WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 11, 603-623. Review Article ISSN 2277– 7105

A CRITICAL REVIEW ON DIFFERENT METHODS OF PREPARATION OF SOLID LIPID NANOPARTICLES AND ITS CHARACTERIZATION

Baskar B.*, Dr. Selvaraju K., Karthikaa T., Sridevi M., Dr. Padma Preetha J., Nithish K.

*Department of Pharmaceutics, KMCH College of Pharmacy, Kalapatti Road, Coimbatore-48, Tamil Nadu, India (The Tamil Nadu Dr. M.G.R. Medical University).

Article Received on
14 August 2019,
Revised on 04 Sept. 2019,
Accepted on 24 Sept. 2019,
DOI: 10.20959/wjpr201911-15961

***Corresponding Author**
Baskar B.
Department of Pharmaceutics, KMCH College of Pharmacy, Kalapatti Road, Coimbatore-48, Tamil Nadu, India (The Tamil Nadu Dr. M.G.R. Medical University).

ABSTRACT

Solid lipid Nanoparticles (SLN) have emerged as a replacement drug delivery system with several applications within the field of pharmaceuticals, cosmetics, research, clinical drugs and different allied sciences. This review gives an overview about the potential advantages and the disadvantages of solid lipid nanoparticles, and the different methods involved in the preparation. SLN comprises the solid and lipid materials which were incorporated and by producing them as a Nanoparticle it is widely used in many of the disease conditions nowadays. The review comprises an overview on drug incorporation models, method of preparation, secondary production steps, characterization, and application. Different production strategies that area unit appropriate for big scale production and applications of solid macromolecule nanoparticles area unit delineated. There is a large analytical techniques for characterization of solid macromolecule nanoparticles like Scanning electron microscopy, differential scanning calorimetry are highlighted. If fittingly investigated, solid macromolecule nanoparticles might open new vistas in medical aid of advanced diseases.

KEYWORDS: Solid lipid Nanoparticles; Drug release; Toxicity aspects; Preparation; Applications.

INTRODUCTION

Targeted drug delivery system is the most challenging research areas in pharmaceutical sciences. By producing colloidal delivery systems like liposomes, micelles and nanoparticles, new challenges have opened for improving drug delivery.[1]

Nanoparticles are the nano sized solid colloidal particles which usually ranges from 10 to 1000 nm (1.0μm), in which active drug or biologically active material are dissolved, entrapped, and/or to which the active principle is adsorbed or attached.[2]

In the last decade, lipids are one of the carriers that have suitable property for the delivery of drugs with poor water solubility. If any therapeutic agent is added into the lipid, therapeutic usefulness of drugs will be maximized. Nowadays, Lipid-based nanocarriers are an acceptable approach and have gained significance in the current era because of their various prominent properties, such as low toxicity, improved bioavailability, high biocompatibility, high drug-loading efficiency, and high protection from degradation in the gastro intestinal tract. Various lipids used for the preparation of lipid nanocarriers are those which are biodegradable and showing biocompatibility in physiological media or biological fluid.[3]

To overcome the limitations of polymeric nanoparticles, lipids are incorporated as a carrier, especially for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting the wide attention of formulators worldwide.[4]

It is the new generation of submicron-sized lipid emulsions in which the liquid lipid has been replaced by a solid lipid. SLN gives a properties like small size, large surface area, high drug loading capacity, interaction of phases at the interfaces, and they are attractive for their potential to improve the performance of pharmaceuticals, nutraceuticals and other materials.[5]

Various Drug Delivery System developed using Nanotechnology principles including Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals.[6]

The Solid Lipid Nanoparticle is most widely used nowadays which has different method of preparation and their advantages and disadvantages were discussed in this particular review.

Classification of Nanoparticles

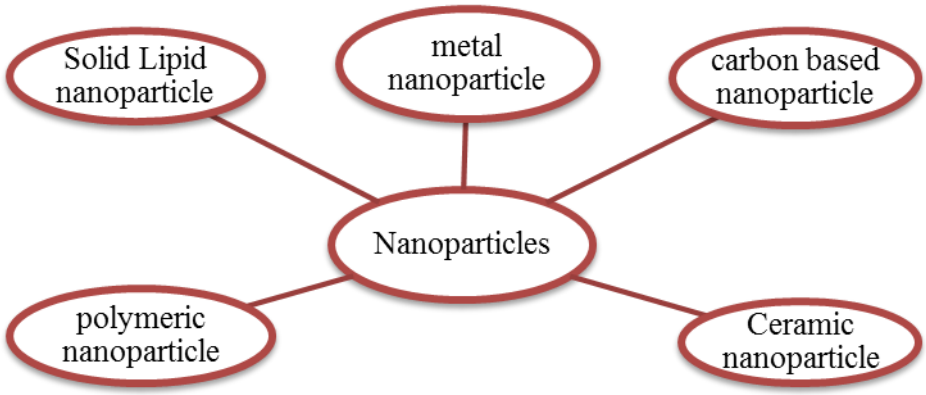


Fig 1: Classification of Nanoparticles.

SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles were discovered by **Gasco and Muller in 1991** it represent an alternative carrier system to tradition colloidal carriers.[7] Lipids have been used as an alternative carrier for polymeric nanoparticles, particularly for lipophilic pharmaceuticals and lipid nanoparticles are known as solid lipid nanoparticles (SLNs).[8] The system consists of spherical solid lipid particles in the ranges of nanometer it is dispersed in water or in aqueous surfactant solution. It is identical for oil-in-water type emulsion for parenteral nutrition but the liquid lipid of the emulsion has been substituted by a solid lipid, which yields a Solid Lipid Nanoparticles.[9] SLNs are colloidal particles derived from oil-in-water emulsions by replacing liquid lipids with a lipid matrix that is solid at body temperature and stabilized by the use of surfactants. SLN are prepared by a combination of lipids, fatty alcohol, wax, triglycerides and surfactants.[10]

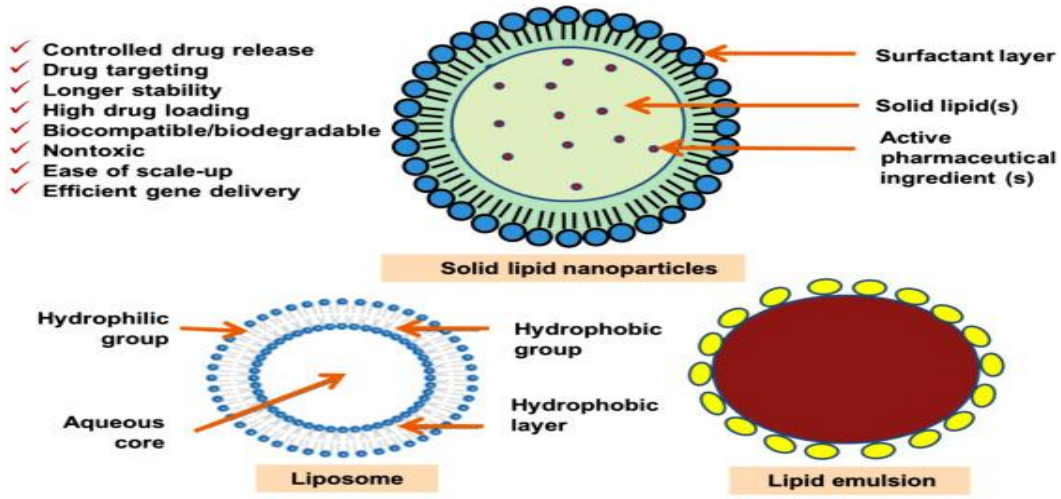


Fig 2: Structure of Solid Lipid Nanoparticles.

Advantages of SLNs[11-13]

The advantages of SLNs including the following such as:

- SLNs can be enhancing the bioavailability of entrapped bioactive.
- Better control over release kinetics of encapsulated compound.
- Drug stability of SLNs for three years has been developed. This is of more importance compared to the other colloidal carrier systems.
- SLNs particularly those in the range of 120 -200 nm are not taken up readily by the cells present in the RES and thus bypass liver and spleen filtration.
- The feasibility of incorporating both hydrophilic and hydrophobic drugs.
- The carrier lipids are biodegradable and safe.
- Avoidance of organic solvents.
- Feasible for large scale production and sterilization.
- In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
- It is easy scale up and excellent biocompatibility.
- Enhanced bioavailability of entrapped bioactive compounds.
- Controlled and targeted release of the incorporated drug can be achieved.
- Increased scope of drug targeting can be achieved by coating with or attaching ligands to SLNs.
- Excellent reproducibility with use of different methods as the preparation procedure.

Disadvantages of SLNs[11-13]

- Relatively high water content of the dispersions (70-99.9%).
- Poor drug loading capacity.
- Drug expulsion after polymeric transition during storage.
- The low capacity to load water soluble drugs due to partitioning effects during production process.
- Particle-particle aggregation due to small size and large surface area.
- Difficult in physical handling.
- Limited drug loading and burst release.

SOLID LIPID NANOPARTICLE COMPOSITION

Table 1: List of excipients used in SLN preparation.

Lipids	Surfactants and Co surfactants
Triglycerols Trilaurin Trimyristin Tripalmitin, Tristearin Tricaprin	**Phospholipids** Soy lecithin Egg lecithin Phosphatidylcholine
Acylglycerols Glycerol monostearate Glycerol palmitostearate Glycerol behenate	**Ethylene oxide/propylene oxide copolymers** Poloxamer 188 Poloxamer 182 Poloxamer 407 Poloxamer 908
Fatty acids Stearic acid Palmitic acid Decanoic acid Behenic acid	**Sarbitan ethylene oxide/propylene oxide copolymers** Polysorbate 20 Polysorbate 60 Polysorbate 80
Waxes Cetyl palmitate	**Alkylaryl polyether alcohol polymers** Tyloxapol
Cyclic complexes Cyclodextrin	**Bile salts:** Sodium cholate Sodium taurocholate Sodium glycocholate Sodium taurodeoxycholate Taurocholic acid sodium salt
Hard fat types Witepsol W 35 Witepsol H 35	**Alcohols** Ethanol Butanol

DRUG RELEASE OF SOLID LIPID NANOPARTICLES[14]

The types of SLNs depend on the chemical nature of the active ingredient and lipid, the solubility of actives in the melted lipid, nature and concentration of surfactants, type of production and the production temperature. Therefore 3 incorporation models have been proposed for study.

Type I or homogenous matrix model

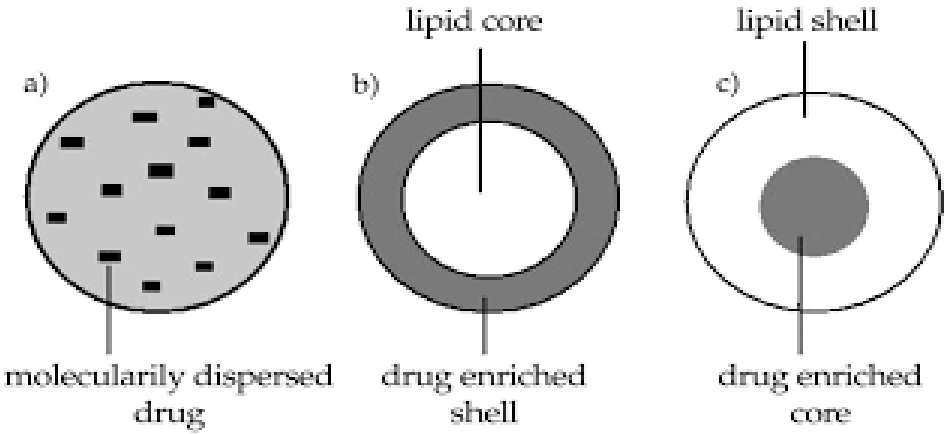
The SLN Type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLN are produced by the cold homogenation method. A lipid blend containing the active material in a molecularly dispersed form is produced. After solidification of this blend, it is ground in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

Type II or drug enriched shell model

It is achieved when SLN are produced by the hot technique, and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w Nano-emulsion the lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The particle enrichment in the outer area which causes burst release. The percentage of active ingredient in the outer shell is adjusted in a manner of controlled shell model is the incorporation of coenzyme.

Type III or drug enriched core model

Core model can be produced while the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. In most conditions cooling down of the hot oil droplets will reduce the solubility of the active in the melt. Active molecules precipitate leading to the formation of a drug enriched core when the saturation solubility exceeds.



TOXICITY ASPECTS OF SOLID LIPID NANOPARTICLES

Materials used in drug delivery systems should be biocompatible and assessment of biocompatibility is an obligatory viewpoint to address. The toxicity of a formulation must be resolved by the *in-vivo* studies, an assortment of *In-vitro* toxicological assays, performed in selected cell lines, produce helpful data. These tests are broadly acknowledged as first markers of toxicity.[15]

Cytotoxicity of SLNs

Assurance of cell toxicity or cell viability are the regular test for the confirmation of biocompatibility or toxicity. SLN prepared using glyceryl monostearate are tested for their cytotoxicity. *In-vitro* test performed on monkey kidney epithelial cells (VERO) and acute

lymphoblastic leukemia cells (L1210) using MTT assay. The 50% inhibitory concentration (IC50) of SLN was found to be 0.7 and 0.4 mg/mL in VERO cells and 0.5 and 0.3 mg/mL in L1210 cells, after 24 and 48 h of incubation, respectively.[16] In another study SLNs prepared using Softisan® 154 and soy lecithin by high-pressure homogenization technique were tested on MCF-7 and MDA-MB231 for the toxicity. The IC50 values reported in this study for MCF-7 cells were found to be approximately 0.28, 0.26, 0.22 mg/mL after 24, 48 and 72 h, respectively. Similarly, IC50 values observed for MDAMB-231 cells were found to be about 0.29, 0.29, 0.27 mg/mL after 24, 48, and 72 h, respectively.[17] It can be concluded that the lipid used to prepare nanoparticle has significant effect on the cytotoxicity of obtained SLNs.

Impact of Surface Charge

The interaction between the colloidal nanoparticles and cells depend on the surface charge of the particles. Cationic surfactants used in SLNs can create deformities in membrane integrity[18] and sensitize the immune system.[19]

Effect of Composition on Cell Viability

Identification of the surfactants used for SLNs, not only in terms of biocompatibility but also for the stability or shelf life, is something very important for the SLNs system. Pluronic ® F-68 and Tween80 were used in topical, oral liquid, and semisolid dosage forms. Assessment of both surfactants (Pluronic ® F-68 and Tween 80) for cell viability incorporated in SLNs was made. Pluronic ® F-68 in SLNs has shown good stability and 90% cell viability, whereas Tween 80 in SLNs with same lipid composition has shown better stability but with 50%cell viability.[20] The nature of surfactant used in SLNs and duration of contact time of SLNs with cells will influences the cell viability percentage.

Genotoxicity

Several studies showed that SLN does not produce damage to DNA or gene related toxicity. Dolatabadi et al. and Bhushan et al. investigated SLN with negative charge by incubating with A549 cells, and found that these did not produce any toxicity or harm to genome DNA determined by gel electrophoresis.[21,22] However, a report showed DNA damage by acetyl shikonin-bearing SLN, which instigated an increase in comet development in A549 cells. SLN-encapsulated drug further increased the DNA damage.[23]

Hemolytic Toxicity

Hemolysis examination was usually performed to evaluate the extent of red blood cell destruction caused by i.v. injection of foreign material.[24] Lakkadwala et al. evaluated SLNs consisting of glycerolmonostearate and polysorbate 80 for their hemotoxicity, and the result showed low hemotoxicity of SLN even at high dose (1mg/mL). Hyaluronic acid coated SLN bearing antineoplastic drug also demonstrated low hemolytic toxicity, regardless of whether the formulation displayed a cationic surface or an anioinic surface.[25] Another cationic SLN bearing doxorubicin was found to be non-hemolytic. This impact was additionally articulated when SLNs were covered with galactose.[26]

PREPARATION OF SOLID LIPID NANOPARTICLES

The performance of SLNs greatly depends on the method of preparation which in turn influences the particle size, drug loading capacity, drug release, drug stability etc. Different approaches exist for the production of finely dispersed lipid nanoparticle dispersions.[27]

Methods of preparation[28]

- High pressure homogenization

a) Hot homogenization.

b) Cold homogenization.

- Ultrasonication/high speed homogenization

a) Probe ultrasonication.

b) Bath ultrasonication.

- Solvent evaporation method.
- Solvent emulsification-evaporation method.
- Supercritical fluid method.
- Microemulsion based method.
- Spray drying method.
- Double emulsion method.
- Precipitation technique.
- Film-ultrasound dispersion.

High pressure homogenization: It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizer push a liquid with high pressure (1002000 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 1000km/h).Very high shear stress and cavitation forces disrupte the particles down to the sub-micron range.

Hot homogenization: Hot homogenization is carried out at temperatures above the melting point of the lipid thus produces homogenised emulsion. A pre emulsion that contains drug loaded lipid melt and the aqueous emulsifier phase is obtained by high-shear mixing device. High pressure homogenization of the pre-emulsion is carried out at temperatures above the melting point of the lipid. Due to the decreased viscosity of inner phase and high temperature result in lower particle size. At high temperatures degradation rate of the drug and the carrier is increased. 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 hot homogenization technique can be used for lipophilic and insoluble drugs. This technique is not suitable for incorporation of hydrophilic drugs into SLNs because higher portion of drugs in water during homogenization results in low entrapment efficiency.

Cold homogenization: Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts.

Table 2: Difference between hot homogenization and cold homogenization technique.

Steps	Hot Homogenization Technique	Cold Homogenization Technique
Step 1.	Melt lipid; dissolve or solubilize active ingredients in the lipid.	
Step 2.	Disperse melted lipid in hot aqueous surfactant solution.	Cooling and recrystallization of the active lipid mixture using liquid nitrogen or dry ice.
Step 3.	Preparation of a preemulsion by means of a rotor-stator homogenizer	Milling of the active lipid mixture by means of a ball mill or a jet mill.
Step 4.	High-pressure homogenization above the melting point of the lipid.	Disperse lipid microparticles in cold aqueous surfactant solution
Step 5.	Cooling and recrystallization	High-pressure homogenization at or below room temperature.

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.

Solvent evaporation method: The lipophilic material is dissolved in a water-immiscible organic solvent (e.g cyclo hexane) 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 25nm mean size. Hence the solution was emulsified in aqueous phase using high pressure homogenization. Finally the organic solvent of the emulsion was removed by evaporation under reduced pressure.

Solvent emulsification-diffusion technique[30] The particles with average diameters of 30-100nm can be obtained by this technique. In this technique, the solvent used must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. To ensure the thermodynamic equilibrium of the liquid such as solvent and water were mutually saturated. While the heating is needed to solubilize the lipid, the saturation step was performed at that temperature.

Then the lipid and drug were dissolved in water saturated solvent and this organic phase (internal phase) was emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) using mechanical stirrer. After the formation of o/w emulsion, water (dilution medium) in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. Here the both the phase were maintain at same elevated temperature and the diffusion step was performed either at room temperature or at the temperature under which the lipid was dissolved. Throughout the process constant stirring was maintained. Finally, the diffused solvent was eliminated by vacuum distillation or lyophilization.

SLN preparation by using supercritical fluid[31] This is a relatively new technique for SLN production and has the advantage of solvent-less processing. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions method. Carbon dioxide (99.99%) was selected as the solvent for this method.

Micro emulsion based method: This method is based on the dilution of microemulsions. As micro-emulsions are two-phase systems composed of an inner and outer phase (e.g. microemulsions). Microemulsion are produced by stirring an optically transparent mixture at 65-70°C, which 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 micro emulsion 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 facilitate rapid crystallization of lipid and prevent aggregation. Due to the dilution step achievable lipid contents are considerably lower compared with the HPH based formulations.

Spray drying method: It is an alternative technique to the lyophilization process. This indicates the use of lipid with melting point more than 70oC. The optimum results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol-water mixture.

Double emulsion method: To prepare the hydrophilic loaded SLNs a novel method based on solvent emulsification-evaporation were widely used. Hence the drug is encapsulated with suitable stabilizer to prevent drug partitioning into external water phase during solvent evaporation in the external water phase of w/o/w double emulsion.

Precipitation technique[32] Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the solution will be emulsified in an aqueous phase. After evaporating the organic solvent the lipid show precipitation forming nanoparticles.

Film-ultrasound dispersion: The lipid and the drug was put into organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution such as the emulsion was added. Finally by using the ultrasound with the probe to diffuser the SLN with small and uniform particle size is formed.

Solvent Injection technique[29] It is a new approach to prepare SLNs. This method of preparation the solid lipid was dissolved in water-miscible solvent (e.g. ethanol, acetone, isopropanol) or a water-miscible solvent mixture. Then this organic solvent mixture was slowly injected through an injection needle in to stirred aqueous phase with or without surfactant. The dispersion was filtered through a filter paper in order to remove excess lipid. The presence of surfactant within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize the formed SLNs until solvent diffusion was complete by reducing the surface tension.

Membrane contactor technique: The liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pores which forms the small droplets. SLNs

were formed by cooling the preparation at room temperature. Here both the aqueous and organic phases were placed in the thermostated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase More recently, a process known as nanotemplate engineering technology (NET) is developed in which "direct cooling" is utilized. The process consists of three steps.

- Melting a pharmaceutically acceptable matrix comprised of lipids, polymers.
- Adding pre-heated water with stirring to form the o/w microemulsion.
- Cooling to room temperature with stirring to generate the SLNs.

Secondary production steps[31,33]

Freeze drying: Lyophilization is a promising way to increase the chemical and physical stability over extended period of time. Lyophilization were choosen as a best method to achieve long term stability for a product containing hydrolysable drugs or a suitable product per oral administration. Hence transformation to solid state would prevent the Oswald ripening and avoid hydrolytic reactions.

In freeze drying of the product, all the lipid matrices were fully used to form a larger solid lipid nanoparticle with wider size distribution which is due to presence of aggregates between the particles. During the freeze drying process, the removal of water promote the aggregation of the solid lipid nanoparticles.

Sterilization: Sterilization of the nanoparticles must be desirable for parenteral administration and autoclaving to formulations containing heat-resistant drugs. Effects of sterilization on particle size have been investigated and it was found to cause a distinct increase in particle size.

Spray drying: Spray drying might be alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a dry product. This method used widely for SLN preparation, while spray drying is cheaper when compared to lyophilization. The lipids with melting point at temperature greater than 70^{o}C had been recommended for spray drying.

Characterization of SLN's[34,36,35,37]

Particle size analysis and Zeta potential: Many techniques are available for particle size analysis and zeta potential like scanning electron microscopy (SEM), atomic force

microscopy (AFM), scanning tunneling microscopy (STM) and photon correlation spectroscopy (PCS). To determine the particle size the best suitable methods are Photon correlation spectroscopy (PCS) and laser diffraction (LD). PCS is also known as dynamic light scattering which measures the fluctuation of the intensity of the scattered light, which is caused by particle movement.

Zeta potential: Zeta potential measurement can be carried out using zeta potential analyzer or zetameter. Zeta potential provides information about the magnitude of the electrostatic repulsion or attraction between particles in the aqueous suspension of SLN. Zeta potential can serve as an important parameter in the predictions for long term stability of the formulations. High values of zeta potential (e.g., more than +30mV or less than-30mV) can stabilize the colloidal suspension by electric repulsion, Electric repulsion generally results in less contact between the particles and less aggregation. For example colloidal systems that containing steric stabilizers which express good and long term stability when the zeta potential is as low as around 0mV.

Electron Microscopy: Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide way to directly observe nanoparticles. SEM is however better for morphological examination. TEM has a small size limit of detection. Transition electron microscopy and light microscopy both are based on same principle but one difference is that in light microscopy light is used instead of electron.

Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry (DSC) which is used to measures differences in the amount of heat required to increase the temperature of a sample compared to a reference. Differences in heat flow may be positive or negative and are presented as function of the temperature. During phase transition there were differences in the samples when compared to the reference. The rate of crystallinity is estimated using DSC by comparing the melting enthalpy/g of the bulk material with the melting enthalpy/g of the dispersion.

X-ray diffraction: A useful technique to exclude aggregate of more than 1μm and substantial polymorphic β1 transition form to stable; thus help in characterizing the crystalline nature of the compound and determine the polymorphic shifts present. X-ray diffraction (XRD) play a prominent role because they are able to provide structural information on the dispersed particles.

Entrapment efficiency: By measuring the concentration of free drug in the dispersion medium the entrapment efficiency of the drug is determined. Ultracentrifugation carried out using the Centrisart, that consist of filter membrane (molecular weight cutoff 20,000Da) at the base of the sample recovery chamber. The SLNs along with encapsulated drug remain in the outer chamber and aqueous phase moves into the sample recovery chamber. The HPLC or UV spectrophotometer method was used to measure the amount of the drug present in the aqueous phase.

Static light scattering (SLS)/Fraunhofer diffraction[38] In this method the pattern of light scattered from a solution of particles is collected and fit to fundamental electromagnetic equations in size is the primary variable. This method is fast but it requires advanced knowledge of particles optical qualities and more cleanliness than DLS.

Nuclear magnetic resonance (NMR): The size and the qualitative nature of nanoparticle can be determine by NMR. The selectivity provided by the chemical shift complements the sensitivity to molecular mobility to provide information on the physicochemical status of components within the nanoparticle.

Dynamic light scattering (DLS): DLS also known as PCS records the variation in the intensity of the scattered light on the microsecond time scale. The variation results from interference of light scattered by individual particles under the influence of Brownian motion and quantified by completion of an auto correlation function. The advantage of the method are the lack of required calibration, sensitivity to submicrometer particles and speed of analysis.

Atomic force microscopy (AFM)[38] In this method, a probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on the forces at play between the tip and the surface. The probe can be dragged across the sample (contact mode), or allowed to hover just above (noncontact mode), with the exact nature of the particular force employed serving to distinguish among the sub techniques. From this approach, ultra-high resolution is obtainable which has ability to map a sample according to properties in addition to size, e.g., colloidal attraction or resistance to deformation, makes AFM a valuable tool.

Acoustic Methods: Another resemble 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 on surface charge.

Co–Existence of Additional Structures[38] 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 SLN dispersion with water that cause the removal of the surfactant molecules from the particle surface and induce changes such as crystallization changes of the lipid modification.

Parameter Method of Analysis[38] Molecular weight gel chromatography, X-ray photoelectron spectroscopy, Surface element analysis Electrophoresis, Laser Doppler anemometry.

Statistical Analysis: Size and entrapment efficiency of SLNs are compared using the Student's t-test. Statistical analyses are also performed.

Stability Studies[38] Drug loaded SLNs are stored at 25 °C for 6 months and average size and entrapment efficiency are determined.

Effect of Sterilization: To see the effect of sterilization on particle size, zeta potential and entrapment efficiency, blank and drug dispersions are autoclave at 121°C for 20 min.

APPLICATION OF SOLID LIPID NANOPARTICLE[39,40]

For ocular drug delivery: SLNs can improve the corneal absorption of drugs and progress the ocular bioavailability of both hydrophilic and lipophilic drugs.

As gene vector carrier: Cationic solid lipid nanoparticles can well bind de-oxy ribo nucleic acid (DNA) directly via ionic interaction and intervene gene transfection and can be used in the gene vector formulation.

A targeted carrier for solid tumors: SLNs have been reported to be useful as drug carriers to treat neoplasms.

Anti-tubercular chemotherapy: SLNs-based drug delivery is pulmonary delivery of antimicrobials to treat tuberculosis, a serious lung infection caused by Mycobacterium tuberculosis is another prominent example.

For topical use: Topical SLN products show enormous prospective for treating dermatological conditions by targeting corticosteroids to dermal disease sites while decreasing systemic drug absorption.

For Parenteral Application: SLN 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.

SLNs as cosmeceuticals: The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers.[41] The in vivo study showed that skin hydration will be increased by 31% after 4 w* by the addition of 4% SLN to a conventional cream.[42] SLN and NLCs have proved to be controlled release innovative occlusive topicals.[43] Vitamin A Produces better localization in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations.[44]

SLNs for potential agriculture application: Essential oil extracted from Artemisia arboreseens when incorporated in SLN were able to reduce the rapid evaporation compared with emulsions and the systems widely used in agriculture as a suitable carrier of ecologically safe pesticides.

SLN 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.[45] New developments in the adjuvant area are the emulsion systems. These are oil-in-water emulsions which degraded 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.[46, 47]

SLN applied to the treatment of malaria: 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 drawbacks of conventional malaria chemotherapy is to develop multiple drug resistance and the nonspecific targeting to intracellular parasites, resulting in increased dose requirements and subsequent intolerable

toxicity. Nanosized carriers have been used in special attention with the aim to minimize the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs. Many nanosized drug delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria. Taking into account the peculiarities of malaria parasites, the focus is placed particularly on lipid-based e. g., liposomes, solid lipid nanoparticle.

CONCLUSION

The SLN are exciting carrier systems for encapsulating bioactive substances and hence widely used nowadays. The present review has concentrated on newer approach of Nanoparticles including Solid Lipid Nanoparticle its advantages, disadvantages, principle of drug release, toxicity aspects and preparation, characterization and application. etc. As SLN have potential of controlled drug delivery to a target tissue, there will be a vast area of investigation in improvement of quality, efficacy and safety of drug in future.

REFERENCES

1. Uddhav S Bagul, Vrushali V Pisal, Nachiket V Solanki and Antara Karnavat. Current Status of Solid Lipid Nanoparticles: A Review, *Modern Application of Bioequivalence and Bioavailability*, 2018; 3(4): 1-10.
2. Verma Surender and Makkar Deepika. Solid Lipid Nanoparticles: A Comprehensive Review, *Journal of Chemical and Pharmaceutical Research*, 2016; 8(8): 102-114.
3. Ayesha Siddiqua Gazi and Abbaraju Krishnasailaja. Solid Lipid Nanoparticles (slns) applications: A Review *Centre for Info Bio Technology Journal of Pharmaceutical Sciences*, 2018; 7(3): 1-10.
4. Jumaa M, Muller BW. Lipid emulsions as a novel system to reduce the hemolytic activity of lytic agents: mechanism of protective effect. *European Journal of Pharmacetical Sciences*, 2000; 9: 285-90.
5. Manoj kumar sarangi, Sasmita padhi. Solid Lipid Nanoparticles–A Review, *Journal of Critical Review*, 2016; *3(3): 5-12.*
6. Verma Surender and Makkar Deepika. Solid Lipid Nanoparticles: A Comprehensive Review, *Journal of Chemical and Pharmaceutical Research*, 2016; 8(8): 102-114.
7. Lin CH, Chen CH, Lin ZC, Fang JY Recent advances in oral delivery of drugs and bioactive natural products using solid lipid nanoparticles as the carriers. *Journal of Food and Drug Analysis*, 2017; 25(2): 219-234.

8. PS Mahajan; KB Mahajan; AB Darekar. A Review on Solid Lipid Nanoparticle (SLN): an advanced treatment modality.*International Journal of Pharmaceutical Science and Research*, 2015; 6(9): 3698-3712.
9. Ramteke KH, Joshi SA, Dhole SN (2012) Solid lipid nanoparticle: A review. *IOSR Journal of Pharmacy*, 2012; 2(6): 34-44.
10. Swathi G, Prasanthi NL, Manikiran SS, Ramarao N Solid lipid nanoparticles: colloidal carrier systems for drug delivery. *International Journal of Pharmaceutical Science and Research*, 2010; 1(12): 1-16.
11. U. Sahul Hameed Niyaz and K. Elango, Recent advances of Solid lipid nanoparticles: a review, *World Journal of Pharmacy and Pharmaceutical Sciences*, 2018; 7(11): 849-873.
12. Rakesh Ramesh Abhang, Kumar Rachana, Jayshri Madagu, Valte Yugesh Balkrishna, Sudarshan Bapurao Aher. Review on Solid Lipid Nanoparticles, 2015; 4(1): 288-301.
13. Prashant Pandey, Prakash Chandra Gupta, Sanjay Yadav. Solid lipid nanoparticle: a potential approach in drug delivery system, *European Journal Of Pharmaceutical And Medical Research*, 2018; 5(9): 225-236.
14. Jawahar. N, Meyyanathan. S, Gowtham Reddy, Sumeet Sood. Solid lipid Nanoparticles for Oral delivery of Poorly Soluble Drugs, *Journal of Pharmaceutical Sciences & Research*, 2012; 4(7): 1848-1855.
15. Winter E, Pizzol, C.D, Locatelli, C, Crezkynski-Pasa, T. B. Development and evaluation of lipid nanoparticles for drug delivery: Study of toxicity *in vitro* and *in vivo. Journal of. Nanoscience and Nanotechnology*, 2016; 16: 1321–1330.
16. Roghayeh, A.; Aref, S.; Rasedee, A. Cytotoxicity effect of solid lipid nanoparticles on human breast cancer cell lines. *Biotechnology*, 2011; 10: 528–533.
17. Bechinger, B.; Lohner, K. Detergent-like actions of linear amphipathic cationic antimicrobial peptides. *Biochim. Biophys. Acta*., 2006; 1529–1539.
18. Xue, H.Y.; Liu, S.; Wong, H.L. Nanotoxicity: A key obstacle to clinical translation of siRNA-based nanomedicine. *Nanomedicine*, 2014; 9: 295–312.
19. Müller, R.H.; Radtke, M.; Wissing, S.A. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Advanced Drug Delivery Reviews*, 2002; 54: 131–155.
20. Weyenberg, F. P.; Van den Plas, D.; Vandervoort, J.; De Smet, K.; Sollie, P.; Ludwig, A. Cytotoxicity of submicron emulsions and solid lipid nanoparticles for dermal application. *International Journal of Pharmacy*, 2007; 337: 291–298.

21. Dolatabadi, J. E.N. Hamishehkar, H. Eskandani, M. Valizadeh, H. Formulation, characterization and cytotoxicity studies of alendronate sodium-loaded solid lipid nanoparticles. *Colloids and Surfaces. B Biointerfaces*, 2014; 117: 21–28.
22. Bhushan, K. V.; Pal, H. C.; Mondhe, D. M.; Kaur, I. P. The augmented anticancer potential of AP9-cd loaded solid lipid nanoparticles in human leukemia Molt-4 cells and experimental tumor. *Chemico-Biological Interactions*, 2016; 244: 84–93.
23. Eskandani, N. H. Self-reporter shikonin-act-loaded solid lipid nanoparticle: Formulation, physicochemical characterization and geno/cytotoxicity evaluation. *Eur. J. Pharma. Sci*, 2014; 59: 49–57.
24. Bansal, K. K.; Gupta, J.; Rosling, A.; Rosenholm, J. M. Renewable poly(δ-decalactone) based block copolymer micelles as drug delivery vehicle: *In vitro* and *in vivo* evaluation. *Saudi Pharmaceutical Journal*, 2018; 26: 358–368.
25. Negi, L. M.; Talegaonkar, S.; Jaggi, M.; Verma, A. K.; Verma, R.; Dobhal, S.; Kumar, V. Surface engineered nanostructured lipid carriers for targeting MDR tumor: Part II. *In vivo* biodistribution, pharmacodynamic and hematological toxicity studies. *Colloids and Surfaces B Biointerfaces*, 2014; 123: 610–615.
26. Kesharwani P, Garg N. K, Jain A, Nirbhavane P, Ghanghoria R, Tyagi, R. K, Katare O. P. Galactose engineered solid lipid nanoparticles for targeted delivery of doxorubicin. *Colloids Surf. B Biointerfaces*, 2015; 134: 47–58.
27. Verma Surender and Makkar Deepika. Solid Lipid Nanoparticles: A Comprehensive Review, *Journal of Chemical and Pharmaceutical Research*, 2016; 8(8): 102-114.
28. Kaur Jaspreet, Singh Gurpreet, Saini Seema, Rana AC Innovative growth in developing new methods for formulating Solid lipid nanoparticles and microparticles ; *Journal of Drug Delivery & Therapeutics*, 2012; 2(5): 146-150.
29. Sandeep Kelepu, Mohanvarma Manthina, Veerabhadhraswamy Padavala. Oral lipid based drug delivery system-an overview. Acta Pharmaceutical Sinica, 2013; 3(6): 361-372.
30. Verma Surender and Makkar Deepika. Solid lipid nanoparticles a comprehensive review. *Journal of Chemical and Pharmaceutical Research*, 2016; 8(8): 102-114. ISSN: 0975-7384.
31. Pavankumar Reddy A, Parthiban S, Vikneshwari, Senthilkumar G P. A modern review on solid lipid nanoparticles as novel controlled drug delivery system. *International Journal of research in Pharmaceutical and Nano Sciences*, 2014; 3(4): 313-325.

32. Rainer H, Muller Karsten Mader, Sven Gohala. Solid lipid nanoparticles for controlled drug delivery. a review of the state of the article. *European Journal of Pharmaceutics and Biopharmaceutics*, 2000; 50: 161-177.
33. Ajay patidar, Devindra singh, Peeyush Kumar, Jhageshwar verma. A review novel lipid based nanocarriers. *International Journal of Pharmacy and Pharmaceutical sciences*, 2010; 2(4): 30-35.
34. Rahul Nair, Ashok C K, Kumar P, Vishnu K, Priya S, Chakrapandi M Yadav Prasanna Y Raju. Formulation and evaluation of chitosan solid lipid nanoparticles of carbamazepine *Lipids in Health and Disease* 2012; 476- 511.
35. Akansha Gard, Deepti Singh, Navneet Guard, Solid lipid nanoparticles formulation methods characterization and applications. *International Current Pharmaceutical Journal*, 2012; 1(11): 384-393.
36. Anandi Tiwari, Surabhi Rasi, Sonia Anand Solid lipid nanoparticles as carrier in drug delivery system. World *Journal of Pharmacy and Pharmaceutical Sciences*, 2015; 4(8): 337-355.
37. Pragati S, Kuldeep S, Ashok S, Satheesh kumar M. Solid lipid nanoparticles: a promising drug delivery technology, 2009; 2(2): 509-516.
38. Rakesh Ramesh Abhang, Kumar Rachana S, Jayshri Madagul, Valte Yugesh Balkrishna, Sudarshan Bapurao Aher. Review on Solid Lipid Nanoparticles; *International Journal for Pharmaceutical Research Scholars*, 2015; 4(1): 288-301.
39. Jawahar N, Meyyanathan S N, Gowtham Reddy and Sumeet Sood. Solid lipid nanoparticles for oral delivery of poorly soluble drugs. *Journal of Pharmaceutical Sciences and Research*, 2012; 4(7): 1848-1855.
40. Poonam Yadav, Girish Soni, Alok Mahor, Shashi Alok, Prem Prakash Singh and Amita Verma. Solid lipid nanoparticles: an effective and promising drug delivery system-a review. *International Journal of Pharmaceutical Sciences and Research*, 2014; 5(4).
41. Yang S, Zhu J, Lu Y, Ling B, Yang C. Body distribution of camptothecin solid lipid nanoparticles after oral administration. *Pharmaceutical Research*, 1999; 16: 751-7.
42. Yang SC, Lu LF, Cai Y, Zhu JB, Liang BW, Yang CZ. Body distribution in mice of intravenously injected camptothecin solid lipid nanoparticles and targeting effect on brain. *Journal of Controlled Release*, 1999; 59: 299-307.
43. Zur Muhlen A, Mehnert W. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. *Pharmazie*, 1998; 53: 552-5.

44. Prow T, Smith JN, Grebe R, Salazar JH, Wang N, Kotov N, et al. Construction, gene delivery, and expression of DNA tethered nanoparticles. *Molecular Vision*, 2006; 12: 606-615.
45. Wissing S, Lippacher A, Muller R. Investigations on the occlusive properties of solid lipid nanoparticles (SLN). *Journal of Cosmetics Science,* 2001; 52: 313-24.
46. Jenning V, Gysler A, Schafer-Korting M, Gohla SH. Vitamin Aloaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. *Europeon Journal of Pharmaceutics and Biopharmaceutics*, 2000; 49: 211-8.
47. B Lu, SB Xiong, H Yang. Solid lipid nanoparticles of mitoxantrone for local injection against breast cancer and its lymph node metastases. *Europeon Journal of Pharmaceutical Science*, 2009; 28: 86-95.