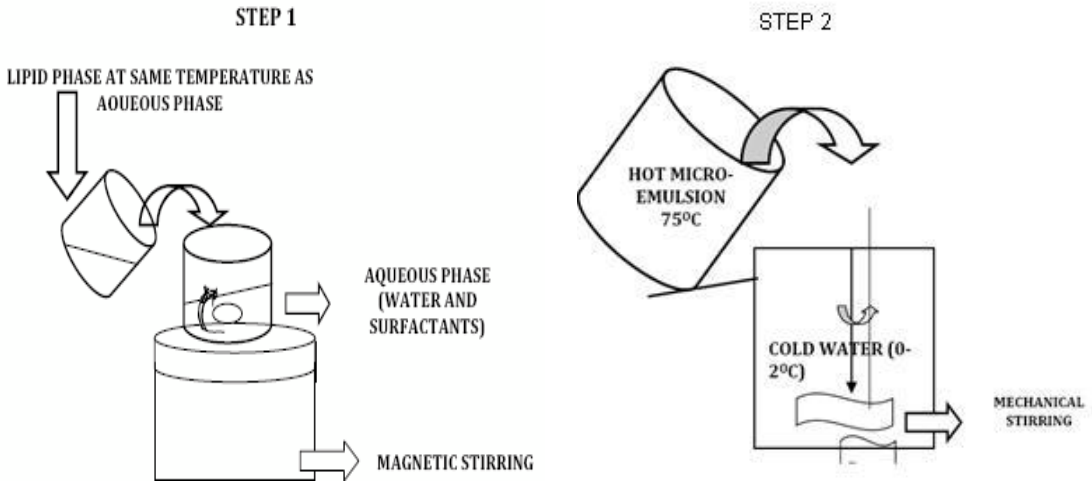

Fig 6: Microemulsion method

Advantages
Low mechanical energy input.
Theoretical stability.

Disadvantages
Extremely sensitive to change.
Labor intensive formulation work.
Low nanoparticle concentrations.

7. Spray drying method

It is an alternative technique to the lyophilization process. This recommends the use of lipid with melting point more than 70^{o}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.

8. Double emulsion method

Here the drug is encapsulated with a stabilizer to prevent the partitioning of drug in to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

9. Precipitation method

The glycerides are 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.

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.

Secondary Production Steps7

Freeze drying

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.

Sterilization

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.

Spray drying

Spray drying might be an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a dry product. This method has been used scarcely for SLN formulation, although spray drying is cheaper as compared to lyophilization.

The lipids with melting points at temperature >70°C had been recommended for spray drying.

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 potential 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.[3]

Parenteral administration

SLN have been administered intravenously to animals. Pharmacokinetic studies of doxorubicin 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 application 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 intraperitonial 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 irritancy compared to injecting drug micro particles.[3]

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.[3]

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).[8]

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 radiolabiled formulations and γ-scintigraphy. The lipids of SLN are easy to metabolize and open a new ways for ophthalmological drug delivery without impairing vision.[9,10]

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.[8]

CONCLUSION

As potential DDS, SLNs and nano-structured phospholipid transporters have attracted a lot of attention throughout the past ten years. Their primary advantage might lie in the use of biodegradable and ecologically friendly ingredients and processing methods. Because of their small size and biodegradable nature, the majority of nanosystems in this class fall into the lowest risk category (class I) of the Keck and Müller proposed nanotoxicological categorization scheme. It should be emphasized, therefore, that a thorough clinical and environmental safety study must be completed prior to moving these systems forward with widespread manufacturing and commercialization. It is imperative to establish a suitable regulatory framework and develop standardized procedures to assess the potential risks associated with nanoparticle exposure.

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