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SOLID LIPID NANOPARTICLE: A NOVEL APPROCHES OF DRUG DELIVERY SYSTEM

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ABSTRACT

Lipid nanoparticles were developed in the last decade of the last century as alternative carrier system to emulsions, liposomes and polymeric nanoparticles. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are the two main types of lipid nanoparticles. The present review focuses on the utility of SLN in terms of their advantages, production methodology, characterization and applications. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The ability to incorporate drugs into nano carriers offers a new prototype in drug delivery that could use for drug targeting. Hence solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence attracted wide attention of researchers. This review presents a broad treatment of solid lipid nanoparticles discussing their aims, production procedures, advantages, limitations and their possible remedies.

KEYWORDS: Solid lipid nanoparticle, liposome, polymeric, emulsion.

INTRODUCTION

Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity.[1] Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant

solution. Generally, they are made of solid hydrophobic core having a monolayer of phospholipids coating. They have many advantages such as good biocompatibility, non-toxic, stable against coalescence, drug leakage, hydrolysis, biodegradable, physically stable and good carrier for lipophillic drugs.[2] The conventional approaches such as use of permeation enhancers, surface modification, prodrug synthesis, complex formation and colloidal lipid carrier based strategies have been developed for the delivery of drugs to intestinal lymphatics. In addition, polymeric nanoparticles, self-emulsifying delivery systems, liposomes, microemulsions, micellar solutions and recently solid lipid nanoparticles (SLN) have been exploited as probable possibilities as carriers for oral intestinal lymphatic delivery.[3]

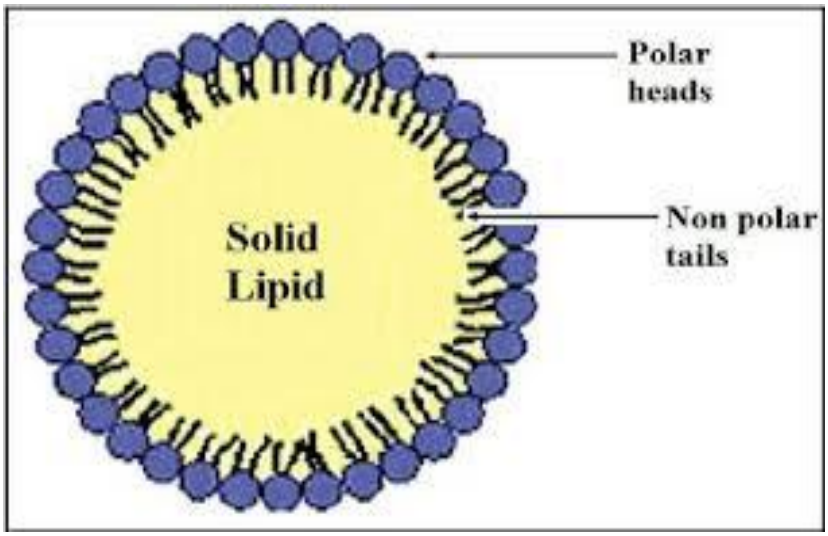

Fig 1: Structure of SLN.[2]

SLNs are colloidal carrier system composed of a high melting point lipid as a solid core coated by aqueous surfactant and the drugs used are of BCS Class II and IV. mainly prepared by high pressure homogenization or micro emulsification. SLNs prepared by any technique are in dispersion form which on long term storage results in instability mainly because of hydrolysis reactions so to increase their stability they can be converted into solid dry reconstituable powders through lyophilisation and a cheap and easy variant to lyophilisation is spray drying technique.[4]

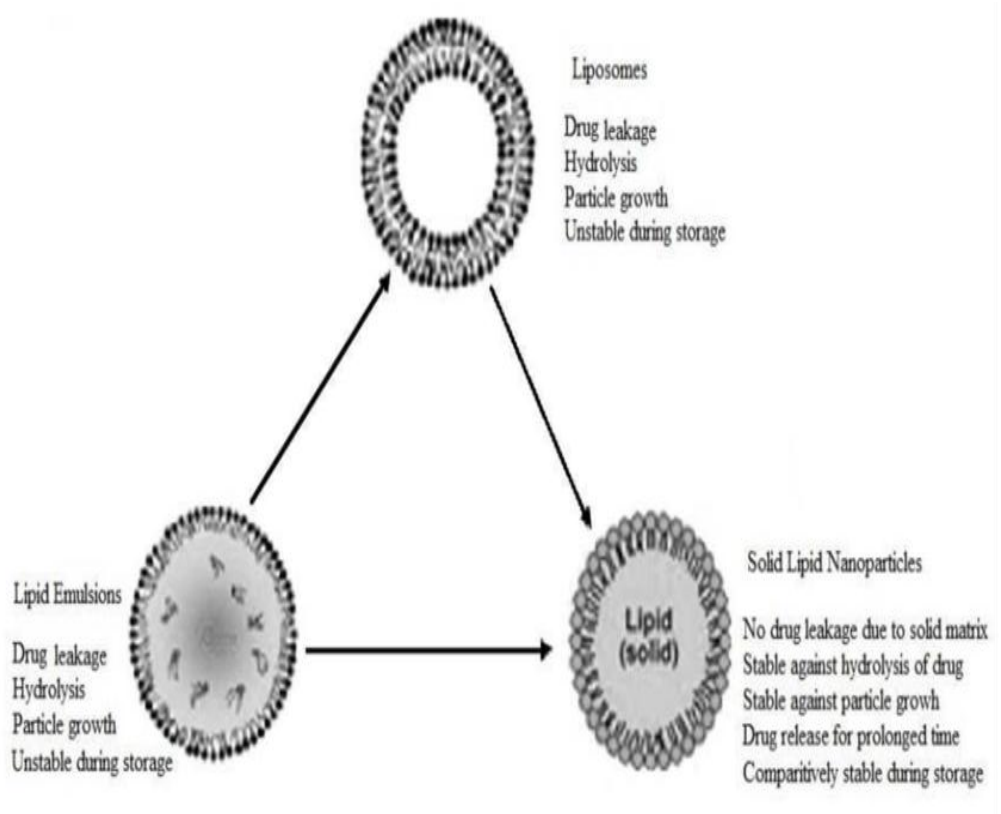

Fig. 2: Shows a diagrammatic representation on SLN over emulsions and liposome.[4]

Aims of solid lipid nanoparticles[4]

- It has been claimed that SLN combine the advantages and avoid the disadvantages of other colloidal carriers. Proposed advantages include-
- Possibility of controlled drug release and drug targeting.
- Increased drug stability
- High drug payload
- No biotoxicity of the carrier
- Avoidance of organic solvents
- No problems with respect to large scale production and sterilization
- Increased Bioavailability of entrapped bioactive compounds

Advantages of SLN[1]

- ✓ Control and/or target drug release.
- ✓ Excellent biocompatibility.
- ✓ Improve stability of pharmaceuticals.
- ✓ High and enhanced drug content.
- ✓ Easy to scale up and sterilize.

- ✓ Better control over release kinetics of encapsulated compounds.
- ✓ Enhanced bioavailability of entrapped bioactive compounds.
- ✓ Chemical protection of labile incorporated compounds.
- ✓ Much easier to manufacture than biopolymeric nanoparticles.
- ✓ No special solvent required.
- ✓ Conventional emulsion manufacturing methods applicable.
- ✓ Raw materials essential the same as in emulsions.
- ✓ Very high long-term stability.
- ✓ Application versatility.
- ✓ Can be subjected to commercial sterilization procedures.

Disadvantages of SLNs[4]

- ✓ Particle growth.
- ✓ Unpredictable gelation tendency.
- ✓ Unexpected dynamics of polymeric transitions
- ✓ Sometimes burst release

Potential problems associated with SLN and its production technology[5]

A potential problem in SLN is the formation of a perfect crystal, which can be compared to a dense 'brick wall'. Using different molecules, i.e. different 'stones' to build the matrix or 'wall leaves enough imperfections to accommodate the drug. Drug load in SLN is limited due to the formation of the lipid crystal. Drug expulsion is caused by an ongoing crystallization process towards a perfect crystal.

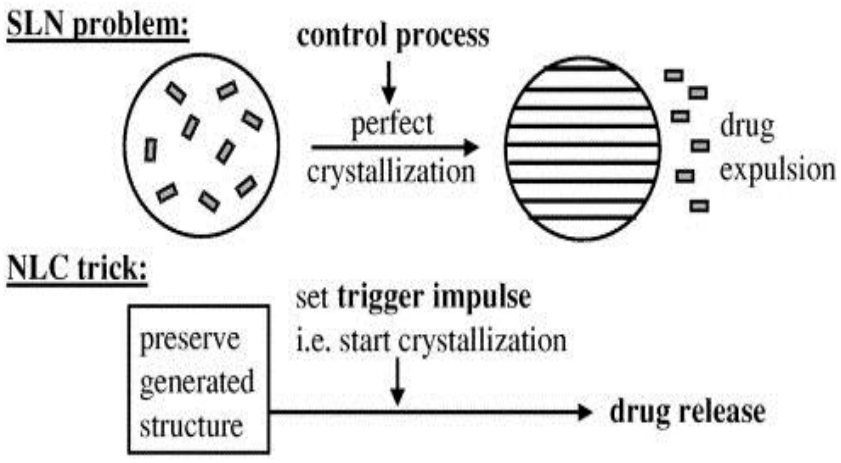

FIG.-3: Mechanism of drug expulsion during storage of SLN dispersions, transition to highly ordered lipid crystal.[5]

List of excipients used in SLN preparation[4,10,12]

Triglycerides Tricaprin Trilaurin Trimyristin (Dynasan 114) Tripalmitin (Dynasan 116) Tristearin (Dynasan 118) Hydrogenated coco-glycerides (SoftisanÒ 142) Hard fat types WitepsolÒ W 35 WitepsolÒ H 35 WitepsolÒ H 45 WitepsolÒ E 85 Acyl glycerols Glyceryl monostearate (ImwitorÒ900) Glyceryl distearate(Precirol) Glyceryl monooleate(Peceol) Glyceryl behenate (CompritolÒ 888 ATO) Glyceryl palmitostearate (PrecirolÒ ATO 5) Waxes Cetyl palmitate Fatty Acids Stearic acid Palmitic acid	**Phospholipids** Soy lecithin (LipoidÒ S 75, LipoidÒ S 100) Egg lecithin (Lipoid□□E 80) Phosphatidylcholine (Epikuron□□170, Epikuron 200) **Ethylene oxide/propylene oxide copolymers** Poloxamer 188 Poloxamer 182 Poloxamer 407 Poloxamine 908 **Sorbitan ethylene oxide/propylene oxide copolymers** Polysorbate 20 Polysorbate 60 Polysorbate 80 **Alkylaryl polyether alcohol polymers** Tyloxapol **Bile salts** Sodium cholate Sodium glycocholate Sodium taurocholate Sodium taurodeoxycholate **Alcohols** Ethanol

➢ PREPARATION OF SLN

1. High pressure homogenization[6]

High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of a few microns). The fluid accelerates on a very short distance to very high velocity (over 1000 Km/h). Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated.

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

A. Hot Homogenization

Hot homogenization is carried out at temperatures above the melting point of thelipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the

melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles.[4]

B. Cold homogenization

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nano emulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a pre-suspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles.[4]

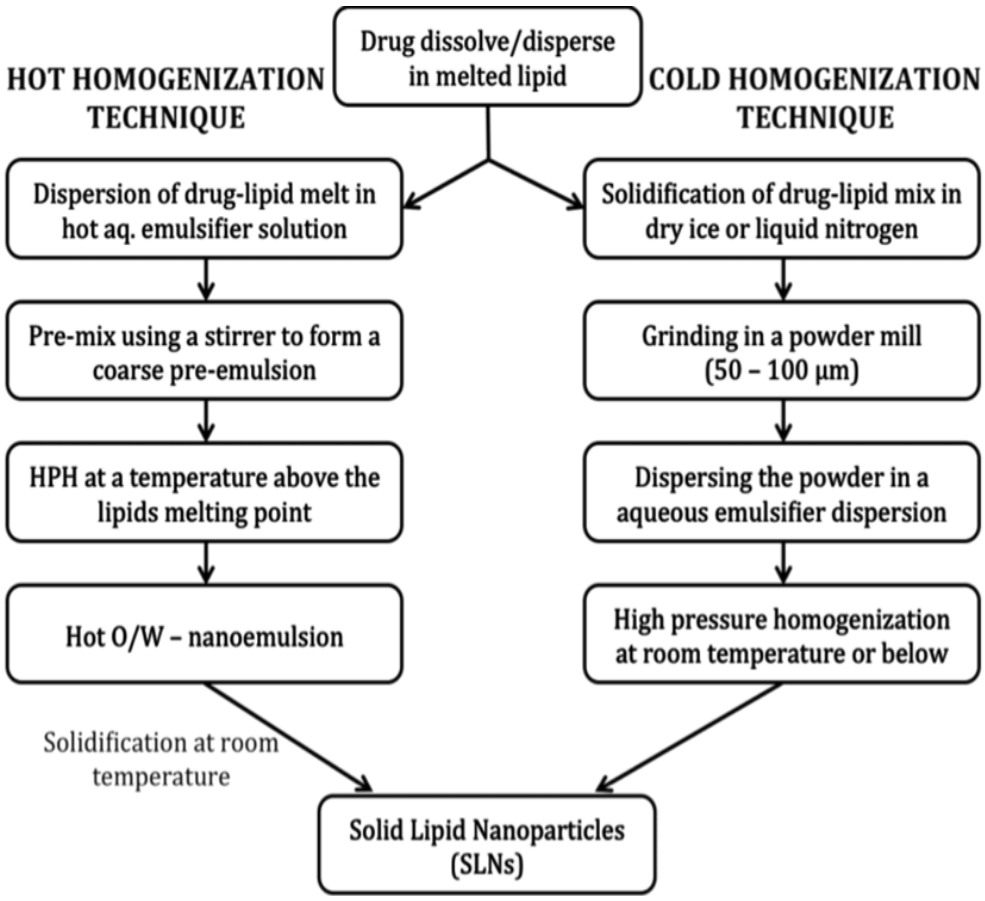

FIG 4: Schematic representation cold and hot homogenization for the preparation of SLNs.[1]

Ultrasonication or high speed homogenization

This ultrasonication technique is a dispersing technique, which was initially used for the production of solid lipid nanodispersion. Ultrasonication based on the mechanism of cavitation. In first step, the drug was added to previously melt solid lipid. In second step, the heated aqueous phase (heated to same temperature) was added to the melted lipid and emulsified by probe sonication or by using high speed stirrer or aqueous phase added to lipid phase drop by drop followed by magnetic stirring. The obtained pre-emulsion was ultrasonicated using probe sonicator with water bath (at 0ºC). In order to prevent recrystalization during the process, the production temperature kept at least 5ºC above the lipid melting point. The obtained nanoemulsion (o/w) was filtered through a 0.45µm membrane in order to remove impurities carried in during ultrasonication. Then they obtained SLN is stored at 4ºC. To increase the stability of the formulation, was lyophilized by a lyophilizer to obtain freeze-dried powder and sometime mannitol (5%) was added into SLNs as cryoprotector.[1,10]

Solvent emulsification evaporation technique

SLNs can also prepared by solvent evaporation method. The lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by giving the nanoparticles of 25 nm mean size. The solution was emulsified in an aqueous phase by high pressure homogenization. The organic solvent was removed from the emulsion by evaporation under reduced pressure 40 – 60 mbar.[7]

Solvent emulsification-diffusion method

SLNs can also be produced by solvent emulsifica-tion-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 an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium.[8]

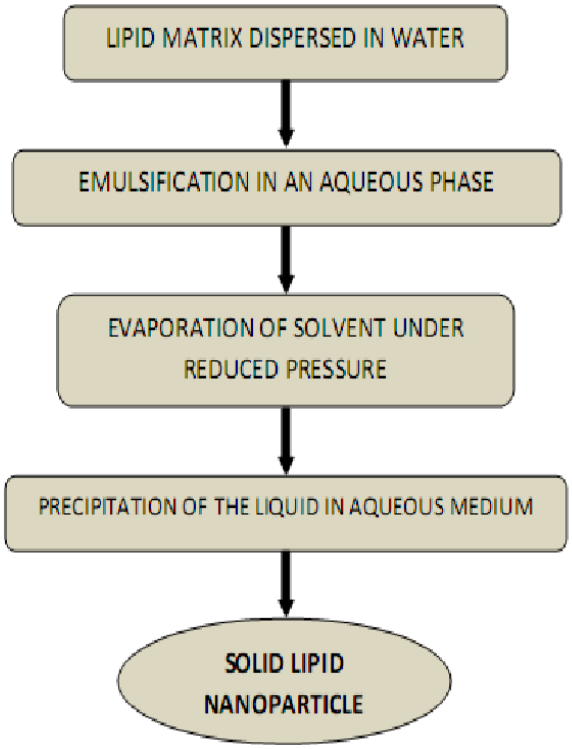

Fig 5: Solvent emulsification-diffusion method.[5]

Representation for emulsification-diffusion method Supercritical fluid technology

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 tempera-ture conditions. Carbon dioxide solution is the good choice as a solvent for this method.[9]

Micro emulsion based techonolgy

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

be removed. High-temperature gradients facilitate rapid lipid crystallization and prevent aggregation. Due to the dilution step; achievable lipid contents are considerably lower compared with the HPH based formulations.[6]

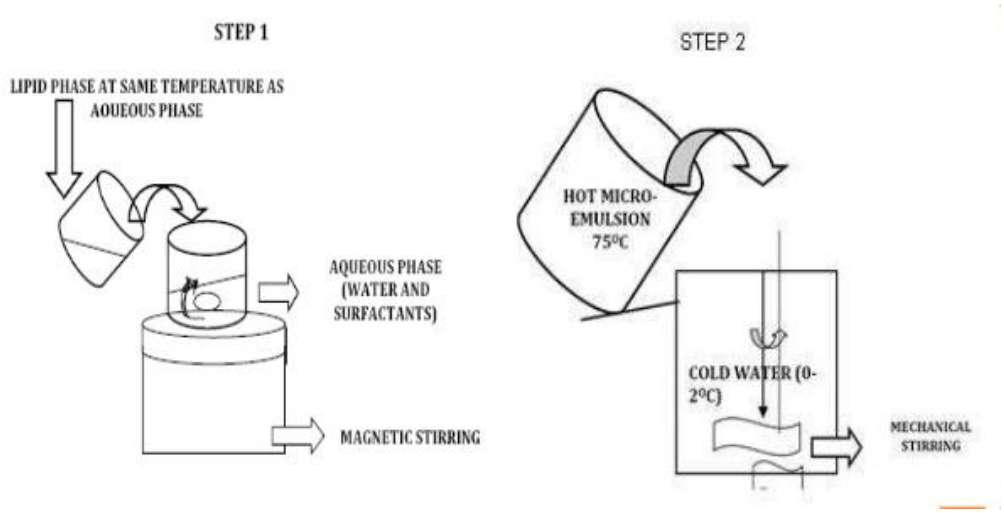

Fig 5: Micro emulsion based techonolgy.

Spray drying method

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

Double emulsion method

In double emulsion technique the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary was stabilized by stabilizer. Then this stabilised primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier. Thereafter, the double emulsion was stirred and was isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of a lipid-PEG derivative. A major drawback of this is the formation of high percentage of micro particles.[11]

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.[11]

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.[6]

Principles of drug release

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

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

Factors contributing to a fast release are the large surface area, a high diffusion co - efficient due to small molecular size, low viscosity in the matrix and a short diffusion distance δ for the drug. The increase in the velocity with decreasing particle size was reported.[12]

Sterilization of SLNs

For intravenous and ocular administration SLN must be sterile. The temperature reach during sterilization by autoclaving presumably causes a hot o/w micro emulsion to form in the autoclave, and probably alters the size of the hot nanoparticles. On subsequent slow cooling, the SLN reformed, but some nano-droplets may coalesce, producing larger SLN than the initial ones. SLN are washed before sterilization, amounts of surfactants and co surfactants present the hot systems are smaller, so that the nano-droplets may be not sufficiently stabilized.[13]

Characterization of SLNs

An adequate characterization of the SLN's is necessary for the control of the quality of the product. Several parameters have to be considered which have direct impact on the stability and release kinetics:

- Particle size and zeta potential.
- Degree of crystallinity and lipid modification.
- Co – existence of additional structures and dynamic phenomena.

Measurement of particle size and zeta potential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for routine measurements of particle size. PCS (also known as dynamic light scattering) measures the fluctuation of the intensity of the scattered light which is caused by particle movement. This method covers a size range from a few nanometers to about 3 microns. PCS is a good tool to characterize nanoparticles, but it is not able to detect larger micro particles. Electron Microscopy provides, in contrast to PCS and LD, direct information on the particle shape. The physical stability of optimized SLN dispersed is generally more than 12 months. ZP measurements allow predictions about the storage stability of colloidal dispersion.[14]

Dynamic light scattering (DLS)

DLS also known as PCS records the variation in the intensity of the scattered light on the microsecond time scale.

Static light scattering (SLS)/fraunhofer diffraction

SLS is an ensemble method in which the light scattered from a solution of particles is collected and fit into fundamental primary variable.

Acoustic methods

It measures the attenuation of the scattered sound waves as a means of determining size through the fitting of physically relevant equations.

Nuclear magnetic resonance (NMR)

NMR can be used to determine both the size and qualitative nature of nanoparticles.

Electron microscopy

Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) are the direct method to measure nanoparticles, physical characterization of nanoparticles with the former method being used for morphological examination. TEM has a smaller size limit of detection.

Method	***Principle***	***Measured size***	***Limitation***
LS	Light Interaction	50nm-1µm	Non-appropriated for very polydisperse populations Indirect method Great influence of aggregates or larger particles
LLD	Light Interaction	1-1000µm	High amount of sample required Indirect method
SEM, TEM	Microscopy	50nm-100µm	Time consuming Influence of the preparation sample
AFM	Microscopy	10nm-1µm	Sampling Non-automated Complexity of the set up Image treatment Subjective
ANUC	Centrifugation		Complex Data Processing
FFF	Elution	20nm-1µm	Difficult to handle Optimization needed for each kind of particles
CE	Electrophoresis	20-500nm	Complexity of the set up
PCH, SEC	Chromatography	<100nm	Long steps of optimization Time consuming

Shows main characteristics of particle size measurement methods

LS, light scattering; LLD, laser light diffraction; SEM, scanning electron microscopy; TEM, transmission electron microscopy; AFM, atomic force microscopy; ANUC, analytical ultracentrifugation; FFF, field flow fractionation; CE, capillary electrophoresis; PCH, packed column hydrodynamic; SEC, size exclusion chromatography.

Atomic force microscopy (AFM)

A probe tip with atomic scale sharpness is rastered across a sample to produce a topological map based on forces at play between the tip and the surface.

Measurement of crystallinity and lipid modifications

Powder X - ray diffraction and differential scanning calorimetry (DSC)

The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the former to be determined thus the degree of crystallinity to be assessed. DSC can be used to determine the nature and the speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperature.

Thermodynamic stability, lipid packing density and quantification are a serious challenge due to the increase, while drug incorporation rates decrease in the following order:
Super cooled melt < α-modification < β9-modification < β-modification.

Due to the small size of the particles and the presence of emulsifiers, lipid crystallization modification changes might be highly retarded. Differential scanning calorimetry (DSC) and X- ray scattering are widely used to investigate the status of the lipid. Infrared and Raman spectroscopy are useful tools for investigating structural properties of lipids. Their potential to characterize SLN dispersions has yet to be explored.[15]

Co – existence of additional structures

The magnetic resonance techniques, nuclear magnetic resonance (NMR) and electron spin resonance (ESR) are powerful tools to investigate dynamic phenomena and the nano-compartments in the colloidal lipid dispersions. Dilution of the original SLN dispersion with water might cause the removal of the surfactant molecules from the particle surface and induce further changes such as crystallization changes of the lipid modification.

Parameter Method of analysis

Molecular weight Gel chromatography
X-ray photoelectron spectroscopy,
Surface element analysis Electrophoresis,
Laser Doppler anemometry

Determination of Incorporated Drug

Amount of drug incorporated in SLNs influences the release characteristics hence it is very important to measure the amount of incorporated drug. The amount of drug encapsulated per unit wt. of nanoparticles is determined after separation of the free drug and solid lipids from the aqueous medium and this separation can be done by ultracentrifugation, centrifugation

filtration or gel permeation chromatography. The drug can be assayed by standard analytical technique such as spectrophotometer, a spectroflurophotometry, HPLC or liquid scintillation counting.

In vitro drug release[16]

- Dialysis tubing
- Reverse dialysis
- Franz diffusion cell

Dialysis tubing: In vitro drug release could be achieved by using dialysis tubing, the sln dispersion placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method.

Reverse dialysis In this technique a number of small dialysis sacs containing 1 mL of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium.

Franz diffusion cell: The SLN dispersion is placed in the donor chamber of a franz diffusion cell fitted with a cellophane membrane, then dialyzed against suitable dissolution medium at room temperature, the sample are withdraw from the dissolution medium at suitable inrtervals and analyzed from drug content using suitable method (U.V. spectroscopy, HPLC etc). the maintenance of condition sink is essential.

APPLICATION

Solid lipid nanoparticles in cancer chemotherapy

From the last two decades several chemotherapeutic agents have been encapsulated in SLN and their *in-vitro* and *in-vivo* efficacy have been evaluated. Outcomes of these studies have been shown to improve the efficacy of chemotherapeutic drugs, simultaneously reduction in side effects associated with them. Improved stability of drugs, encapsulation of chemotherapeutic agents of diversified physicochemical properties, enhanced drug efficacy, improved pharmacokinetics and less *in-vitro* toxicity are the important features of SLN which make them a suitable carrier for delivering chemotherapeutic drugs. Several obstacles frequently encountered with anticancer compounds, such as normal tissue toxicity, poor

specificity and stability and a high incidence of drug resistant tumor cells, are at least partially overcome by delivering them using SLN. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle to targeting tissues elsewhere in the body, such as bone marrow and solid tumors.

Solid lipid nanoparticles in tuberculosis disease

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

Solid lipid nanoparticles for lymphatic targeting

Several researchers have shown the enhancement of oral bioavailibility of poorly water soluble drugs when encapsulated in solid lipid nanoparticle. This enhanced bioavailibility is achieved via lymphatic delivery. To elucidate the absorption mechanism, from solid lipid nanoparticle, human excised Caco-2 cell monolayer could be alternative tissue for development of an in-vitro model to be used as a screening tool before animal studies are undertaken. The results obtained in this model suggested that the main absorption mechanism of carvedilol loaded solid lipid nanoparticle could be endocytosis and, more specifically, clathrin-mediated endocytosis.[16]

Targeted delivery of solid lipid nanoparticles for the treatment of lung diseases

Targeted delivery of drug molecules to organs or special sites is one of the most challenging research areas in pharmaceutical sciences. By developing colloidal delivery systems such as liposomes, micelles and nanoparticles a new frontier was opened for improving drug delivery. Nanoparticles with their special characteristics such as small particle size, large surface area and the capability of changing their surface properties have numerous advantages compared with other delivery systems. Targeted nanoparticle delivery to the lungs is an emerging area of interest.[17]

Solid lipid nanoparticles for parasitic diseases

Parasitic diseases (like malaria, leishmaniasis, tryanosomiasis) are one of the major problems around the globe. Antiparasitic chemotherapy is the only choice of treatment for these parasitic infections, the reason for this is that these infections do not elicit pronounced immune response hence effective vaccination may not be possible.[18,5] Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) represent a second generation of colloidal carriers and have emerged as an effective alternative to liposomes mainly due to their better stability profile, ease of scalability and commercialization and relative cost efficacy. Moreover, SLN and NLC due to their particulate nature and inherent structure exhibit good potential in the treatment of parasitic infections. Recent reports including our investigation have validated their utility at least to some extent. However, the need of hour is to undertake extensive investigations on SLN and NLC matrices in order to extend their versatility with respect to encapsulation ability and target ability and to arrive at a versatile, effective and economical approach for the delivery of anti-parasitic drugs.[19,5]

CONCLUSION

Solid lipid nanoparticle drug delivery technology presents considerable opportunities for improving medical therapeutics, but the technology's potential remains unrealized. The results cannot simply be regarded as nanoemulsions with a solid core. Clear advantages of SLN include the composition (physiological compounds), the rapid and effective production process including the possibility of large scale production, the avoidance of organic solvents and the possibility to produce carriers with higher encapsulation efficiency. Because of the SLN potential for facilitating controlled drug delivery to a target tissue and its biocompatibility, there will be much investigation in improvement of quality, efficacy, and safety profile of drugs using them in the future.

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