WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 3, 352-370. Review Article ISSN 2277– 7105

SOLID LIPID NANOPARTICLES AS NOVEL DRUG DELIVERY SYSTEM: AN OVERVIEW

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Article Received on
16 Dec 2014,

Revised on 10 Jan 2015,
Accepted on 04 Feb 2015

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ABSTRACT

Solid lipid nanoparticles are at the vanguard of the rapidly growing field of nanotechnology with numerous prospective applications in drug delivery, clinical research, Biotechnology, Cosmetology and in addition to other diverse sciences. Solid lipid nanoparticle offers great advantages over a traditional drug delivery system. A solid lipid nanoparticle (SLN) is a typically colloidal spherical with an average diameter between 10 to 1000 nm. Solid lipid nanoparticles hold a solid lipid core matrix that can solubilize lipophilic molecules as well as hydrophilic drugs. The lipid core of SLNs is stabilized by the surfactants (emulsifiers). Due to their inimitable size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The potential to incorporate drugs into nanocarriers offers a new archetype in drug delivery that could hold an immense promise in accomplishing the bioavailability enhancement accompanied by controlled and site specific drug delivery. Solid lipid nanoparticles offers enhance bioavailability by improving drug dissolution and permeability across intestinal cell wall by incorporation of drug in solid lipid nanoparticle .This review presents a discussion on the introduction, advantages, disadvantages, Nano structured lipid carrier, lipid drug conjugate, production procedures, Principle of drug release from SLN, pharmaceutical applications, characterization studies, and evaluation of SLNs.

KEYWORDS: Solid lipid nanoparticles, NLC, LDC, nanocarriers, production techniques.

INTRODUCTION

For decades, various pharmaceutical dosage forms such as tablets, capsules, liquids, suppositories, creams, ointments, injections, aerosols, etc. have been used as drug delivery systems for treatments of acute and chronic diseases. Colloidal drug delivery systems namely oil-in-water emulsions, liposome's, micelles, microparticles and nanoparticles opened a new area for targeting drugs and pharmaceuticals. Nanoparticles are solid colloidal particles in which the active principles are dissolved, entrapped, and/or to which the active principle is adsorbed or attached. Nanoparticles offer several advantages in drug delivery owing to their small particle size, large surface area and the capability of changing their surface properties. In general, nanoparticles can be used to target the delivery of drugs, to sustain its effect, to improve bioavailability, to solubilize it for intravascular delivery and to improve its stability against enzymatic degradation. Based on the type of the inactive ingredient used, there are four classes of nanoparticles: Lipid based nanoparticles, polymeric nanoparticles, metal based nanoparticles and biological nanoparticles.

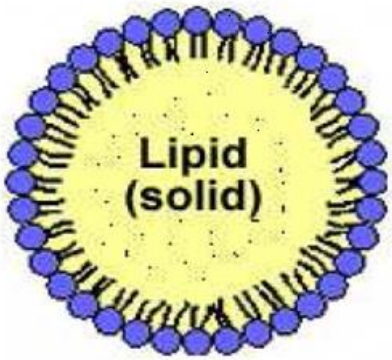

Fig.1 Structure of Solid Lipid Nanoparticles (SLN)

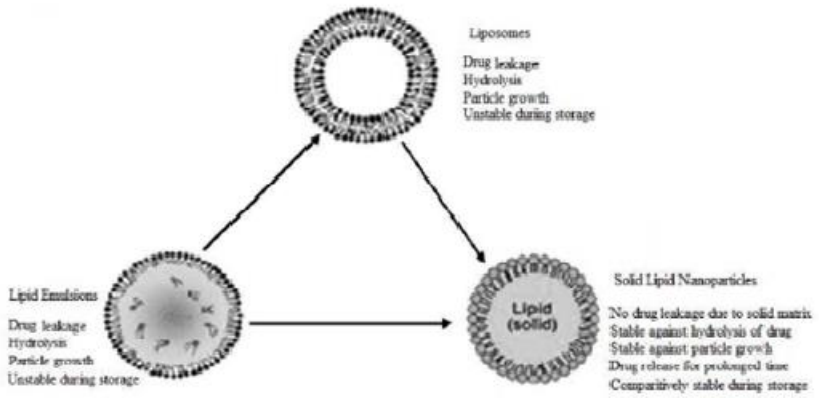

Fig. 2 diagrammatic representation on SLN over emulsions and liposome's advantages of SLN

Solid lipid nanoparticles (SLNs) have been used as an alternative drug delivery system to colloidal drug delivery systems namely oil-in-water emulsions, liposome's, microparticles and polymeric nanoparticles. They consist of spherical lipid particles in nanometre size range. SLNs are used for the controlled and targeted delivery of drugs and for the incorporation of hydrophilic and lipophilic drugs. SLNs are made up of solid lipids, emulsifier and/or co-emulsifier and water. A typical solid lipid that is used in such delivery systems melts at temperatures exceeding body temperature (37°C). Examples of some of the lipids that have been investigated are fatty acids, steroids, waxes, triglycerides, acylglycerols and their combinations. All classes of emulsifiers, either by itself or in combination have been utilized to stabilize the lipid dispersion. Examples of some of the emulsifiers that have been investigated are lecithin, bile salts such as sodium taurocholate, non-ionic emulsifiers such as ethylene oxide/propylene oxide copolymers, sorbitan esters, fatty acid ethoxylates, and their combinations. Deionized water is used as a dispersion medium.

Solid lipid nanoparticles (SLN) are a new pharmaceutical delivery system or pharmaceutical formulation. These are made of solid lipids which remain solid at room temperature. Advantages of SLN are the use of physiological lipids, the avoidance of organic solvents, a potential wide application spectrum (dermal, per os, intravenous) and the high pressure homogenization as an established production method. Additionally, improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light) and even controlled release characteristics were claimed by incorporation of poorly water soluble drugs in the solid lipid matrix. SLNs do not show biotoxicity as they are prepared from physiological lipids.[1,2]

ADVANTAGES OF SLN'S

SLNs offer many benefits in comparison to other colloidal carriers which include:

1. Improved solubility and bioavailability of lipophilic drugs.
2. Provide long-term stability against environmental degradation.
3. Surface modification can be easily done.
4. Controlled release of active drug through lipid matrix.
5. Excellent biocompatibility of excipients used for SLNs.
6. Much easier to manufacture than biopolymeric nanoparticles

7. Topical treatment of skin diseases with SLNs has the advantage that high drug levels can be achieved at the site of disease and systemic side effects can be reduced compared to oral or parenteral drug administration.
8. High drug payload.
9. SLN formulation can remain stable for even the years.
10. SLNs having the particle size range of 120-200nm are not taken up readily by the cells of the RES and thereby bypass liver and spleen filtration.
11. Excellent reproducibility by use of cost effective high pressure homogenization method as a method of preparation.
12. The feasibility of incorporating both hydrophilic and hydrophobic drugs.
13. The incorporated active ingredients/ drugs can be protected against chemical degradation in solid matrix of SLN. The carrier lipids are biodegradable and hence safe.
14. The use of organic solvents is avoided.
15. Large scale production and sterilization is possible.[3]

ADVANTAGES OF SLNS OVER MICROPARTICLES

1. Smallest blood capillaries in body are approximately 5-6 μm and hence particles should be less than 5 μm in the blood stream without forming aggregates to minimize embolism. Therefore SLNs are better suited for I.V. delivery.
2. Size of the microparticles is a limitation to cross the intestinal lumen into lymphatic system following oral delivery of vaccines, peptides, and other bio macromolecules. Microparticles remain in Payer's patches while SLNs are disseminated systematically.

ADVANTAGES OF SLNS OVER LIPOSOMES

1. Avoidance of organic solvents when desired.
2. Excellent reproducibility and feasible large scale production.
3. Unique ability to create controlled release and drug targeting by coating/attaching ligands to SLNs.
4. Increased product stability of about 1 year.[4]

ADVANTAGES OF SLNS OVER POLYMERIC NANOPARTICLES

1. Lipids are biodegradable and hence have better biocompatibility
2. Avoidance of organic solvents when desired
3. Feasibility of large scale production and sterilization

4. Excellent reproducibility with cost effective high pressure homogenization method as the preparation method
5. Increased stability of the active ingredient

DISADVANTAGES OF SLN'S

Some problems reported with SLNs are

1. Particle growth and crystallization of drugs.
2. Unpredictable gelatine tendency.
3. Unexpected dynamics of lipid transitions.
4. Drug loading capacity may be limited in some cases.
5. Drug expulsion from lipids.
6. High pressure induced drug degradation.
7. Water content of dispersion is relatively high.

NANOSTRUCTURED LIPID CARRIER

A new generation of NLCs consisting of a lipid matrix with a special nanostructure has been developed. This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%.Carrier system. However, the NLC system minimizes or avoids some potential problems associated with SLN.

1. Payload for a number of drugs too low
2. Drug expulsion during storage of Formulation
3. High water content of formulated SLN dispersions.

The NLC are produced successfully by the high pressure homogenization method and it is possible to obtain particle dispersions with a solid content of 50 or 60%. The particle dispersions thus produced have a high consistency with a cream-like or almost solid appearance. NLC were introduced to overcome the potential difficulties with SLNs. The goal to develop NLC was to increase the drug loading and to prevent drug expulsion. This could be seen in three ways. In the first model, spatially different lipids composed of different fatty acids are mixed which leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal. The highest drug load could be achieved and maintained by mixing solid lipids with small amounts of liquid lipids (oils) which is called imperfect type NLC. Drugs which shows higher solubility in oils than in solid lipids can be

dissolved in the oil and yet be protected from degradation by the surrounding solid lipids which is called as multiple types NLC, and are analogous to w/o/w emulsions since it is an oil-insolid lipid-in-water dispersion. Because of their properties and advantages, NLC may find extensive application in topical drug delivery, oral and parenteral administration of cosmetic and pharmaceutical actives. The NLCs have been investigated in the topical and dermatological preparations, in the delivery of clotrimazole, ketoconazole and other antifungal imidazoles. The NLCs were also prepared to investigate whether the duration of brain targeting and accumulation of drugs in the brain can be enhanced by intravenous delivery. Apomorphine as a model drug has been targeted, through certain vessels, to selected brain regions by in vivo real-time bioluminescence imaging of the rat brain.

Lipid drug conjugates (LDC): LDC nanoparticles can be termed as a special form of nanoparticles consisting of 100% LDC or a mixture of LDC with suitable lipids. Only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix. In order to overcome this problem, the so called LDC nanoparticles with improved drug loading capacities have been developed. An insoluble drug-lipid conjugate bulk is first prepared either by covalent linking or by salt formation. The obtained LDC is then processed with an aqueous surfactant solution to a nanoparticle formulation using high pressure homogenization technique. Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections.

Method of preparation

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below.

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 fabrication 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 at a 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 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 therefore 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.

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 modificationsand/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.

Advantages

1. Low capital cost.
2. Customary at lab scale.

Disadvantages

1. Energy intensive process.
2. Polydisperse distributions.
3. Unproven scalability.

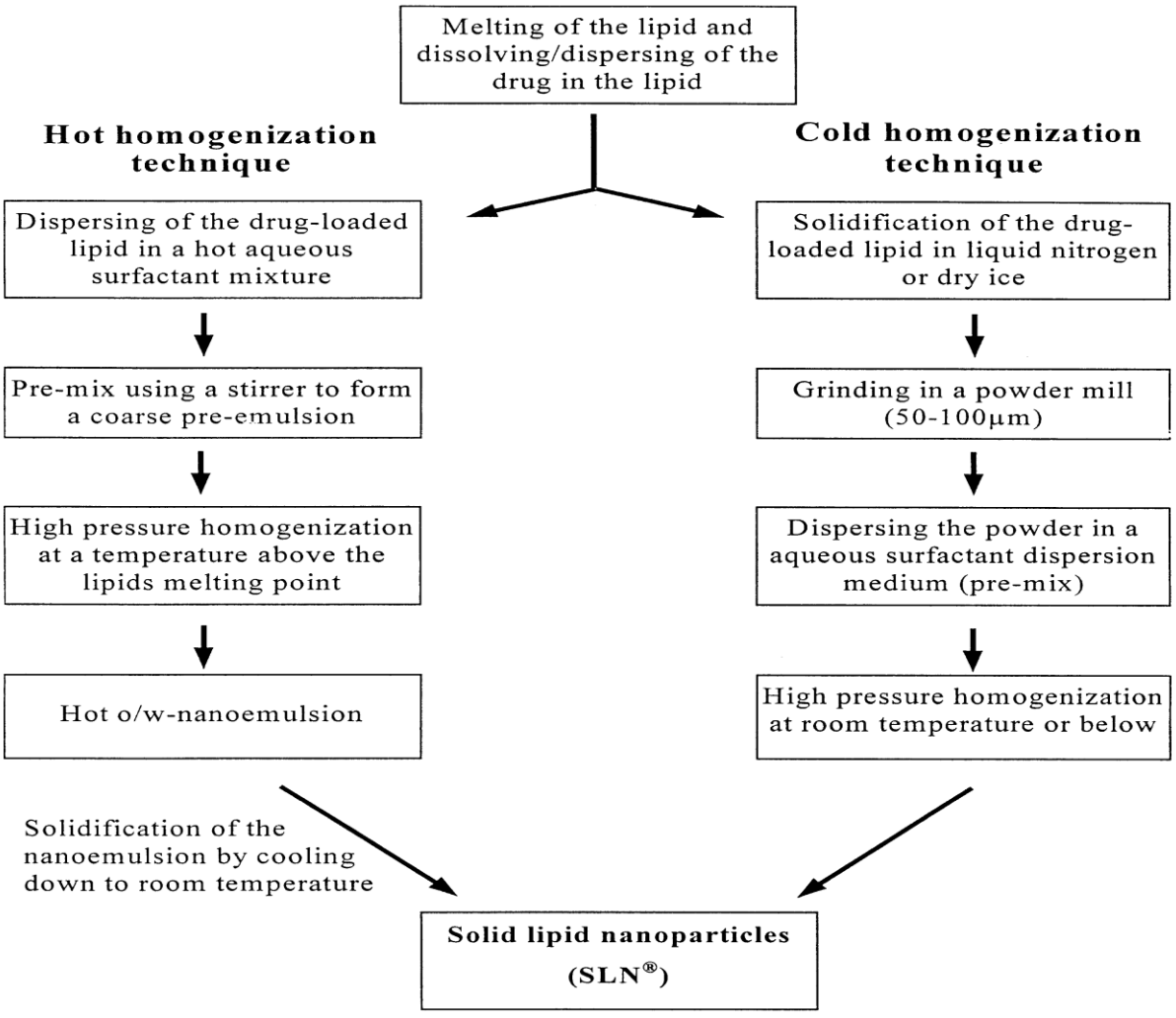

Fig.3 Schematic procedure of hot and cold homogenization techniques for SLN production

2. Ultrasonication / high speed homogenization

SLNs are also prepared by ultrasonication or high speed homogenization techniques. To achievesmaller particle size, combination of both ultrasonication and high speed homogenization is required.

Advantages

1. Reduced shear stress.

Disadvantages

1. Potential metal contamination.
2. Physical instability like particle growth upon storage.

3. Solvent evaporation

SLNs can be 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

1. Scalable.
2. Mature technology.
3. Continuous process.
4. Commercially demonstrated.

Disadvantages

1. Extremely energy intensive process.
2. Polydisperse distributions.
3. Biomolecule damage.

4. Solvent emulsification-diffusion method

SLNs can also be produced by solvent emulsification-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in anaqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium.

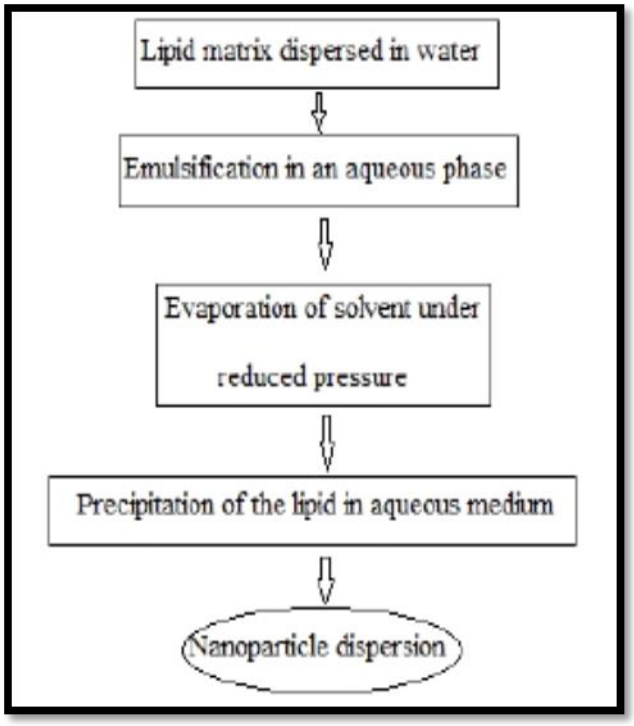

Fig.4 Systematic representation for emulsification-diffusion method

5. Supercritical fluid method

This is a novel technique recently applied for the production of SLNs. A fluid is termed supercritical when its pressure and temperature exceed their respective critical value. The ability of the fluid to dissolve compounds increases. This technology comprises of several processes for nanoparticle production such as rapid expansion of supercritical solution (RESS), Particles from gas saturated solution (PGSS), aerosol solvent extraction solvent (ASES), supercritical fluid extraction of emulsions (SFEE). The advantages of this technique includes avoidance of the use of solvents, particles obtained as a dry powder, instead of suspensions, requires mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method.

Advantages

1. Avoid the use of solvents.
2. Particles are obtained as a dry powder, instead of suspensions.
3. Mild pressure and temperature conditions.
4. 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. 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.

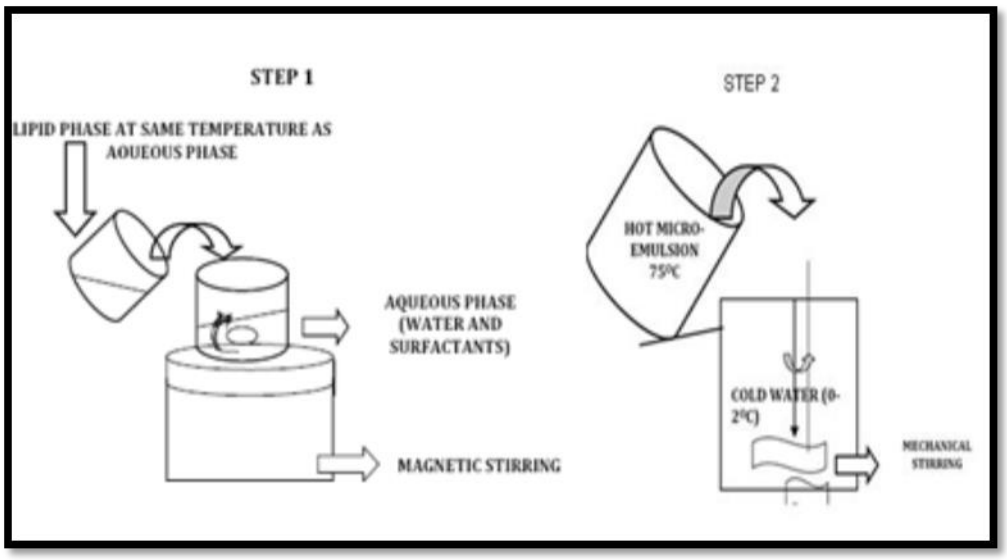

Fig.5 Microemulsion method

Advantages

1. Low mechanical energy input.
2. Theoretical stability.

Disadvantages

1. Extremely sensitive to change.
2. Labor intensive formulation work.
3. Low nanoparticle concentrations.

7. Spray drying method

It is an alternative technique to the lyophilisation 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.

Table: 1 Example of various drugs encapsulated in SLN[8]

Drug	lipid	Surfactant
Paclitaxel	Emulsifing wax	Polyoxyl 20 stearyl stearate
Camtothecin	Stearic acid	Pluronic F68
Idarubicin	Stearic acid	Epicuron 200
Etoposide	Tripalmitin	Soya phospatidyl choline
Tobramycin	Stearic acid	Epicuron 200
Lovastatin	Dynasan 114,dynasan 116	Epicuron 200,poloxamer 118
Miconazole	Campritol 888 ATO	Tween 80

Tab: 2 Advantages And Drawbacks Of Existing Sln Formulation Techniques[6]

SR.NO	TECHNIQUE	ADVANTAGES	DRAWBACKS
1	Micro emulsion precursors technique	Low mechanical energy ,input ,theoretical stability	Extremely sensitive to change, labour intensive formulation process
2	Contact ultra sonication	Reduced shear stress, effective at lab scale	High metal contamination potential, energy intensive process, unproven scalability.
3	High pressure homogenization	Scalable, well developed technology, continues operation.	Extremely energy intensive process, poly-dispersed distribution, biomolecule damage.
4	Hot homogenization technique	Applicable to lipopholic and insoluble drug, exposure time to high temperature is short.	Low entrapment efficiency for hydrophilic drugs
5	Cold homogenization technique	Best for thermolabile, thermosensitive and hydrophilic drugs	Exposure to heat can not be completely avoided.
6	Solvent evaporation technique	No dilution solidification step, monodispersed distribution	Residual organic solvent.

Principles of drug release from SLN

Drug release is affected by particle size, where tiny particles have larger surface area,therefore, the majority of the drug associated would be at or close to the particle surface, leading to quick drug release. Whereas, larger particles have bulky cores which permit moredrug to be encapsulated and gradually diffuse out. It is a challenge to formulate nanoparticles with the smallest size possible and with maximum stability. The common ideology of drug release from lipid nanoparticles is as follows.

There is an opposite association between drug release and the partition coefficient of the drug.

Larger surface area due to smaller particle size in nanometric range gives high drug release. When the drug is homogenously dispersed in the lipid matrix, slower drug release can be achieved. It depends on type of drug entrapment model of SLN.

Higher surface area due to smaller particle size in nanometer range gives higher drug release. Slow drug release can be achieved when the drug is homogenously dispersed in the lipid matrix. It depends on type and drug entrapment model of SLN.

Crystallisation behaviour of the lipid carrier and high mobility of the drug lead to fast drug release. There is an inverse relationship between crystallization degree and mobility of drug. Rapid initial drug release exists in the first few minutes in the drug-enriched shell model as a result of the outer layer of the particles due to the bigger surface area of drug deposition on the particle surface. Fast initial drug release (burst effect) exists in the first 5 minutes in the drug-enriched shell model (i.e. about 100% within <5 min) as a result of the outer layer of the particles due to the large surface area of drug deposition on the particle surface. The burst release is reduced with increasing particle size and prolonged release could be obtained when the particles were sufficiently large, i.e. lipid microparticles. The type of surfactant and its concentration, which will interact with the outer shell and affect its structure, should be noted as the other important factor, because a low surfactant concentration leads to a minimal burst and prolonged drug release. In the drug-enriched core model, the drug release is membrane controlled and is governed by the Fick law diffusion since the lipid surrounds the drug as a membrane. The type of surfactant and its concentration, which will interact with the outer shell and affect its structure, should be noted as the other important factor, because a low surfactant concentration leads to a minimal burst and prolonged drug release. The praziquantal loaded hydrogenated castor oil SLNs were formulated to enhance the bioavailability and prolong the systemic circulation of the drug.

In vitro release of praziquantal loaded hydrogenated castor oil SLNs exhibited an initial burst release followed by a sustained release. In the case of the new generation SLN, the lipid content of the particles dissolves the drug and combines controlled release character with high drug loading capacity. The particle dimension that affects drug release rate directly depends on a variety of parameters such as composition of SLN formulation such as surfactant/surfactant mixture, amount of drug incorporated, structural properties of lipid and drug, production methods and conditions.

In the case of NLC – the new generation SLN – the oil content of the particles solves the drug and combines controlled release characteristics with high drug loading capacity. In the literature it is reported that the imperfect type and amorphous type of NLC, in particular, provide much more flexibility to achieve the desired prolonged release. The particle size that affects drug release rate directly depends on various parameters such as composition of SLN formulation (such as surfactant/surfactant mixture, amount of drug incorporated, structural properties of lipid and drug), production methods and conditions (such as time, production

temperature, equipment, sterilization and lyophilization). All those parameters have been extensively investigated and data have been reported in the literature for years.

VARIOUS CHARACTERIZATION METHODS

1. Drug incorporation and loading capacity

The crucial ingredients for SLNs contain lipids, and a single or a combination of emulsifiers. Depending on the lipid, emulsifier and the method of preparation the particle size, and the surfactant used for the preparation of SLNs is found to vary. Factors that influence the loading capacity of a drug in the lipid are:

1. Drug solubility in the melted lipid.
2. Miscibility of lipid melt and the drug melt.
3. Chemical and physical arrangement of solid lipid matrix.
4. Polymorphic condition of lipid material. The condition to obtain a adequate loading capacity is a sufficiently high solubility of the drug in the lipid melt. Usually, the solubility must be higher in the melted state than that essential in the solid state because the solubility reduces when the melt cools and might even be lesser in the solid lipid.

2. Determination of incorporated drug

It is of primary importance to determine the sum of drug incorporated in SLN, since it influences the release characteristics. The degree of encapsulation can be assessed ultimately by determining the quantity of drug remaining in supernatant after centrifugation of SLN suspension or otherwise by dissolution of the sediment in a suitable solvent and subsequent analysis. Standard analytical techniques such as spectrophotometry, high performance liquid chromatography, or liquid scintillation counting can be used to assay the drug.

3. Determination of particle size

Particle size and size distribution are the essential characteristics of nanoparticle systems. They decide the *in vivo* distribution, biological fate and the targeting capability of nanoparticle drug delivery systems. In addition, they can also control the drug loading, drug release and stability of nanoparticles.

4. Electron microscopy

Scanning electron microscopy and transmission electron microscopy offer a way to directly observe nanoparticles and physical characterization of nanoparticles. Transmission electron microscopy has a smaller size limit of detection. Currently, the fastest and most routine

method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. It was observed that SLNs, variations in size were greater and particle size also increased over time in all batches; this effect may have been caused by a probable expulsion of the drug due to the lipid's partial rearrangement

5. Dynamic Light Scattering (DLS)

DLS or quasi-elastic light scattering 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.

6. Entrapment efficiency

The entrapment efficiency of the drug is determined by measuring the concentration of free drug in the dispersion medium. Ultracentrifugation was carried out to analyse the sample. The SLNs along with encapsulated drug remain in the outer chamber and aqueous phase moves into the sample recovery chamber. The amount of the drug present in the aqueous phase is determined by HPLC or UV spectrophotometer.

7. Differential Scanning Calorimeter (DSC) and X-Ray Diffraction (XRD)

Among the large number of analytical techniques engaged for that purpose, DSC and XRD play important role because they are able to afford structural information on the dispersed particles. DSC and XRD are renowned typical techniques in the area of pharmaceutics and since data evaluation from these methods is usually straightforward. Most popular applications of DSC and XRD is identification of crystal structures, particle sizes and shapes as well as quantitative phase analysis and determination of crystallinity indices. Structural modifications of materials are accompanied by heat exchanges, e.g., uptake of heat during melting or emission of heat during crystallization. DSC is planned to measure these heat exchanges at some stage in controlled temperature programs and allows to draw conclusions on the structural properties of a sample. DSC and X ray neutron diffraction and scattering techniques are crucial tools for SLN characterization and offer many possibilitiesto gain information on the properties of the dispersed particles.[9]

8. Nuclear Magnetic Resonance (NMR) and Electron Spin Resonance (ESR)

NMR and ESR are dominant tools for investigating dynamic phenomena of nanocompartments in colloidal drug delivery systems. Due to the different chemical shifts it

is likely to feature the NMR signals to particular molecules or their segments. Simple NMR spectroscopy allows simple and rapid detection of supercooled melts due to the low line widths of the lipid protons. This technique is based on the different proton relaxation times in the liquid and solid state. Protons in the liquid state provide sharp signals with high signal amplitudes, while solid protons give weak and broad NMRsignals under these conditions. It also allows for the characterization of liquid nanocompartments in recently developed lipid particles, which are made from blends of solidand liquid lipids. ESR allows the straight, repeatable and non invasive characterization of the distribution of the spin probe among the aqueous and the lipid phase. Investigational results reveal that storage-induced crystallization of SLN leads to an exclusion of the probe out of the lipid into the aqueous phase.[10]

9. In-vitro drug release

The SLNs dispersion is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed alongside an appropriate dissolution medium at room temperature, the samples are withdrawn at suitable intervals from the dissolution medium, centrifuged and analyzed for drug content using a appropriate analytical method. This method however suffers from the disadvantage of a lack of direct dilution of the SLNs by the dissolution medium. Secondly, in reverse dialysis technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN dispersion. The direct dilution of the SLNs is attainable with this process; however the fast release cannot be quantified with this technique.

APPLICATION OF SLNS IN DRUG DELIVERY SYSTEM

1. SLNs are composed of physiological lipids and hence the pathways for lipid transportation and metabolism already present in the body determine the *in vivo* fate of the carrier. Enzyme lipases are most important for SLN degradation.
2. SLNs are stable for a long period of time and easy to scale up when compared to other colloidal systems and thus may be important for many modes of targeting.
3. Anticancer agents are usually delivered systemically. SLNs can be administered intravenously owing to their small size. They have been reported to be useful as drug carriers to treat tumors.
4. They provide a novel and a unique drug delivery system to prevent rapid clearance by the immune system. Stealth nanoparticles can be used to target specific tissues in accessible

cells. Fluorescent SLNs prepared using fluorescent markers and drugs have been successfully tested in animal models.

5. Tumor targeting has been reported with SLNs loaded with methotrexate and camptothecin. Longer circulation times have been reported to be achieved with paclitaxel.
6. SLNs can penetrate the BBB due to adsorption of blood proteins such as apolipoproteins on lipid nanoparticles surface which in turn may lead to interactions with endothelial cells that facilitate crossing the BBB. Such properties have been reported for the drugs such as tobramycin, doxorubicin and idarubicin.
7. SLN can be used in the formulation for delivery of gene vector. DNA degradation can be avoided and target specific delivery can be achieved by its incorporation in the SLN. Increase in the bioavailability and decrease in the dosing frequency has been reported to be achieved by incorporating antitubercular drugs such as rifampicin, isoniazid, and pyrazinamide in the SLNs.
8. SLNs have been used for topical application of various drugs as it gives potential advantage of delivering the drug directly to the site of action.
9. Research has been done for the incorporation of active ingredients such as anticancer drugs, imidazole, antifungals, DNA, flurbiprofen, Glucocorticoids,isotretinoin, triptolide, and Vitamin A into the SLNs.
10. SLNs are known to be suitable as carriers for UV-blockers due to their particulate character and adhesive properties. SLNs aid in achieving better localization, occlusiveness, controlled release and increased skin hydration in topical formulations.[7]

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