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SOLID LIPID NANOPARTICLES-A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Solid lipid nanoparticles (SLN) developed in early 90's was considered as an alternative and novel drug delivery systems to existing traditional drug delivery systems with auspicious delivery of active pharmaceutical substances with enhanced bioavailability, biocompatibility and reduced toxicity. SLN's are solid colloidal carriers with spherical shape ranging from 10-1000 nm in diameter replacing liquid lipid with solid lipid which eventually developed into solid lipid nanoparticles. Solid lipids incorporated in SLN's are solid at room temperature and resembles similar to physiological lipids with site specific and targeted drug delivery. The drug is dispersed and/or dissolved in solid lipid core matrix cable of carrying both hydrophilic and lipophilic drugs. This review article focuses on various methods of preparation of SLN's, their characterizations. The analytical techniques for characterization of solid lipid nanoparticles like photon correlation spectroscopy, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) were also highlighted. Current trends in SLN's have great scope for targeted and controlled drug delivery in treating various diseases with improved bioavailability, reduced dose and fewer side effects. Hence, solid lipid nanoparticles are attracting a wide group of researchers around the globe for exploiting their benefits.

KEYWORDS

Novel nanotechnology, Solid lipid nanoparticles, Preparation methods, Characterizations and Applications.

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INTRODUCTON

Nanoparticles are defined as the solid colloidal carriers in nanometre range, ranging from 10-1000nm. Solid lipid nanoparticles are aqueous colloidal dispersions, which comprises of solid spherical biodegradable lipids suspended in water or hot aqueous surfactant core solution[1], which were introduced in 1991, as an alternative drug delivery system to existing traditional delivery systems such as emulsions, polymeric micro and nanoparticles,

liposomes attracting chief attention as novel colloidal drug carrier[2]. The solid lipid core contains the drug either dissolved or dispersed in the high melting solid fat matrix, they can carry both water soluble or water insoluble drugs or diagnostic agents in their lipid matrix[3] (Shown in Figure No.1). Nanotechnology had many advantages which provide targeted drug delivery and control release of drugs to achieve improved efficacy, precise pharmacokinetics, pharmacodynamics, and non-specific toxicity of drugs. Nanotechnology based drug delivery systems with an appropriate particle size and narrow size range, ensures reduced irritation, enhanced bioavailability and biocompatibility, which has high effective delivery strategies for the treatment of diseases. For the past few decades, colloidal carriers have been widely developed with the objective to improve the specificity in target drug delivery, to allow easier drug penetration through biological membranes, to minimize drug degradation or inactivation.

Nanosized emulsions (both nanoemulsions and micro emulsion) are thought-provoking submicron carriers found to be suitable for drug delivery. They are homogenous, transparent colloidal dispersions consisting of two immiscible liquids, of which one liquid being dispersed as small spherical droplets in another liquid. Nanosized emulsions have been intensively exploited for their efficient applications in various therapeutics. The multipurpose properties include high drug loading capacity along with sufficient protection of drugs in the biological environment. Some multifunctional nanocarriers also direct the drugs to specific targets with attached homing molecules guiding them to the required site of action. As a drug carrier, nanoparticles have significant advantages like better bioavailability, systemic stability, high drug loading, long blood circulation time and selective distribution in the organs/tissues with longer half-life.

Solid lipid nanoparticles were prepared from lipid than polymer and these lipids are solid at room temperature. Solid lipid nanoparticles combine the properties of liposomes like biocompatibility and polymeric particles stability, higher production efficiency and the surface of solid lipid nanoparticles can be modified for drug targeting by attaching ligand or by PEGylation. They are prepared by homogenization or emulsion precipitation for delivering drugs as a solid molecular dispersion or as a drug encapsulating lipid shell. Several formulations including micelles, liposomes, polymeric nanoparticles, nanoemulsions, solid dispersions and nanocapsules were developed successfully. A promising strategy to overcome these problems involve development of suitable drug carrier system like solid lipid nanoparticles. In the middle of the 1990's, the attention of different research groups focused on alternative nanoparticles made from solid lipids, the so-called solid lipid nanoparticles (SLNs). Solid lipid nanoparticles are at the forefront of the rapidly developing field of nanotechnology with several potential applications in drug delivery, clinical medicine and research as well as in other fields. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics[1]. Successful incorporation of drugs into nanocarriers emerged as a new prototype in drug delivery and could be used for effective drug targeting. Hence, solid lipid nanoparticles are reaching the goal of targeting the drug in a controlled manner and also offers site-specific drug delivery and hence attracting the attention of researchers around the globe[4].

LIPID-BASED SYSTEMS ARE DEVELOPED FOR FOLLOWING REASONS

1. For enhancing oral bioavailability and for reducing plasma profile fluctuations.
2. The lipoid excipients can be efficiently characterized.
3. Scale-up techniques in manufacturing and key issues in technology transfer can be addressed effectively.
4. An improved ability to address the key issues of technology transfer can be achieved.
5. Poor absorption, rapid metabolism and elimination of drug can be minimised.
6. Poor drug solubility and high toxicity (eg: cancer drugs) can be reduced.

The main objectives of solid lipid nanoparticles include[5,6,10]

1. Controlled and targeted drug release.
2. For enhancing stability of drug.
3. High drug content can be entrapped.
4. Lipophilic and hydrophilic drugs can be entrapped.
5. Lower cost than polymeric/surfactant-based carrier systems.
6. Reduced toxicity due to biodegradable and physiologically similar lipids and organic solvents can also be avoided.

Benefits of SLN's include

1. Stability enhancement of drugs.
2. Solubility enhancement for poorly soluble drugs.
3. Drug targeting.

Advantages of SLN's[2,7-10]

- Their small size and relatively narrow size distribution permits size specific drug delivery.
- Controlled and sustained release of drugs can be achieved.
- Improved bioavailability, protection of sensitive drug molecules from the outer environment (water, light).
- Controlled release by incorporation of poorly water-soluble drugs in the solid lipid matrix
- Easy to scale up and sterilize.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than bio polymeric nanoparticles.
- No special solvent required.
- Conventional emulsion manufacturing methods are applicable.
- Raw materials essential are the same as used for emulsions.
- Very high long-term stability.
- Application versatility.
- Can be subjected to commercial sterilization procedures.

Disadvantages of SLN's[5,9,10]

1. Solid lipid nanoparticles have limited drug entrapment efficiency due to drug solubility in the lipid melts.
2. Leaching of drug may be observed during the storage due to perfect crystal formation, which helps in leaching.
3. The particles have gelation tendency and size may be increased.
4. Uncertain dynamics of polymorph transition.
5. Higher aqueous content is present in SLN's dispersion (i.e. 70-99.9%).
6. Adjustment of drug release profile.

Excipients generally used for preparing SLN's

The following excipients were used to prepare solid lipid nanoparticles (shown in Table No.1 and No.2) and the selection of ingredient depend on the purpose of formulation like site of targeting, controlling the drug release, particles homogeneity, route of administration, stability on storage and also on charge modifier. Co-surfactants, cryoprotectants and preservatives were also used as additives.

Preparation techniques for SLN's[1,9-16]

Different techniques available for the production of lipid nanoparticles (shown in Figure No.2) have been described. They are as follows:

High pressure homogenization

a) Hot homogenization

b) Cold homogenization

Ultra-sonication technique

a) Probe sonication

b) Bath sonication

Microemulsion based SLN preparation

Solvent emulsification-diffusion technique

Solvent emulsification-evaporation technique

Melting dispersion method (Hot melt encapsulation method)

Double emulsion technique

Membrane contactor technique

Supercritical fluid technology

Solvent Injection Technique

Secondary production steps

a) Sterilization

b) Lyophilization
c) Spray drying method

Mechanical technology

Mechanical technology is widely used to reduce the particles into small particles by mechanical milling and high-pressure homogenization using high energy input which results in high impact due to which particle size reduction takes place.

High pressure homogenization

SLNs are produced by high-pressure homogenization methods, using a high-pressure homogenizer. High pressure homogenization (HPH) is a reliable and powerful technique for the preparation of lipid nanoparticles. In this method a high shear pressure is used to break down the particles in to small nanoparticles, a high pressure (100-200 bars) pushes the lipids to pass through a narrow gap, this causes turbulence, cavitation's and collision of particles to each other which results in breakdown of the particles into nanorange. The fluid circulated to a very small distance at high viscosity of about 1000-1200 km/h. Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Typical lipid contents are in the range of 5-10% and represent no problem to the homogenizer. High pressure homogenization is of two types: Hot homogenization and Cold homogenization techniques, used for the production of SLN's, which requires a preparatory step involving the drug incorporation in to the bulk lipid by dissolving or dispersing in the lipid melt. This technique has many advantages compared to the other methods, e.g. easy scale up, avoidance of organic solvents and short production time and no scaling problems.

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. In this method, first a pre-emulsion of molten lipid containing drug and aqueous phase having an emulsifier is prepared by using the equal temperature with the help of a high shear mixing equipment. For this, lipid is melted above the melting point of the lipid. A hot o/w emulsion is prepared on cooling of the emulsion, crystallization of lipid takes place and solid lipid nanoparticles are formed, due to lowered viscosity of the lipid at higher temperatures very small particle are produced. In general, higher temperatures result in lower particle size due to the decreased viscosity of the inner phase. However, high temperatures may also increase the degradation rate of the drug and the carrier. The homogenization step is repeated several times. High pressure homogenization increases the temperature of the sample approximately 10°C for 500 bar. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result of the high kinetic energy of the particles, therefore 3-5 homogenization cycles at 500-1500 bar are sufficient. Ananoemulsion is formed which on cooling to room temperature, the liquid is converted into solid particles. The sample may remain as a super cooled melt for several months due to the small particle size and the presence of emulsifiers which retards lipid crystallization.

b. Cold homogenization[10]

Cold homogenization has been developed to overcome various problems associated with hot homogenization technique 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. However, exposure of the drug to temperature cannot be completely avoided due to solubilization of the drug in melted lipid and also temperature generated during homogenization process. The drug is dissolved in the melted lipid followed by rapid cooling by means of liquid nitrogen or dry ice to obtain drug loaded lipid. The rapid cooling leads to the formation of a solid solution (presuspension) of the drug in the lipid matrix. The solid solution is then ground to microparticles by means of ball mill or mortar. Then, solid lipid microparticles are dispersed in a cool aqueous phase containing emulsifiers and subsequently homogenized at or below room temperature and the gravitation force is strong

enough to break the lipid microparticles directly to solid lipid nanoparticles.

Ultra-sonication/high speed homogenization

Ultra-sonication or high-speed homogenization techniques are used to prepare smaller solid lipid nanoparticles and are used in combination. It is a simple, sensitive and reproducible method to prepare SLN's in laboratory. In brief, drug, lipid, and emulsifier were dissolved in a common solvent and evaporated under reduced temperature to obtain solvent free drug dissolved or dispersed in lipid phase. Drug loaded lipid melt was homogenized with hot aqueous surfactant solution for three minutes using homogenizer, mechanical stirrer or sonication to get coarse emulsion or the lipid in aqueous phase can be emulsified by dissolving the lipid in a water-immiscible organic solvent (e.g. cyclohexane). Then the organic solvent is evaporated from the emulsion by evaporation under reduced pressure (40–60 mbar) in rotary evaporator, precipitation of the lipid dispersion in the aqueous medium takes place and SLN's are formed. The coarse emulsion so obtained was ultra-sonicated using ultra sonicator to obtain nano emulsion. SLNs are formed upon cooling to room temperature. This process is done at low shear stress but metal contamination and particle growth upon storage, to big particles are observed. If the coarse emulsion is immediately homogenized the efficiency of fine emulsification can be improved.

Micro emulsion based method

Micro emulsions are clear, thermodynamically stable, micro heterogenous dispersions being composed of lipophilic phase (lipid), a surfactant, co-surfactant, and water. Addition of micro emulsions to water leads to precipitation of the lipid phase forming fine particles. Solid lipid nanoparticles prepared by micro emulsification followed by dilution of micro emulsions. The micro emulsion is prepared by stirring the low melting fatty acid in aqueous solution of an emulsifier and co surfactant at 65-70°C to form a transparent micro emulsion. The low melting fatty acid i.e. (stearic acid) is used and emulsifiers like (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co emulsifiers (sodium monooctylphosphate) are used. The prepared hot micro emulsion is then dispersed in ice-cold water (2-4°C) under stirring. The dilution process is critically determined by the composition of the microemulsion. Volume ratios of the hot microemulsion to cold water are in the range of 1:25 and 1:50. Rapid recrystallization of oil droplets upon dispersion in cold aqueous medium, produces SLN's. It should be noted that SLN's are formed due to precipitation and not due to stirring process. The obtained lipid nanoparticles dispersion can be washed with water after filtration and lyophilized.

Solvent emulsification-diffusion technique

In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl lactate, ethyl acetate, isopropyl acetate, methyl acetate) must be partially miscible with water and this technique can be carried out either in aqueous phase or in oil. Initially, both the solvent and water were mutually saturated in order to ensure the initial thermo dynamic equilibrium of both liquids. Then, the lipid is dissolved in the water-saturated solvent and subsequently emulsified with solvent-saturated aqueous surfactant solution at elevated temperatures. The SLN precipitate after addition of excess water (typical ratio 1:5 – 1:10) due to diffusion of the organic solvent from the emulsion droplets to the continuous phase. Further, the suspension is purified by ultra-filtration and almost 99.8% of benzyl alcohol is eliminated.

Solvent emulsification-evaporation technique

In solvent emulsification-evaporation method, the lipophilic material and hydrophobic drug were dissolved in a water immiscible organic solvent (e.g. cyclohexane, dichloromethane, toluene, chloroform) and then it was emulsified in an aqueous phase using high speed homogenizer. To improve the efficiency of fine emulsification, coarse emulsion was passed through micro fluidizer. Thereafter, the organic solvents were evaporated by mechanical stirring at room temperature and reduced pressure (e.g. rotary evaporator) leaving lipid precipitates of SLN's. Here the mean particle size depends on the concentration of lipid in organic phase. Very small particle size could be obtained with low lipid load (5%) related to organic solvent.

The great advantage of this technique is the avoidance of any thermal stress, which makes it suitable for the incorporation of highly thermo labile drugs. A clear disadvantage is the use of organic solvent which may interact with drug molecules and limited the solubility of the lipid in the organic solvent.

Melting dispersion method (or) hot melt encapsulation method

In melting dispersion method, the first step involves melting of drug and solid lipid in an organic solvent which was regarded as oil phase and simultaneously water phase was also heated to same temperature as oil phase. Then in the second step, the oil phase was added into a small volume of water phase and the resulting emulsion was stirred at higher rpm for few hours and at last, it was cooled down to room temperature to give SLN's. The last step was same as solvent emulsification evaporation method except in melting dispersion method no organic solvent had to be evaporated. Reproducibility was less than that of solvent emulsification-evaporation method but more than ultra-sonication method.

Double emulsion method

A hot double micro emulsion (w/o/w type) was prepared in two steps, in the first step the melted lipid was added to an aqueous solution containing drug, surfactant and co-surfactant the processing temperature was slightly above the melting point of lipid to prepare w/o micro emulsion. In the second step, to prepare a clear w/o/w system the prepared w/o micro emulsion was then poured into the combination of aqueous surfactants and co surfactants solution to get a double emulsion. Then the warm double micro emulsion was dispersed in ice cold water, and then washing is done by ultra-filtration system.

Membrane contactor technique

It is a novel technique to prepare the SLN's. In membrane contactor technique the liquid phase was pressed at a temperature above the melting point of the lipid through the membrane pores (Kerasep ceramic membrane with an active ZrO_2 layer on an AlO_2-TiO_2 support) allowing the formation of small droplets. The aqueous phase was stirred continuously and circulated tangentially inside the membrane module, and sweeps away the droplets being formed at the pore outlets. SLN's were formed by the cooling of the preparation to room temperature. Here both the phases were placed in the thermo stated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase.

Supercritical fluid method

A new technique is used nowadays for the preparation of solid lipid nanoparticles in which solvent is not needed for processing. A supercritical fluid especially carbon dioxide, is used in this technology because carbon dioxide has low toxicity, low cost, high solubility power and having a low critical temperature of 31.1^{o}C at a pressure of 73 bar. When the pressure and temperature of a fluid was increased to the critical value it is known as supercritical fluid and the solubilizing capacity of that fluid also increases. Two methods are commonly employed, one is rapid expansion of supercritical solution (RESS) and second one is rapid expansion from supercritical to aqueous solution of emulsion (RESAS).

Rapid expansion of supercritical solution (RESS)

Solid lipid nanoparticles are prepared by the rapid expansion of supercritical carbon dioxide solution method. In this method supercritical fluid (CO_2) is used as solvent, containing the solute dissolved in it which was then expended through nozzle to the collection chamber at atmospheric pressure, the atomization and evaporation of fluid cause nucleation and precipitation of solute into nanoparticles.

Rapid expansion from supercritical to aqueous solution of emulsion (RESAS)

In RESS method particles get aggregated, but in RESAS method small particles are produced. In this method the surfactant gets diffused on to particles surface and prevent particles from agglomeration, this method is used to form nanoparticles of water insoluble drugs.

Solvent injection technique

The basic principle for the formation of SLN's was similar to the solvent diffusion method. In this method, the solution of SLN's was prepared in water-miscible solvent system (e.g. ethanol,

acetone, isopropanol and methanol) or a combination of two or more water miscible solvents. To prepare the nanoparticles, lipid solution was rapidly injected using an injection needle into aqueous phase with a constant stirring, which may or may not contain surfactant. A dispersion is then obtained which is then filtered with a filter paper in order to remove any excess lipid. The emulsifier is basically used in the aqueous phase to produce lipid droplets at the site of injection and stabilize solid lipid nanoparticles until solvent diffusion is completed by reducing the surface tension between water and solvent. By using this method, we can obtain particles of 80-300 nm, depending on the preparation conditions. About 96.5% of the employed lipid was transformed into SLN's and the formation of SLN's seems to be diffusion controlled.

Secondary production steps a. Sterilization

If nanoparticles are given by parenteral route, the sterilization of formulation is required. For sterilization mainly autoclaving is done which uses the moist heat. When the sterilization is to be done various factors to be considered regarding the drug and excipients of the formulation. If drug is temperature sensitive, at higher temperatures the drug gets degraded. The particles size can be changed due to the effects of sterilization, generally it is found to cause an increase in particle size. The critical parameters include sterilization temperature and the composition of SLN's. Also, the selection of a good emulsifier has a significant and important role on the physical stability of the sample at high temperature. If the temperature is increased, it can change the mobility and the water solubility of all emulsifiers to a different extent. Steam sterilization causes the formation of ano/w type emulsion due to the melting of the lipid particles. Solid particles are formed after recrystallization. γ-irradiation could be an alternative method to steam sterilization for temperature sensitive samples.

b. Lyophilization

To enhance the chemical and physical stability of hydrolysable drugs for a long period of time, lyophilization or freeze drying is the most promising way. In case of nanosuspension for orally administered drugs which can be precipitated due to transformation of product into solid state due to Ostwald ripening of drug, which can result in hydrolytic degradation of drug, to prevent such condition an adequate amount of cryoprotectant can be added to prevent SLN's aggregation at the time of lyophilization process.

c. Spray drying method

It is a cheaper alternative technique to freeze-drying method. The lipids having high melting value are used. The carbohydrates and low lipid content are added in this, which helps to preserve the size of colloid particles in spray drying. To prevent the melting of the lipid, ethanol–water mixtures can be used in place of using water because on cooling small and heterogeneous crystals formation takes place, at the low in let temperature. These particles can aggregate because of the high temperature, high shear force and partial melting of the particles.

Characterization of SLN's

Adequate and proper characterization of the SLN's is necessary for its quality control. However, characterization of SLN's is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system.

Particle size and zeta potential analysis[19]

The particle size/size-distribution may be studied using photon correlation spectroscopy (PCS), transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), scanning tunneling microscopy (STM), or freeze fracture electron microscopy (FFEM).

PHOTON CORRELATION SPECTROSCOPY (PCS)

Laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. The Coulter method is rarely used to measure SLN particle size because of difficulties in the assessment of small nanoparticle and the need of electrolytes which may destabilize colloidal dispersions. PCS (also known dynamic light scattering or quasi-elastic light scattering (QELS)) measures the fluctuation of the intensity of the

scattered light which is caused by the particle movement. PCS yields the mean particle size and the polydispersity index (PI) as a measure of the width of the distribution. This method covers a size range from a few nanometers to about 3 microns. This means that PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. They can be visualized by means of LD measurements. This method is based on the dependence of the diffraction angle on the particle radius (Fraunhofer spectra). Smaller particles cause more intense scattering at high angles compared to the larger ones. A clear advantage of LD is the coverage of a broad size range from the nanometer to the lower millimetre range. The development of polarization in tensity differential scattering (PIDS) technology greatly enhanced the sensitivity of LD to smaller particles. However, despite this progress, it is highly recommended to use PCS and LD simultaneously. It should be kept in mind that both methods do not 'measure' particle size. Rather, they detect light scattering effects which are used to calculate particle size. Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artefacts which may be caused by the sample preparation. For example, solvent removal may cause modifications which will influence the particle shape.

Zeta potential

It is an important characteristic of SLN's since its high value is expected to lead to de-aggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. The zeta potential is determined by Laser Doppler Anemometry (Zetasizer IV, Malvern Instruments, UK) using the Helmholtz-Smoluchowski equation. Zeta potential is the potential difference between the dispersion medium and the stationary layer of fluid attached to the dispersed particle. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. For molecules and particles that are small enough, a high zeta potential will confer stability, i.e. the solution or dispersion will resist aggregation. When the potential is low, attraction exceeds repulsion and the dispersion will break and flocculate. So, colloids with high zeta potential (negative or positive) are electrically stabilized while colloids with low zeta potentials tend to coagulate or flocculate.

Static light scattering/fraunhofer diffraction[16,17]

Static light scattering (SLS) is an ensemble method in which the pattern of lights cattered from a solution of particles is collected and fit to fundamental electromagnetic equations in which size is the primary variable. The method is fast and rugged, but requires more cleanliness than DLS method, and advance knowledge of the particle's optical qualities.

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 on surface charge.

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.

Electron microscopy[17]

SEM and TEM provide a way to directly observe size and shape of nanoparticles, physical characterization of nanoparticles with the former method being better for morphological examination. Samples are diluted with ultra-purified water and sonicated to obtain a suitable concentration. Then, the samples are spread on a sample holder and dried using vacuum. They are subsequently coated with gold (SCD 040) and examined by a scanning electron microscope. TEM has a smaller size limit of detection and it is a good validation for other methods, and affords structural required, and one must be cognizant of the statistically small sample

size and the effect that vacuum can have on the particles.

Atomic force microscopy (AFM)

In this technique, a probe tip with atomic scales 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. That ultra-high resolution is obtainable with this approach, which along with the 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.

Differential scanning calorimetry (DSC)[16]

It is performed in order to determine the degree of crystallinity of the lipid nanoparticles. DSC can be used to determine the nature and speciation of crystallinity with in nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies. Samples containing SLN's dispersions accurately weighed in 40 ml aluminium pans and cold sealed. The reference pan kept empty and sealed in the same manner. Heating curves are recorded and the crystallization index (Cl) is calculated for the samples.

X-ray diffraction[18]

X-ray diffraction investigations have been most valuable in the elucidation of the manner of arrangement of lipid molecules, their multiple-melting phenomena, phase behaviour and the characterization and identification of the structure of lipid and drug molecules. X-ray measurement is performed by wide-angle X-ray scattering (WAXS). Aqueous dispersions are transformed into a paste using a special gum (locust bean gum) as a thickening agent. Briefly, a small amount of gum was primarily mixed with the aqueous dispersion obtaining a paste which was placed into a thin X-ray glass fibre and then transferred to the camera for analysis. Polarized light microscopy to investigate drug crystals in the lipid melts (i.e. solubility studies), a polarized light micro scope equipped with a digital camera at the magnification powers of l00x, 400x and l000x is applied. The absence of drug crystals indicates that the active ingredient is completely dissolved in the lipid.

Thermal gravimetric analysis

It is carried out for the determination of chemical stability of the drug at higher temperatures. Samples of ~15mg are heated in an aluminium oxide crucible (Mettier TG-DTA analyser) and the loss of weight is recorded.

***In-vitro* drug release**[19]

A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLN's. Various methods are available to study the *in-vitro* release of the drug. They are:

- Dialysis bag diffusion technique.
- Reverse dialysis bag technique.
- Franz diffusion cells or USP type II dissolution apparatus.
- Side by side diffusion cells with artificial or biological membrane.
- Agitation followed by ultracentrifugation or centrifugal ultra-filtration

Dialysis bag diffusion technique

For dialysis bag diffusion technique, the SLN's dispersion was placed in pre - washed dialysis bag/tubing which can be hermetically sealed (molecular weight cut off 12000-14000) and immersed in phosphate-buffer saline at pH 6 with paddle rotation at 50 rpm. Aliquots of 0.5 ml dissolution medium are removed and the same volume of fresh dissolution medium was added periodically. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, the aliquots may be diluted with suitable solvent before analysis, centrifuged and analysed for the drug content using a suitable analytical method.

Reverse dialysis bag technique

In this technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN's dispersion. The SLN's are then displaced into the medium and the samples are withdrawn at suitable intervals and analysed.

Franz diffusion cell

The SLN's dispersion is placed in the donor chamber of Franz diffusion cell fitted with a cellophane membrane. The dispersion is then analysed against a suitable dissolution medium; the samples are withdrawn from the dissolution medium at suitable intervals and analysed for drug content using suitable methods like spectroscopy and HPLC methods.

Determination of incorporated drug (loading efficiency and entrapment efficiency)

It is of prime importance to measure the amount of drug in corporated in SLNs, since it influences the release characteristics. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium. This separation can be carried out using centrifugation filtration or gel permeation chromatography. Standard analytical techniques such as UV spectrophotometry, spectro fluorophotometry, high performance liquid chromatography, or liquid scintillation counting can be used to assay the drug.

Storage stability of sln's[10]

The physical properties of SLN's during prolonged storage can be determined by monitoring changes in zeta potential, particle size, drug content, appearance and viscosity as the function of time. External parameters such as temperature and light appear to be of primary importance for long-term stability. The zeta potential should be in general, remain higher than -60m V for a dispersion to remain physically stable. The temperature of 4°C is most favourable storage temperature, 20°C is used for long term storage temperature, but did not result in SLN's aggregation or loss of drug and 50°C causes rapid growth of particle size.

Applications of SLN's through various routes of administration[20]

There are several potential applications of SLN's which are administered by various routes and some of them are given below. The *in-vivo* behaviour of the SLN's mainly depends on the route of administration of drugs which are as follows:

Administration route

Interaction of the SLN's with the biological surroundings including: distribution processes (adsorption of biological material on the particle surface and desorption of SLN's components into to biological surroundings) and enzymatic processes. Various administration routes of SLN's are as follows:

Oral administration

For the drugs having low bioavailability through the oral route, SLN's are very useful approach for their delivery. These systems have controlled release behaviour and by pass the gastric and intestinal degradation of the drug and provide transport of drug though GIT mucosa. The adhesive property of SLN's also reported to increase bioavailability and reduce or minimize erratic absorption.

Parenteral administration

SLN's consist of physiologically well-tolerated ingredients and have fine storage capabilities after lyophilization, which are very appropriate for systemic delivery. 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[21]. When injected intravenously, SLN are sufficiently small to circulate in the micro vascular system and prevent macrophage uptake in case of hydrophilic coating. Therefore, SLN's have been suggested for viral and non-viral gene delivery.

Rectal administration

Rectal route is used for paediatric patients due to easy application. In some circumstances, when faster pharmacological action is needed, rectal route is preferred. With similar dose, rectal route reported superior plasma levels and therapeutic effectiveness than oral or intramuscular route. PEG coating seems to be a promising approach on rectal delivery and enhances bioavailability of drug[22].

Nasal administration

Nasal administration was a promising alternative non-invasive 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 in

sufficient transport across epithelial cell layers[23]. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and pro drug derivatization have been employed. In a recent report, coating polymeric nanoparticles with PEG gave promising results as vaccine carriers[24]. The role of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecule was reported to be successful. Nasal route can also be used for targeting the brain by bypassing BBB.

Respiratory delivery

Respiratory route for SLN's is a novel approach for delivery of drugs. This route through lungs avoids first pass effect by of feringa high surface area for drug absorption. Solid lipid particles have effective carrying capacity for anti-tubercular drugs, anti-asthmatic drugs and anticancer drugs, enhancing their bioavailability and reducing the dosing frequency for better management of pulmonaryaction.

Transdermal route

SLN's are having lipid contents, which are having great penetrating power across the skin. They are well suitable for use on inflamed or damaged skin because they are based on non-toxic and non-irritant lipids. SLN's 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. A completely new, recently discovered area of application is the use of SLN in sun-protective creams[25].

Ocular route

Eyes have multiple barriers resisting penetration of drugs. Ocular delivery is considered as the most difficult thing to achieve. Drug absorption and bioavailability is poor by ocular route. To overcome these challenges, SLN's having muco-adhesive properties improve interaction with eye mucosa and prolong corneal resisting time of drug which gives improved bioavailability and targeting effect.

Table No.1: Excipients used in solid lipid nanoparticle (SLN) drug delivery system

LIPIDS	SURFACTANTS
Acylglycerols	**Sorbitan ethylene oxide/propylene oxide copolymers:**
Glyceryl behenate (Compritol 888 ATO),	Polysorbate 20
Glyceryl palmitostearate (Precirol ATO 5),	Polysorbate 60
Glycerol monostearate (Imwitor 900),	Polysorbate 80
Glyceryl caprate [Campul® MCM C10]	Polysorbate 85
Glyceryl distearate (Precirol)	**Alkylaryl polyether alcohol polymers**
Glyceryl monooleate (Peceol)	Tyloxapol
Triacylglycerols	**Amphoteric: (Phospholipids)**
Glyceryl trilaurate (Dynsan 112)	Soybean lecithin (Lipoid S75, Lipoid S I00),
Glyceryl trimyristate (Dynsan 114)	Egg lecithin (Lipoid E 80),
Glyceryl tristearate (Dynsan 118)	Phosphatidylcholine (Epikuron 170, Epikuron 200)
Glyceryl behenate (Compritol)	**Anionic: (Bile salts)**
Glyceryl tripalmitate (Dynsan 116)	Sodium cholate
Tricaprin,	Sodium glycocholate
Fatty acids	Sodium taurocholate
stearic acid,	Sodium taurodeoxycholate
palmitic acid,	Sodium tauroglycocholate
Decanoic acid,	Sodium dehydrocholate
Behenic acid,	Sodium lauryl sulphate
Acidan N12	**Cationic**
Steroids	Cetrimonium bromide
Cholesterol	DOTAP
Waxes	DOTMA
Beeswax, Paraffin	Chlorhexidine salts

Behenic acid, Carnauba wax Caprylic/capric triglyceride (Miglyol) Miglyol 812 Cetylpalmitate Cacao butter, Monostearin, Lecithin, **Hard fat types** Witepsol W35, Witepsol H35, Witepsol H42, Witepsol H 45, Witepsol E 85, Witepsol E 85/cetyl alcohol (75:25), Witepsol S 51 Witepsol S 55, Witepsol H5 **Hydrogenated coco-glycerides** Softisan 142/cetyl alcohol (75:25) Softisan 142 **Cyclic complexes** Cyclodextrin, para-acyl-calix-arenes **Free fatty alcohols** Stearyl alcohol, Cetyl alcohol Myristyl alcohol, Lauryl alcohol **Oils** Miglyol 812, Capmul, Capryol 90, Capryol PGMC, Labrafil, Labrasol, Tocopherol caprylic glycoside, hydrodenated fish oil, paraffin, caprylic capric triglyceride	Dimethyldiocta- decylammonium bromide **Ethylene oxide/propylene oxide copolymers** Poloxamer (182, 188, 407, 908, 237, 238, 239, 338) **Alcohols** Butanol, Ethanol, Butyric acid Dioctyl sodium sulfosuccinate Monooctylphosphoric acid sodium **Others** Pluronics F 68, Sodium oleate, Tween 80, tween 60, tween 20 Span 60, span 20, span 80 Cremophor EL, Solutol HS 15 PEG 660, Polyvinyl alcohol Polyoxyethylene-glycerine monostearate Macrogol (15) hydroxystrearate PEG caprylic/capric triglycerides Polyglyceryl-3 methyl glucose distearate Polyglyceryl-6 distearate

Table No.2: Excipients used in solid lipid nanoparticle (SLN) drug delivery system

LIPIDS	CO-SURFACTANTS
Ethoxylated castor oils Castor oil Hydrogenated castor oil Hydrogenated palm oil Cacao butter Goat fat Anhydrous milk fat **Others** Monostearate monocitrate glycerol (Acidan N12) Monosyeol (Propylene glycol palmitic stearate) Precirol ATO 5 (mono, di, triglycerides of C16-C18 fatty acids) Solid paraffin Superpolystate Synrowax HRSC (mixture of glycerol tribehenate and calcium behenate)	Tyloxopol Taurocholate sodium salt Taurodeoxycholicacid sodium salt Sodium dodecyl sulphate Sodium glycocholate Sodium oleate Cholesteryl hemisuccinate Butanol benzlkonium chloride, glycerol.
Cryoprotectants	Trehalose, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl pyrolidone (PVP), Polyvinyl alcohol (PVA), Gelatin
Charge modifiers	Stearylamine, Dicetylphosphate Dipalmitoyl phosphatidyl choline (DPPC). Dimyristoyl phosphatidyl glycerol (DMPG).
Stealthing agents (Agents for improving circulation time)	Polyethylene glycol, poloxamer
Preservatives	Thiomersal
Dispersing agents	Polyvinylalcohol
Shell forming material	Curdlan

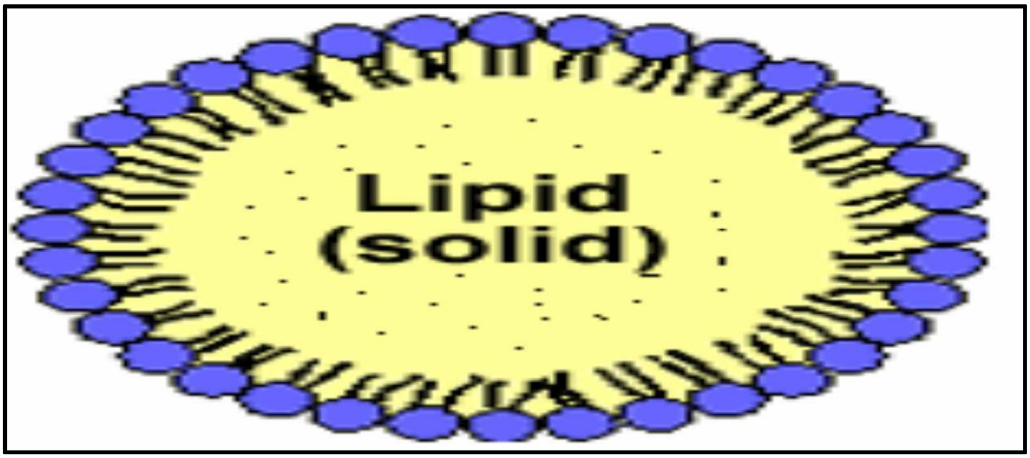

Figure No.1: Structure of solid lipid nanoparticle (SLN) (adopted from Muller, R H, *et al* 2000)

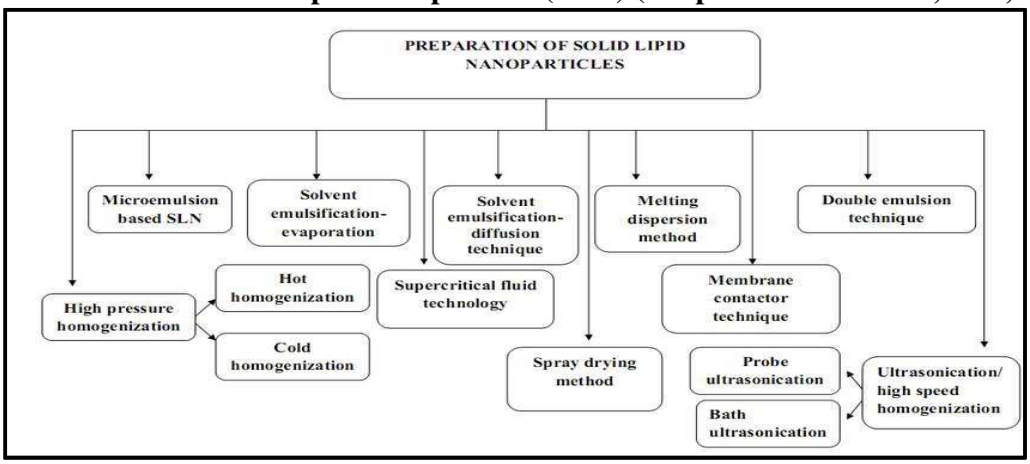

Figure No.2: Flow chart for various methods of preparation of solid lipid nanoparticles

CONCLUSION

SLN's as colloidal drug carriers combines the advantage of polymeric nanoparticles and fat emulsions due to various advantages, including feasibility of incorporation of lipophilic and hydrophilic drugs, good physical stability, they are available at low cost, ease of scale-up, and easy to manufacture etc. As many drugs are successfully marketed as solid lipid-based formulations, the solid lipid-based drug delivery system has a wide scope in terms of solubility and bioavailability enhancement. This review focused on the current trends in formulation development and their characterization. The selection of appropriate drug carrier, possessing non-toxicity and neutrality to our body system and crucially, compatible with the active substance, is a very smart task not an easy one. In recent years, the solid lipid nanoparticles have proved to be the ideal solution to this problem and an alternative to traditional colloidal and vesicular systems. The SLN's are exciting carrier systems for encapsulating bioactive substances with considerable potential for application. Along with a number of advantages discussed earlier, SLNs have certain grey areas, which include low drug loading capacity, product stability aspect which is associated with the possibility of gelation, particle size increase (agglomeration) and drug releasing characteristics. So, it can be concluded that the future holds great promise for its systematic investigation and exploitation.

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CONFLICT OF INTEREST

No potential conflicts of interest were disclosed.

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