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Solid Lipid Nanoparticles: The Frontier in Drug Delivery.

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ABSTRACT

Solid lipid nanoparticles (SLNs) have emerged as a forefront drug delivery system with diverse potential applications in pharmaceutical and cosmeceutical research, nanomedicine and other allied branches of science. Recently, increasing attention has been focused on these SLNs as colloidal drug carriers for incorporating hydrophilic or lipophilic drugs. Proteins and antigens intended for therapeutic purposes can also be incorporated or adsorbed onto SLNs, and further administered by parenteral route or by alternative routes such as oral, nasal and pulmonary etc. Due to their unique size dependent properties SLNs offer possibility to develop new therapeutics. The ability to incorporate drugs into these nanocarriers offers a new prototype in drug delivery that could use for drug targeting. Hence SLNs hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers. Also the problems associated with conventional chemotherapy can be overcome by encapsulating them in SLNs. The present review focuses on SLNs brief introduction, utility in terms of their advantages, production methodology, characterization and applications and their possible remedies. Further investigation and research related to SLNs may open new vistas in nanotechnology and in therapy of multifaceted diseases.

Keywords: Nanomedicine, Solid Lipid Nanoparticle, Nanocarrier, Drug Delivery.

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INTRODUCTION

Solid lipid nanoparticles (SLNs) introduced in 1991 represent an alternative carrier system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles.[1]Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLNs are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLNs offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals.[2-4]In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid; which eventually transformed into solid lipid nanoparticles.

The reasons for the increasing interest in lipid based system are many folds and include:

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipoid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up.

SLNs are one of the novel potential colloidal carrier systems as alternative material to polymers; which are identical to oil in water emulsions for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid as shown in Figure. 1. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by SLNs and the system is physically stable.[5]

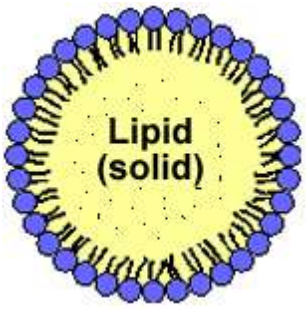

Figure. 1: Structure of a solid lipid nanoparticle.

History

Decades ago submicron-sized vegetable oil-in-water (O/W) emulsion were introduced as carrier systems for poor water soluble drugs. These O/W emulsions are claimed to be biodegradable, biocompatible and easy to manufacture. However, only a few drug containing emulsions have

reached the market because of several formulation problems. Traditionally O/W emulsion were considered to be unsuitable for sustained release because of the low viscosity of the dispersed liquid phase, combined with high specific surface area of colloidal dispersion that causes rapid diffusion out of the droplet.[5] So, colloidal carriers such as liposomes were developed to get the sustained release effect of the drug. Here the drug is enclosed in phospholipids in aqueous solution. The phospholipids are sensitive to the temperature and pH change and therefore, were not easy to manufacture and administer. Later on liposomes were replaced by the niosomes because of non-ionic surfactants were employed instead of phospholipids. Further nanoparticles were introduced with aim to overcome the deficiencies in colloidal carriers. The polymers used as the building blocks of nanoparticle composites, belongs to natural or synthetic origins. The polymers of natural origin however, suffer from some disadvantages including batch-to-batch variation, conditional biodegradability and antigen city. Parental administration of polymeric nanoparticles has hurdles mainly due to antigenicity.[6]Then SLNs were introduced in the early 1990's by replacing liquid (oil) of emulsions for the parenteral nutrition by a solid lipid. Formulation ingredients typically include a lipid carrier, a drug (generally lipophilic for satisfactory encapsulation efficiency), water as dispersion phase, and surfactant and/or a co-surfactant. These ingredients, after undergoing various formulation techniques, can entrap or absorb the drug into the particle surface.[7]

SLNs are considered to be the most effective lipid based colloidal carriers and one of the most popular approaches to improve the oral bioavailability of the poor water soluble drugs. The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in Table 1 and Figure. 2 which depicts that SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes together.

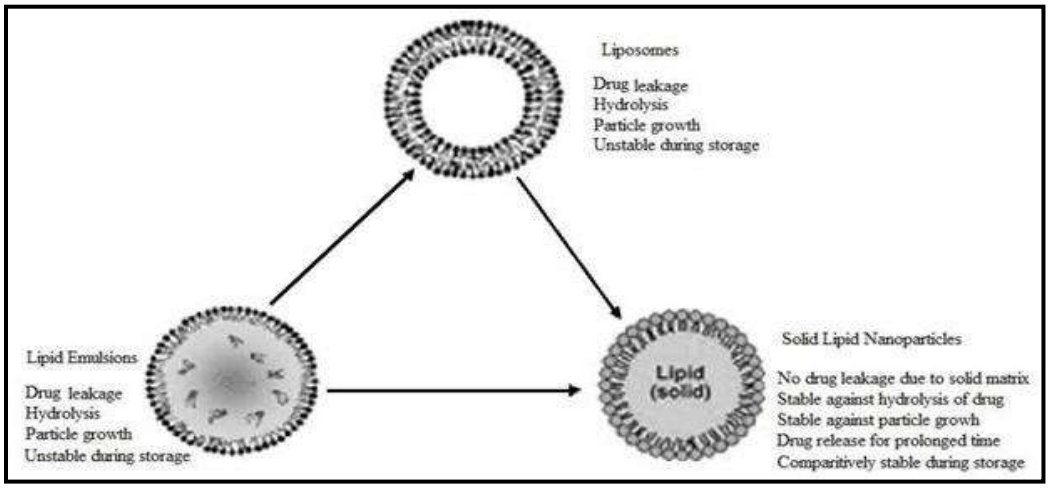

Figure. 2: Diagrammatic comparison of SLNs with emulsions and liposomes.

Table 1: Comparative properties of SLNs, polymeric nanoparticles, liposomes and lipid emulsions.

Sr. No.	Property	SLNs	Polymeric Nanoparticles	Liposomes	Lipid Emulsions
1	Systemic toxicity	Low	≥ to SLNs	Low	Low
2	Cytotoxicity	Low	≥ to SLNs	Low	Low
3	Residues from organic solvents	No	Yes	May or may not	No
4	Large scale production	Yes	No	Yes	Yes
5	Sterilization by autoclaving	Yes	No	No	Yes
6	Sustained release	Yes	Yes	≥ to SLNs	No
7	Avoidance of RES	Depend on size and coating	No	Yes	Yes

Advantages of SLNs[1,2,8]

- Controlled and/or targeted drug release.
- Excellent biocompatibility.[3]
- Improved stability of pharmaceuticals.[9]
- High and enhanced drug content.
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Much easier to manufacture than bio-polymeric nanoparticles.
- Conventional emulsion manufacturing methods are applicable.
- Raw materials essential are same as in the emulsions.
- Very high, long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.
- Use of biodegradable physiological lipids, which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods.[10]
- Improved bioavailability of poor water soluble molecules.[11]
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment.
- SLNs have better stability compared to liposomes.
- High concentration of functional compound achieved.

Disadvantages of SLNs[4,9]

- Particle growth.
- Unpredictable gelation tendency.
- Unexpected dynamics of polymeric transitions.
- Poor drug loading capacity.
- Drug expulsion after polymeric transition during storage.
- Relatively high water content of the dispersions (70-99.9%).[12,13]

Preparation of Solid Lipid Nanoparticles

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods, which are discussed below.[1-4,8,9,14-16]

Methods of Preparation of SLNs

1. High Pressure Homogenization.

A. Hot Homogenization.

B. Cold Homogenization.

2. Ultrasonication/High Speed Homogenization.

A. Probe Ultrasonication.

B. Bath Ultrasonication.

3. Solvent Evaporation Method.

4. Solvent Emulsification-diffusion Method.

5. Supercritical Fluid Method.

6. Microemulsion Based Method.

7. Spray Drying Method.

8. Double Emulsion Method.

9. Precipitation Technique.

10. Film-ultrasound Dispersion.

1. High Pressure Homogenization (HPH):

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. The schematic presentation of this method is given in Figure. 3.

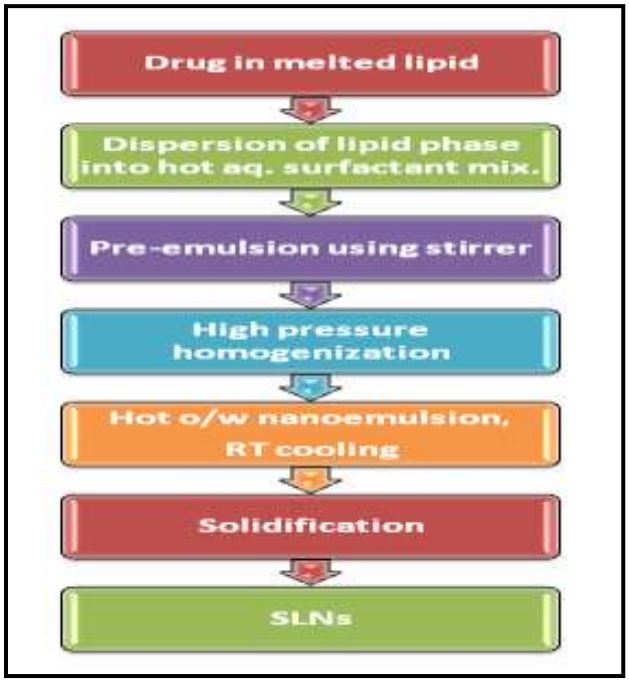

Figure. 3: Schematic presentation of hot homogenization method.

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 nano-emulsion 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 (Figure. 4).

Figure. 4: Schematic presentation of cold homogenization method.

Merits

- Low capital cost.
- Demonstrated at lab scale.

Demerits

- Energy intensive process.
- Demonstrated at lab scale biomolecular 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. The advantage of this method is that the equipments used are commonly available at lab scale. However, this method suffers from problems such as broader size distribution ranging into micrometer range. Potential metal contaminations, physical instability like particle growth upon storage are other drawbacks associated with this technique.

Merits

- Reduced shear stress.

Demerits

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

3. Solvent Evaporation:

For the production of nanoparticle dispersions by precipitation in o/w emulsions, the lipophilic material is dissolved in water-immiscible organic solvent (cyclohexane) that is emulsified in an aqueous phase.[17] Upon evaporation of the solvent nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25 nm with cholesterol acetate as model drug and lecithin/sodium glycocholate blend as emulsifier. The reproducibility of the result was confirmed by Siekmann and Westesen (1996); who produced the cholesterol acetate nanoparticles of mean size 29 nm.

Merits

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

Demerits

- 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. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium (Figure. 5).

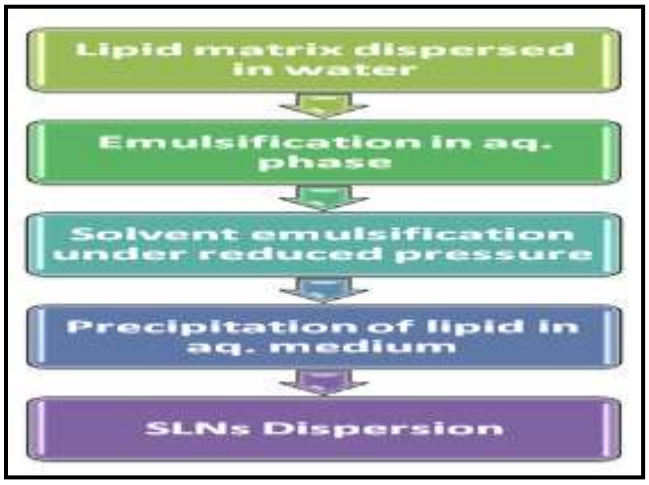

Figure. 5: Schematic presentation of solvent-emulsification diffusion method.

5. Supercritical Fluid Method:

This is an alternative method of preparing SLNs by particles from gas saturated solutions (PGSS). This is a novel technique which recently applied for the production of SLNs. A fluid is qualified as supercritical when its pressure and temperature exceed their respective critical value. Above the critical temperature, it is not possible to liquefy a gas by increasing the pressure. The supercritical fluid has unique thermo-physical properties. As the pressure is raised, the density of the gas increases without significant increase in viscosity while the ability of the fluid to dissolve compounds also increases. A gas may have little to no ability to dissolve a compound under ambient condition can completely dissolve the compound under high pressure in supercritical range. Therefore, its solvation power is altered by careful control of changes in temperature and pressure. Many gases like, CO_2, ammonia, ethane and CH_2FCF_3 were tried, but CO_2 is the best option for SCF technique because, it is generally regarded as safe, easily accessible critical point (31.5ºC, 75.8 bar), does not causes the oxidation of drug material, leaves no traces behind after the process, is inexpensive, noninflammable, environmentally acceptable and easy to recycle or to dispose off. In the SCF phase of this technique generally organic solvents used (e.g. DMSO, DMFA) because they are fully miscible in SCF-CO_2. This technology comprises several processes for nanoparticles production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution(PGSS), gas/supercritical antisolvent (GAS/SAS), aerosol solvent extraction solvent (ASES), solution enhanced dispersion by supercritical fluid (SEDS),supercritical fluid extraction of emulsions (SFEE). Mainly SAS and PGSS were used for SLN preparation.[18-20]

Merits

- 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 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 into 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.

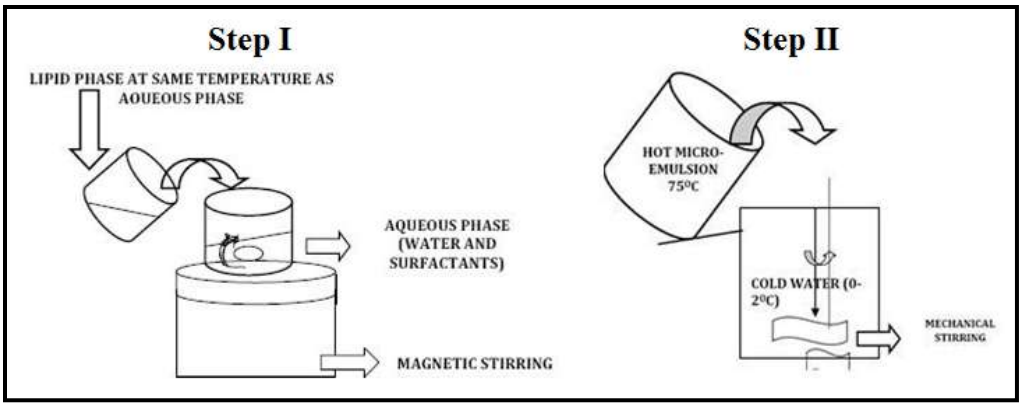

Figure. 6: Steps in microemulsion method.

Merits

- Low mechanical energy input.
- Theoretical stability.

Demerits

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

7. Spray Drying Method:

It is an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into drug product. This is a cost-effective method than lyophilization and recommends the use of lipid with melting point >70°C. This method causes particle aggregation due to high temperature shear forces and partial melting of the particle. According to Freitas and Mullera (1998) best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

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. In double emulsion technique the drug (mainly hydrophilic drugs) are dissolved in aqueous solution, and then are emulsified in melted lipid. This primary emulsion is stabilized by stabilizer. Then this stabilized primary emulsion is dispersed in aqueous phase containing

hydrophilic emulsifier. Thereafter, the double emulsion is stirred and is isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of a lipid-PEG derivative. A major drawback of this is the formation of high percentage of micro particles.[19,20]

9. Precipitation Method:

The glycerides are dissolved in an organic solvent (e.g. chloroform) and the solution is emulsified in an aqueous phase. After evaporation of the organic solvent the lipid get precipitated forming nanoparticles.[13,20]

10. Film-ultrasound Dispersion:

The lipid and the drug are 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 is added. Using the ultrasound with the probe to diffuser at last, the SLNs with the little and uniform particle size are formed.[20]

Table 2:List of drugs and polymers used for the preparation of SLNs using different methods.

Drug	Polymer	Method of Preparation
Olanzapine	Hydrogenated soyaphosphatidylcholine	Modified high pressure homogenization
Rizatriptan	Tristearin,Phospholipon80	Modified solvent injection method
Alendronate NP	PLGA,Ethyl acetate, PF68	Double emulsion solvent diffusion
Clozapine	Dynasan114,116,	Hot homogenization
Tetracaine	Tristearin,Dynasan112,	Hot homogenization
Etomidate	Campritol 888ATO,	Hot homogenization
Prednisolone	Lipoid S75	Hot homogenization
Vitamin A Retinol	Compritol 888ATO, Miglyol 812, Dynasan 116	Hot homogenization
Gatifloxacin	Chitosan-Na aliginate	Modified co-acervation
Insulin	PEG'Glycol-grafted chitosan	Ionic gelation
Paclitaxel	Tripalmitin, phosphatidylcholine	Microemulsion
Insulin	Hydrophobized cholesterol bearing pullulan	Ultra sonication
Mitoxantrone	Glycerylbehenate, Campritol 888ATO, lecithin	Ultra sonication
Vinpocetine	Glycerylmonostearate,DCM, soyalecithin	Ultrasonic solvent emulsification
Insulin	Cetylpalmitate	Solvent emulsification evaporation
5-Fluorouracil	Dynasan 114,118, triglyceride, soyalecithin	Double emulsion solvent evaporation
Methotrexate	Cetyl alcohol, Campritol 888 ATO,Tween 80	Microemulsion congealing technique

Secondary Production Steps[20]

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 Ostwald ripening and avoid hydrolytic reactions. In case of freeze drying of the product, all the lipid matrices used, form larger SLNs 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 SLNs during the freeze drying process.

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 SLNs 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.

Sterilization

Sterilization of the nanoparticles is desirable for parenteral administration and autoclaving which inapplicable 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.

Formulation Variables[9,21,22]

Particle Size

Alteration of the size significantly affects the physical stability, bio-fate of the lipid particles, and release rate of the loaded drug. Hence the size of the SLNs has to be controlled within reasonable range. Well formulated systems (liposomes, nanospheres and nanoparticles) should display a narrow particle size distribution in the submicron size range (as having size below 1µm), according to the definition of colloidal particles.

Influence of Ingredients on Product Quality

The particle size of lipid nanoparticles is affected by various parameters such as composition of the formulation (such as surfactant/ surfactant mixture, properties of the lipid and the drug incorporated),production methods and conditions (such as time, temperature, pressure, cycle number, equipment, sterilization and lyophilization). Large particle size is obtained at lower processing temperature. The hot homogenization technique gives a smaller particle size,

generally below 500 nm, and a narrow particle size distribution as compared to cold homogenization. Mean particle size as well as polydispersity index (PI)values are reported to be reduced at increasing homogenization pressure up to 1500 bar and number of cycles (3-7 cycles).

Influence of Lipids

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. However, other critical parameters for nanoparticle formation will be different for the different lipids. The examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties and the shape of the lipid crystals (and therefore the surface area).Further, increasing the lipid content over 5-10% resulted in larger particles (including microparticles) and broader particle size distribution in most cases.

Influence of Emulsifiers

The concentration of the surfactant/surfactant mixture strongly affects the particle size of the lipid nanoparticles. In general, smaller particle sizes were observed when a higher surfactant/lipid ratio was chosen. The decrease in surfactant concentration resulted in increase of particle size during storage. Surfactants decrease the surface tension between the interface of the particles causing portioning of the particles and thereby increasing the surface area.

Drug Release from SLNs

There are mainly three drug incorporation models which describe the incorporation of drug into SLNs[18]

1. Homogenous matrix model.
2. Drug enriched shell, core shell model.
3. Drug enriched core, core shell model.

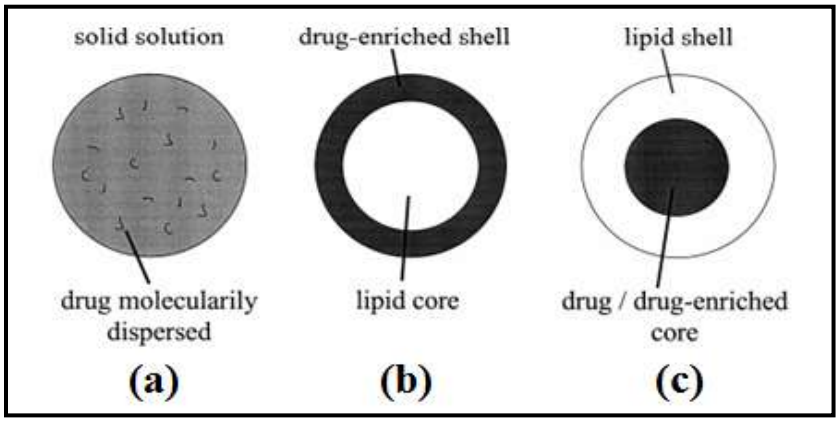

Figure. 7: Models for incorporation of APIs in SLNs; (a) Homogeneous matrix, (b) Drug enriched shell with lipid core, (c) Drug enriched core with lipid shell.

Homogenous matrix model or solid solution model with drug being present in amorphous clusters or molecularly dispersed is mainly obtained when incorporating highly lipophilic drugs into SLNs with using hot homogenization technique or applying cold homogenization method or by avoiding potentially drug solubilizing surfactants. In the cold homogenization technique the drug (in molecularly dispersed form) is dispersed in bulk of melted lipid, then the mechanical force of high pressure homogenization leads to the breakdown of molecular form to nanoparticles and giving rise to homogenous matrix model as shown in Figure 7(a). Etomidate SLNs represents the homogenization matrix model.

The drug enriched shell with core shell model will be obtained when during the production, the drug partitioned to water phase. Upon cooling, the lipid precipitates first, forming a practically drug free lipid core due to phase separation. At the same time, the drug re-partitions into the remaining liquid-lipid phase and drug concentration in the outer shell increases gradually. Finally drug enriched shell crystallizes as depicted in Figure 7(b). The amount of drug partitioning to the aqueous phase is increased with the increase of solubility of drug in the aqueous phase. Mainly two factors, increasing temperature of the aqueous phase and increasing surfactant concentration, are increasing the saturation solubility of drug in water phase. Tetracaine SLNs prepared by hot HPH shows drug enriched shell model.

A drug enriched core obtained when dissolving a drug (e.g. prednisolone) in the lipid melts at or close to its saturation solubility. In this model, cooling of the formed nanoemulsions lead to supersaturation of drug in melted lipid and it further leads drug precipitation prior to lipid precipitation. Further cooling gives rise to precipitation of lipid surrounding the drug enriched core as a membrane as indicated in Figure 7(c). Due to increased diffusional distance and hindering effect of surrounding solid lipid shell, the carrier system shows sustained release profile.[18]

Drug Incorporation and Loading Capacity

The particle size, loading capacity and the size distribution of SLNs is found to vary with lipid(triglycerides, fatty acids, steroids, waxes etc.), emulsifier (anionic, cationic, non-ionic) and the method of preparation etc.[9,23]

Factors determining the loading capacity of the drug in the lipid are:

• Solubility of the melted lipid.

• Miscibility of the drug melt in the lipid melt.

• Chemical and physical structure of solid lipid matrix.

• Polymorphic state of lipid material.

The pre-requisite to obtain a sufficient loading capacity is a sufficiently high solubility of the drug in the lipid melt. Typically the solubility should be higher than required because, it decreases when cooling down the melt and might be even lower in the solid lipid. To enhance the solubility in the lipid melt one can add solubilizers. In addition, the presence of mono and diglycerides in the lipid used matrix material promotes drug solubilization. The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice lead drug expulsion.[4,9,23]

Estimation of Incorporated Drug

Entrapment Efficiency[1,4,24-26]

This is of prime importance in SLNs, since it influences the release characteristics of drug molecule. The amount of drug encapsulated per unit weight of nanoparticle is determined after separation of the entrapped drug from the SLN formulation. This separation can be carried out using the techniques such as ultracentrifugation, centrifugation filtration and or gel permeation chromatography. The drug can be assayed by standard analytical techniques such as spectrophotometer, spectroflurophotometry, HPLC or liquid scintillation counting.

Entrapment efficiency can be calculated with the help of equation 1:

$$EE\% = (W_{initial\ drug} - W_{free\ drug} / W_{initial\ drug}) * 100\% \quad \text{.....Equation 1}$$

Principles of Drug Release

The general drug principles of drug release from lipid nanoparticles are as follows:

- There is an inverse relationship between drug release and the partition co-efficient of the drug.
- Higher surface area due to smaller particle size in the nanometer size range gives higher drug release.
- Slow drug release can be achieved when drug is homogenously dispersed in the lipid matrix. It depends on the type and the drug entrapment model of SLNs.
- Crystallinity behavior of the lipid and high mobility of the drug lead to fast drug release. There is an inverse relationship between crystallization degree and mobility of drug.

Factors contributing to a fast release are the large surface area, a high diffusion coefficient due to small molecular size, low viscosity in the matrix and a short diffusion distance δ for the drug. The increase in the velocity with decreasing particle size was reported.[4,23]

***In-vitro* and *Ex-vivo* Methods for Assessment of Drug Release from SLNs[27-29]**

A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLNs, various methods used to study the *in-vitro* release of the drug are:

• Side by side diffusion cells with artificial or biological membrane.[20]

• Dialysis bag diffusion technique.[30]

• Reverse dialysis bag technique.[27]

• Agitation followed by ultracentrifugation or centrifugal ultra-filtration.[25]

In-vitro Drug Release[21]

Dialysis Tubing

In-vitro drug release could be achieved using dialysis tubing. The SLNs 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 SLNs are then displaced into the medium.

Ex-vivo Model for Determining Permeability Across the Gut[27,31]

Ahlin*et al.* demonstrated the passage of enalapril SLNs across rat jejunum.[13]Inshort 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 pyloricsphincter); jejunum (15 cm to pyloric sphincter), ileum (20 cm proximal to cecum) and colon (2 cm distal tocecum) and were immediately cannulated and ligated and both sides used for their permeability studies.

Analytical Characterization of SLNs

An adequate characterization of the SLNs is necessary for the control of quality of 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 SLNs dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion.[29,31]

Static Light Scattering (SLS)/Fraunhofer Diffraction

This method based on studying the pattern of light scattered from a solution of particles which is then fitted into fundamental electromagnetic equations in which size is the primary variable. It is fast and rugged method but requires more cleanliness than DLS, and advance knowledge of the particles optical qualities.

Dynamic Light Scattering (DLS)

DLS, also known as PCS or quasi-elastic light scattering (QELS) records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion, and is quantified by compilation of an autocorrelation function. The advantages of the method are the speed of analysis, lack of required calibration and sensitivity to submicrometer particles.

Nuclear Magnetic Resonance (NMR)

NMR can be used to determine both the size and the qualitative nature of nanoparticles. The selectivity afforded by chemical shift complements the sensitivity to molecular mobility, to provide information on the physicochemical status of components within the nanoparticle.[25]

Electron Microscopy

Electron microscopy methods are used to measure the overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions. 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. SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample. TEM has a smaller size limit of detection.[33,34]

Atomic Force Microscopy (AFM)

A probe tip with atomic scale sharpness is raftered across a sample to produce a topological map based on forces at play between the tip and the surface. It is an advanced microscopic technique which is applied as a new tool to image the original unchanged shape and surface properties of the particles. AFM measures the force acting between surface of the sample and the tip of the

probe, when the probe is kept in close proximity to the sample which results in a spatial resolution of up to 0.01 nm for imaging.

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 transition and melting point temperature.[29,35]

Rheology

Rheological measurements of formulations can be performed by Brookfield viscometer or any other viscometer, using a suitable spindle number. The viscosity depends on the dispersed lipid content. As the lipid content increases, the flow becomes non-Newtonian from Newtonian.

Acoustic Methods

Another ensemble approach, Acoustic Spectroscopy, measures the attenuation of sound waves as a means of determining size through the fitting of physically relevant equations. In addition, the oscillating electric field generated by the movement of charged particles under the influence of acoustic energy can be detected to provide information about the surface charge.

Measurement of Crystallinity and Lipid Modifications

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 hasyet to be explored.[9,27,35]

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 and changes related to the lipid modification. An overview of all characterization methods with parameters evaluated are summarized in Table 3.

Table 3: Characterization methods for SLNs.

Sr. No.	Parameters	Characterization Methods
1	Molecular Weight.	Gel chromatography, X-ray photoelectron spectroscopy.
2	Particle Size and Size Distribution.	Photon Correlation Spectroscopy (PCS), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), Mercury porositometer.
3	Charge Determination.	Laser droplet anemometry, zeta potential.
4	Surface Hydrophobicity.	Water contact angle measurements, Rose Bangle (dye) binding, hydrophobic interaction chromatography, X-ray photoelectron spectroscopy.
5	Chemical Analysis of Surface.	Static secondary ion mass spectrometry
6	Carrier Drug Interaction.	Differential Scanning Calorimetry (DSC)
7	Release Profile.	*In-vitro* release characteristic under physiologic and sink condition.
8	Drug Stability	Bioassay of drug extracted from nanoparticles, chemical analysis of drug.

Sterilization of SLN

For intravenous and ocular administration SLNs must be sterile. The temperature reached during sterilization by autoclaving presumably causes a hot o/w micro emulsion to form in the autoclave, and probably alters the size of the hot nanoparticles. On subsequent slow cooling, the SLNs reformed, but some nano-droplets may coalesce, producing larger SLNs than the initial one. SLNs are washed before sterilization, amounts of surfactants and co-surfactants present in the hot systems are smaller, so that the nano-droplets may be not sufficiently stabilized.[3,21]

Storage Stability of SLN

The physical properties of SLNs 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. At 4^{o}C- most favorable storage temperature,20^{o}C- long term storage did not result in drug loaded SLNs aggregation or loss of drug,50^{o}C- a rapid growth of particle size is observed.[27,30]

SLNs Biodistribution[2,8,23,15,36]

The *in-vivo* behavior of the SLNs mainly depends on the following points: Interactions of the SLNs with the biological surroundings including: distribution processes(adsorption of biological

material on the particle surface and desorption of SLN components into the biological surroundings) and enzymatic processes. Various administration routes are:

Parenteral Administration

Peptide and proteins drugs are usually available for parenteral use in the market. Since their conventional oral administration is not possible due to enzymatic degradation in GI tract. Parenteral ingestion of SLNs reduces the possible side effects of drug incorporated with the increased bioavailability. These systems are even very suitable for drug targeting.

Oral Administration

The oral route continues to be a challenge as well as the most attractive way to administer drugs because of its unquestionable commercial potential. Incorporation of drugs into SLNs opens the perspective of enhanced and/or less variable bioavailability and prolonged plasma levels. While these systems may provide the greatest flexibility in the modulation of the drug release profile within GIT and provide protection against chemical degradation for labile drug molecules (peptide drugs).Controlled release behavior of SLNs is reported to enable the bypass of gastric and intestinal degradation of the encapsulated drug, and their possible uptake and transport through the intestinal mucosa. However, the assessment of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration.[9,37]

Rectal Administration

When rapid pharmacological effect is required, in some circumstances, parenteral or rectal administration is preferred. This route could be used for pediatric patients due to ease of administration.

Nasal Administration

Nasal route is preferred due to its fast absorption and rapid onset of drug action, also avoiding degradation of labile drugs in the GIT and insufficient transport across epithelial cell layers.

Pulmonary Administration

Nebulisation of SLNs carrying anti-tubercular drugs, anti-asthmatic drugs and anti-cancer drugs is observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary action.

Ocular Administration

Biocompatibility and mucoadhesive properties of SLNs improve their interaction with ocular mucosa and prolonging corneal residence time of the drug, with the aim of ocular drug targeting.

Topical Administration

SLNs are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

Applications of SLNs

There are several potential applications of SLNs some of which are given below:

As Potential New Adjuvant for Vaccines

Adjuvants are used in vaccination to enhance the immune response. The safer new subunit vaccines are less effective in immunization and therefore effective adjuvants are required. New developments in the adjuvant area are the emulsion systems. These are oil-in-water emulsions that degrade rapidly in the body. Being in the solid state, the lipid components of SLNs will be degraded more slowly providing a longer lasting exposure to the immune system.[9,36,38]

In Cancer Chemotherapy

From the last two decades several chemotherapeutic agents have been encapsulated in SLNs and their *in-vitro* and *in-vivo* efficacies have been evaluated. Outcomes of these studies have been shown to improve the efficacy of chemotherapeutic drugs, simultaneously reduction in side effects associated with them. Improved stability of drugs, encapsulation of chemotherapeutic agents of diversified physicochemical properties, enhanced drug efficacy, improved pharmacokinetics and less *in-vitro* toxicity are the important features of SLNs which make them a suitable carrier for delivering chemotherapeutic drugs. Several obstacles frequently encountered with anticancer compounds, such as normal tissue toxicity, poor specificity and stability, and a high incidence of drug resistant tumor cells, are at least partially overcome by delivering them using SLNs. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle for targeting tissues elsewhere in the body, such as bone marrow and solid tumors.

Tamoxifen is an anticancer drug incorporated in SLNs to prolong the release of drug after IV administration in breast cancer. Tumor targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin.[38]Mitoxantrone-loaded SLNs local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug.[40] Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the doxorubicin was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded SLNs. The system has enhanced efficacy and reduced breast cancer cells.[27,30,39]

In Delivery of Peptides and Proteins

Solid lipid particulate systems such as solid lipid nanoparticles (SLN), lipid microparticles (LM) and lipospheres have been sought as alternative carriers for therapeutic peptides, proteins and antigens. The research work in this area confirms that under optimized conditions they can be produced to incorporate hydrophobic or hydrophilic proteins and seem to fulfill the requirements for an optimum particulate carrier system. Proteins and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLNs, and further administered by parenteral routes or by alternative routes such as oral, nasal and pulmonary. Formulation in SLNs confers improved protein stability, avoids proteolytic degradation, as well as sustained release of the incorporated molecules. Important peptides such as cyclosporine A, insulin, calcitonin and somatostatin have been incorporated into SLNs and are currently under investigation. Several local or systemic therapeutic applications may be foreseen, such as immunization with protein antigens, infectious disease treatment, chronic diseases and cancer therapy etc.[41]

In Targeted Brain Drug Delivery

The extremely small particle size of SLNs, which are less than 50 nm, might be beneficial with respect to drug targeting. Small carrier size generally favors reduced uptake by the reticulo-endothelial system. Drug targeting might also be possible by surface modification of SLNs. SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. In a study to overcome the limited access of the drug 5-fluoro-2'-deoxyuridine (FUdR) to the brain, 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine (DO-FUdR) was synthesized and incorporated into SLNs (DOFUdR-SLN).[43]The state of the art on surfactant coated poly (alkylcyanoacrylate) nanoparticles specifically designed for brain targeting is given by emphasizing the transfer of this technology to solid lipid matrices. The potential advantages of the use of SLNs over polymeric nanoparticles are accounted on the basis of a lower cytotoxicity, higher drug loading capacity, and best production scalability. SLNs physicochemical characteristics are also particularly regarded in order to address the critical issues related to the development of suitable brain targeting formulations.[9,42]

In Parasitic Diseases

Parasitic diseases (like malaria, Leishmanasis and tryanosomiasis) are one of the major problems around the globe. Anti-parasitic chemotherapy is the only choice of treatment for these parasitic infections, the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible. Despite the fact that we live in an era of

advanced technology and innovation, infectious diseases, like malaria, continue to be one of the greatest health challenges worldwide. The main drawbacks of conventional malaria chemotherapy are the development of multiple drug resistance and the nonspecific targeting to intracellular parasites, resulting in high dose requirements and subsequent intolerable toxicity. Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria. A number of strategies to deliver antimalarials using nanocarriers and the mechanisms that facilitate their targeting to *Plasmodiumsp.* infected cells are reported.[38]SLNs and nanostructured lipid carriers (NLCs) represent a second generation of colloidal carriers and have emerged as an effective alternative to liposomes mainly due to their better stability profile, ease of scalability and commercialization, and relative cost efficacy. Moreover, SLNs and NLCs due to their particulate nature and inherent structure exhibit good potential in the treatment of parasitic infections. Recent reports including our investigation have validated their utility at least to some extent. However, the need of hour is to undertake extensive investigations on SLNs and NLCs matrices in order to extend their versatility with respect to encapsulation ability and targeting ability and to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.[9,38,42]

In Ultrasonic Drug and Gene Delivery

Drug delivery research employing micelles and nanoparticles has wide application in ultrasonic drug and gene delivery in recent years. Of particular interest is the use of these nanovehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the agent's side effects on the rest of the body. Ultrasound, traditionally used in diagnostic medicine, is finding a place in drug delivery in connection with these nanoparticles. In addition to their non-invasive nature and the fact that they can be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological agents from nanocarriers, as well as rendering cell membranes more permeable. Ultrasonic drug delivery from micelles usually employs polyether block copolymers and has been found effective *in-vivo* for treating tumors. Ultrasound releases drug from micelles, most probably via shear stress and shock waves from the collapse of cavitation bubbles. Liquid emulsions and SLNs are used with ultrasound to deliver genes *in-vitro* and *in-vivo*. The small packaging allows nanoparticles to extravagate into tumor tissues. Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the

wide variety of drugs and genes that could be delivered to targeted tissues by fairly non-invasive means.[9,43]

In Delivery of Anti-retroviral Drugs to the Brain

Human immunodeficiency virus (HIV) can gain access to the central nervous system during the early course of primary infection. Once in the brain compartment the virus actively replicates to form an independent viral reservoir, resulting in debilitating neurological complications, latent infection and drug resistance. Current anti-retroviral drugs (ARVs) often fail to effectively reduce the HIV viral load in the brain. This, in part, is due to the poor transport of many ARVs, in particular protease inhibitors, across the blood brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB). Studies have shown that nanocarriers including polymeric nanoparticles, liposomes, SLNs and micelles can increase the local drug concentration gradients, facilitate drug transport into the brain via endocytosis pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites. By delivering ARVs with nanocarriers, significant increase in the drug bioavailability to the brain is expected to be achieved. Recent studies show that the specificity and efficiency of ARVs delivery can be further enhanced by using nanocarriers with specific brain targeting, cell penetrating ligands or ABC transporters inhibitors. Future research focused on achieving brain delivery of ARVs in a safe, efficient and yet cost-effective manner could lead to a fangled brain drug delivery system.[38]

In Treatment of Pulmonary Diseases

Targeted delivery of drug molecules to organs or special sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles a new frontier is opened for improving targeted drug delivery. Nanoparticles with their special characteristics such as small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems. Targeted SLNs delivery to the lungs is an emerging area of interest.[9,44]

SLNs have longer stability and better encapsulation efficiency than liposomes and as opposed to polymeric nanoparticles, the production process involves minimal amounts of organic solvents. SLNs have been used to encapsulate Anti Tubercular Drugs (ATDs) and were proved to be successful in experimental tuberculosis. ATDs such as rifampicin, isoniazid and pyrazinamide SLNs systems were able to decrease the dosing frequency and to improve patient compliance. ATDs were co-incorporated into SLNs to evaluate the potential of these carriers in tuberculosis chemotherapy via the oral route. The finding of these studies suggested that SLNs have great

potential in the delivery of ATDs by reducing frequency of doses and improving patient compliance by better management of tuberculosis.[9,38]

As Transfection Agent

Cationic SLNs for gene transfer are formulated using the same cationic lipid as for liposomal transfection agents. The differences and similarities in the structure and performance between SLNs and liposomes were also investigated. PCS showed that the prepared SLNs were smaller in diameter than the corresponding liposomes while AFM supported the expected structural differences. DNA binding differed only marginally. Cationic lipid composition governs the *in-vitro* transfection performance than the colloidal structure it is arranged in. Hence, cationic SLNs extend the range of highly potent non-viral transfection agents by one with favorable and distinct technological properties. Combination of cationic SLNs with the nuclear localization signal TAT2 increased transfection efficiency hundredfold.[45]

In Cosmetic and Dermatological Preparations

An area of big potential for SLNs and with a short time-to market are topical products based on the SLNs technology, that means pharmaceutical as well as cosmetic formulations. SLNs are considered as being the next generation of delivery system after liposomes.[41] Due to the lower risk of systemic side effect topical treatment of skin diseases appears favourable, yet the stratum corneum counteracts the penetration of xenobiotics into viable skin. Particulate carrier systems may mean an option to improve dermal penetration. Since epidermal lipids are found in high amounts within the penetration barrier, lipid carriers attaching themselves to the skin surface and allowing lipid exchange between the outermost layers of the stratum corneum and the carrier appear promising. Besides liposomes, SLNs and nano structured lipid carriers (NLCs) have been studied intensively.[41] Following the evaporation of water from the lipid nanodispersion applied to the skin surface, lipid particles form an adhesive layer occluding the skin surface. Then hydration of the stratum corneum may increase by which reducing corneocyte packing and widening of the inter-corneocytes gaps can facilitate drug penetration into deeper skin strata. Occlusive effects appear strongly related to particle size. Nanoparticles have turned out 15-fold more occlusive than microparticles, and particles smaller than 400 nm in a dispersion containing at least 35% lipid of high crystallinity has been most potent.[46]

In Lymphatic Targeting

The SLNs were successfully developed and evaluated for the lymphatic uptake after in traduodenal administration to rats.[9]

In Agriculture

Essential oil extracted from *Artemesiaarboreseens L.* when incorporated into SLNs, were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as suitable carrier of safe pesticides.[24]

In Topical Drug Delivery

SLNs and NLCs are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.[47] Researchers have reported intensively on the topical application of SLNs. During the last few years, SLNs and NLCs have been studied with active compounds such as vitamin E[48], tocopherol acetate[49], retinol[50], ascorbylpalmitate, clotrimazole, triptolide, phodphyllotoxin and a nonsteroidal anti-androgen RU 58841for their topical application. A completely new, recently discovered area of application is the use of SLNs in sun-protective, fairness creams.[51]

In Parenteral Drug Delivery

Wissing*et al*. 2003,intensively reviewed parenteral use of SLNs, SLNs are very suitable for systemic delivery because they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization and/or sterilization. When injected intravenously, SLNs are sufficiently small to circulate in the microvascular system and prevent macrophage uptake in case of hydrophilic coating. Therefore, SLNs have been even suggested for viral and non-viral gene delivery. Cationic SLNs has been demonstrated to bind genes directly via electrostatic interactions, and have potential benefits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules.[52]Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass blood brain barrier (BBB). Hydrophilic coating of colloids improves the transport of these through BBB and tissue distribution. Fundaro *et al.* 2000, prepared doxorubicin loaded stealth and non-stealth SLNs and observed that the stealth nanoparticles were present in blood at higher concentrations than non-stealth SLNs after 24 h following intravenous administration.[15,20]

In Nasal Drug Delivery

Nasal administration was a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers.[53] In order to improve drug absorption through the nasal mucosa, approaches such as formulation

development and prodrug derivatization have been employed. SLNs has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups.[54] In a recent report by Villa *et al.* 2004, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers.[55] The role of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecule reported to be successful by Tobio*et al.*, 1998. This concept can be useful for SLNs.

In Pulmonary Drug Delivery

The lungs offer a high surface area for drug absorption by avoiding first-pass effects. Rapid drug absorption by aerosolization of drugs (in the 1-3 μm size range) occurs since the walls of alveoli in the deep lung are extremely thin.[56] Lymphatic drainage plays an important role in the uptake of particulates in the respiratory system. SLNs can be proposed as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. Assessment of inhaled radio-labeled SLNs bio-distribution has been described and the data showed an important and significant uptake of the radio-labeled SLNs into the lymphatic after inhalation.[57] In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of SLNs ranged from 1.1-2.1 μm and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery.[58] Nebulization of SLNs carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency.

In Ocular Drug Delivery

Ocular drug administration via SLNs has been reported several times. Bio-compatibility and mucoadhesive properties of SLNs improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Cavalli*et al.*2002, evaluated SLNs as carriers for ocular delivery of tobramycin in rabbit eyes. As a result SLNs significantly enhanced the drug bioavailability in the aqueous humor. Cavalli*et al.*1995, also studied pilocarpine delivery via SLNs, which is commonly used in glaucoma treatment. They reported very similar results in order to enhance the ocular bioavailability of drug.[20,36,59]

In Rectal Drug Delivery

A few reports are also available on the rectal drug administration via SLNs in the literature. Sznitowska *et al.* 2001, incorporated diazepam into SLNs for rectal administration in order to provide a rapid action. They applied SLNs dispersions on rabbits and performed bioavailability studies. They found that lipid matrix which is solid at body temperature is not an advantageous

system for diazepam rectal delivery. They decided to employ lipids which melt around body temperature in their next experiments. This area seems very open to investigation, especially when the benefits of rectal route are taken into consideration. PEG coating seems to be a promising approach on rectal delivery and consequently, enhancement of bioavailability.[60]

SLNs: Future Prospects

The future vision of SLNs as drug delivery system is to develop a self-actuated therapy with good perspectives to be marketed very successfully. The reason for this is that they were developed considering industrial needs, e.g. scale up, qualification and validation, simple technology, low cost, regulatory excipient status (e.g. GRAS), tolerability etc. Research must continue to develop a therapy through localized medical implants. Yih*et al.* in 2002 and 2005 had developed bio-micro electro mechanical (BioMEMS) micropumps for controlled localized drug delivery using hydrogel nanoparticles system. These systems when implanted, will be able to determine the necessary dose via sensory systems. The implants are normally designed to operate for a long period of time, possibly for months. The stability and usefulness of nanoparticles delivery systems might be influenced by time. Implantable devices or nanochips promise improved therapeutics in various disease management and may be potentially applied as antitumor therapy, gene therapy, or vaccines. Nanochipsbe used to assist in repairing damaged tissue, detecting mutated genes, or detecting high hormone levels indicative of certain malignancies. It is capable of triggering immediate responses to inflamed, ischemic, or neoplastic tissues and simultaneously provides therapy. Surprisingly, a silicon based nano-channel has already been developed to deliver antitumor agents locally with zero order kinetics. Thus, further studies are essential to evaluate their efficacy over time when encapsulated and stored. The smart SLNs as the new generation offer much more flexibility in drug loading, modulation of release and improved performance in producing final dosage forms such as creams, tablets, capsules and injectable. In addition, research must continue in such a direction to provide improved efficacy, drug loading, targeting and lowering of the drug dose, thereby overcoming the toxicity challenges of this carrier system. Structure and dynamics of SLNs on the molecular level, both *in-vitro* and *in-vivo*, stability, targeting, toxicity and aspects related to interactions of SLNs with their biological surrounding pose a challenge that should be explored in the near future by various research groups around the globe.

CONCLUSION

SLN as colloidal drug carrier combines the advantage of polymeric nanoparticles, fat emulsions

and liposome; due to various advantages, including feasibility of incorporation of lipophilic and hydrophilic drugs, improved physical stability, low cost, ease of scale-up and manufacturing. SLNs are prepared by various advanced techniques. The site specific and sustained release effect of drug can better achieved by using SLNs. Nanoparticles have been used extensively for applications in drug discovery, drug delivery and diagnostics, and for many other applications in medical field. They are relatively novel drug delivery systems, having received primary attention from the last decade of 20th century and future holds great promise for its systematic investigation and exploitation.

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