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Solid lipid Nano particles-A versatile carrier system

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ABSTRACT

Solid lipid nanoparticles (SLN) have been sought as alternative carriers for therapeutic agents it is administered by parenteral, oral, nasal and pulmonary routes. The research works in this area suggest that optimized conditions is required to incorporate hydrophobic or hydrophilic drugs and seem to fulfil the requirements for an optimum particulate carrier system. Solid lipid nanoparticles (SLNs) have been proposed as suitable colloidal carriers for delivery of drugs with limited solubility. Several obstacles frequently encountered with many compounds, with poor specificity and stability are at least partially overcome by delivering them using SLN.In this review it is intended to discuss the recent advances, various method of prepararion,methods of evaluation, various routes of administration, stability and pharmaceutical applications of SLN were discussed.

Key words: Solid lipid nanoparticles; Solubility; Zeta potential; Hydrophobic; Colloidal carrier.

1. Introduction

Colloidal delivery systems have recently gained great interest as potential carriers in the field of drug delivery. Solid lipid nanoparticles (SLN) are attracting major attention as novel colloidal drug carriers as alternative system to existing traditional carriers such as emulsion, liposome and nanoparticles[1].It plays a vital role as a lipid matrix made from physiological lipids which free from the risk of acute and chronic toxicity. The development of drug delivery carriers is often very challenging, due to the physico-chemical properties of the drug such as poor solubility, low permeability, short half-life, and high molecular weight. Solid lipid nanoparticles (SLN) as a novel drug delivery system for pharmaceutical drugs in various application routes to overcome these challenges. SLN as solid lipids (i.e. lipids solid at room temperature and also at body temperature) and stabilized by surfactant(s). The lipids used are triglycerides, complex glyceride mixtures or hard fat waxes[2]. Due to their unique size dependant properties lipid nanoparticles offers the possibility to develop new therapeutics. The ability to incorporative drugs into lipid nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. Hence solid lipid nanoparticles hold great promise for reaching goals of controlled and site specific drug delivery[3]

Solid lipid nanoparticles (SLN) have gained increased attention in the pharmaceutical and food industries because of their ability to overcome deficiencies of both microcapsules and nanoscalar colloidal carrier systems. They are the latest generation of nanoscalar encapsulation systems and combine the advantages of the parent liquid nanoemulsions or microemulsions of high dissolution velocities associated with high permeability of the active compound through the gut wall, while simultaneously solving existing problems associated with physical and chemical stability of the encapsulated compound and ease of handling[4].

SLNs are composed of physiological and compatible lipids with a high melting point as the solid core, which is coated by nontoxic amphiphilic surfactants as the outer shell[5]. As suggested by the obstacles nanoparticle size in and out of the body should be same range in submicron size (50–1000 nm)[6].The physiochemical characteristics and stability of drug-loaded SLNs depend on the properties of drug and ingredients is reveled by the literatures[7]. Appropriate choice of lipids, surfactants, and their composition affect the particle size, long-term stability during storage, drug loading, and release behavior[8]. It means that there is an optimal SLN formulation for each drug that can be obtained by investigating the effect of process variables on the characteristics of desired carriers The final SLN depends upon several factors such as drug substance physicochemical properties, surfactant type and concentration, lipid type and crystallization pattern and the method of production which gives the drug substance distribution and incorporation efficiency of the SLN[9,10] .Usually, the drug substance is dissolved or dispersed in the melted lipid phase before preparation by homogenization to achieve efficient encapsulation in the lipid[11]. The incorporation efficiency is likely depending on the drug substance lipophilicity and solubility in the two phases

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.2.Solid Lipid Nanoparticles (SLNs)

SLN's are sub-micron colloidal carriers composed of biodegradable physiological lipids generally recognized as safe and due to this biodegradable nature SLN's are less toxic when compared to polymeric nanoparticles. Solid lipid nanoparticles (SLN) are attracting major attention as novel colloidal drug carriers as alternative system to existing traditional carriers such as emulsion, liposome and nanoparticles .It plays a vital role as a lipid matrix made from physiological lipids which free from the risk of acute and chronic toxicity.The development of drug delivery carriers is often very challenging,

The lipids used are triglycerides, complex glyceride mixtures or hard fat waxes. In the middle of the 1990s, the attention of different research groups has focused on alternative nanoparticles made from solid lipids, the so-called solid lipid nanoparticles.

The SLN combine the advantages of other innovative carrier systems (e.g. physical stability, protection of incorporated labile drugs from degradation, controlled release, excellent tolerability) while at the same time minimizing the associated problems. SLN formulations for various application routes (parenteral, oral, dermal, ocular, pulmonary, rectal) have been developed and thoroughly characterized in *vitro* and *in vivo* . A first product has recently been introduced to the Polishmarket (Nanobase, Yamanouchi) as a topically applied moisturizer. At the turn of the millennium, modifications of SLN, the so-called nanostructured lipid carriers (NLC) and the lipid drug conjugate (LDC) nanoparticles have been introduced .

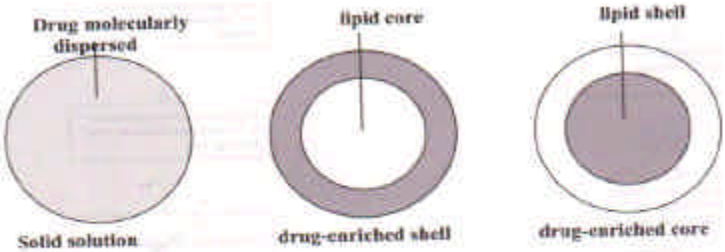

Fig.1 Solid lipid nanoparticle (SLN)

2.1. Advantages of SLN

1. Use of biodegradable physiological lipids.
2. Avoidance of organic solvents related to the production method or methods.
3. Wide application spectrum (oral, i.v., dermal).
4. Improved bioavailability of poorly water- soluble molecules.
5. Site specific delivery of drugs via i.v. injection route.
6. Enhanced drug penetration into the skin, localization in certain skin layers, via dermal application.
7. Possibility of scaling up to industrial production level, by high-pressure homogenization, at low cost and in a relatively simple way.
8. Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment.
9. SLNs have better stability and ease of upgradability to production scale as compared to liposome.
10. In SLNs the lipid matrix is made from physiological lipid which decreases the danger of acute and chronic toxicity.
11. Very high long-term stability.
12. It is easy to manufacture than bipolymeric nanoparticles.
13. Better control over release kinetics of encapsulated compound.
14. SLNs can be enhancing the bioavailability of entrapped bioactive.
15. Chemical protection of labile incorporated compound.
16. Raw material which are to be required are same as that of emulsion.
17. Large scale production is possible.
18. High concentration of functional compound can be achieved.
19. Lyophilization possible.

Common disadvantages of SLN are their particle growing, their unpredictable gelation tendency, their unexpected dynamics of polymorphic transitions and their inherent low incorporation rate due to the crystalline structure of the solid lipid.

2.2. Essential excipients Used for the Preparation of Solid LipidNanoparticles[1]

Various methods have been developed for the preparation of SLNs which uses biocompatible
lipids or lipid molecules with a history of safe use in medicine. The essential excipients of SLNs
are solid lipid as matrix material, emulsifier and water. The term lipid is used here in a broader
sense and includes
a. Saturated monoacid triglycerides- tristearin, tripalmitin, trilaurin, trimyristin
b. Partial glycerides - glyceryl monostearate, glyceryl behenate, glyceryl palmitostearate
c. Fatty acids- stearic acid, behenic acid, palmitic acid, decanoic acid
d. Steroids- cholesterol and
e. Waxes - cetyl palmitate.

All classes of emulsifiers have been used but physiologically compatible emulsifiers such as phospholipids (Soyabean lecithin, egg lecithin, phosphatidyle choline), bile salts (Sodium cholate, Sodium taurocholate, sodium glycholate) and poloxamers (Poloxamer- 188, 182, 407) are preferred as stabilizers and in few cases co-emulsifiers (e.g. butanol) are used.

3. Various techniques Used for the Preparation of Solid Lipid Nanoparticles

3.1.High pressure homogenization technique

In high pressure homogenization technique lipids are pushed with high pressure (100-200 bars)through a narrow gap of few micron ranges. So shear stress and cavitations (due to sudden decrease in pressure) are the forces which cause the disruption of particle to submicron range.Normally the lipid contents are in the range of 5-10%. At this concentration it does not cause any problem to homogenizer. SLN can be stabilized by wide range of surfactants or polymers and their mixture but the emulsion for parenteral nutrition is stabilized by lecithin only. In contrast to other preparation technique high pressure homogenization does not show scaling up problem.Basically, there are two approaches for SLN production by high pressure homogenization, hot and cold homogenization techniques**.** For both the techniques depicted in **Fig.2.** The drug is dissolved or dispersed or solubilized in the lipid being melted at approximately 5-10^{o}c above the melting point.

3.1.1. Hot homogenization technique

For the hot homogenization technique the drug loaded melted lipid is dispersed under stirring by high shear device (e.g. Ultra Turrax) in the aqueous surfactant solution of identical temperature.The pre-emulsion obtained is homogenized by using a piston gap homogenizer (e.g. Macron LAB 40 or Macron LAB 60 or APV-2000) and the produced hot o/w nanoemulsion is cooled down to room temperature. At room temperature the lipid recrystallizes and leads to formation of SLNs . In case of glycerides composed of short chain fatty acids (e.g. Dynasan-112) and glycerides with low melting point (too close to room temperature), it might be necessary to cool the nanoemulsion to lower temperature than room temperature to start recrystallization .

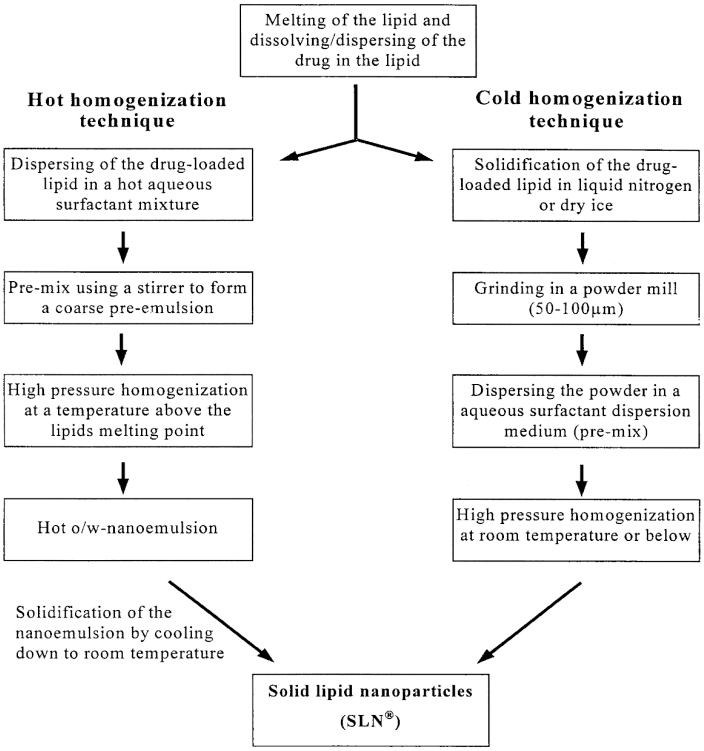

Fig. 2. Schematic representation of SLN preparation by hot and cold homogenization

In general, high temperature results in lower particle size due to the decreased viscosity of the inner phase, but the disadvantage is that, at high temperature the rate of drug and carrier degradation is more and further due to small particle size and presence of emulsifier, lipid crystallization may be highly retarded and the sample remains as super cooled melt for several months . A great disadvantage of hot homogenization technique is that, it is a poor technique for hydrophilic drug candidate because during heating the drug partitions into aqueous phase and when cooled, most of drug particle remained at the outer layer of the solid lipid nanoparticles, which leads to burst release.

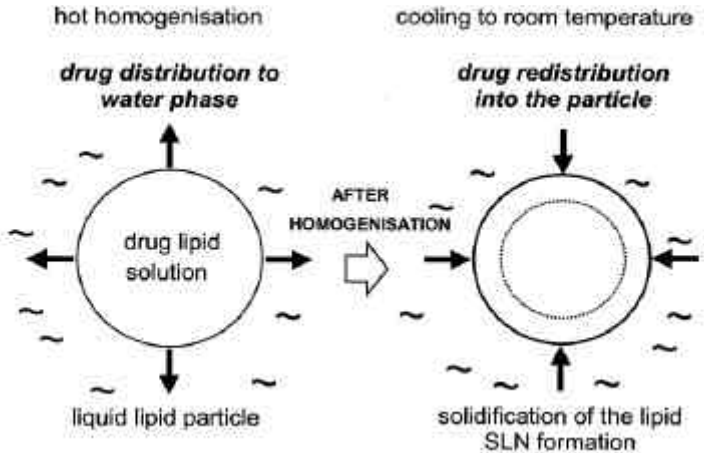

Fig.3.Redistribution of the drug into SLN on cooling after homogenization.

3.1.2. Cold homogenization technique

Cold homogenization is carried out with the solid lipid containing drug and therefore called as milling of a suspension. Cold homogenization has been developed to prevent:

- Temperature induced drug degradation
- Partitioning of hydrophilic drug from lipid phase to aqueous phase
- Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts

The first step of preparation is same as hot homogenization which includes dispersion or dissolving or solubilisation of the drug in the melted lipid. Then the drug lipid mixture is rapidly cooled either by means of liquid nitrogen or dry ice. The drug containing solid lipid is milled by means of mortar or ball mill to micron size (50-100 micron) and these microparticles are dispersed in chilled emulsifier solution yielding a pre-suspension. Then this pre-suspension is subjected to high pressure homogenization at room or below room temperature, where the cavitation force is strong enough to break the microparticles to SLNs. This process avoids or minimizes the melting of lipid and therefore minimizing loss of hydrophilic drug to aqueous phase . Another method to minimize the loss of hydrophilic drug to aqueous phase is to replace water with other media (e.g. oil or PEG 600) with low solubility for the drug. In comparison to hot homogenization, in cold homogenization particle size and polydispersity index are more. The cold homogenization only minimizes the thermal exposure of drug, but it does not avoid completely it due to melting of the lipid/drug mixture in the first step of preparation. High pressure homogenization increases the temperature of the sample (e.g. 10-20ºC for each homogenization cycle) . In most of the cases, 3-5 homogenization cycles at 500-1500 bar are sufficient to prepare SLN. Increasing the number of homogenization cycle or the homogenization pressure resulted in increase of particle size due to particle coalescence which resulted from high kinetic energy of particles.

3.2. Microemulsion technique

Microemulsions are clear, thermodynamically stable system composed of a lipophilic phase, surfactant and co-surfactant (in most cases) and water..Microemulsion needs to be produced at a temperature above the melting point of the lipids, so the lipid should have melting point above room temperature. At first solid lipids are taken (approximately 10%) and melted at a temperature 65-70°C. Separately, a mixture of surfactant of 15%, co-surfactant of 10% and water were heated to same temperature as the lipid and then added to melted lipid under mild stirring. A transparent, thermodynamically stable system was formed which was then dispersed under stirring in excess cold water (2-3°C) in the typical ratio of microemulsion to cold water ranges from 1:10 to 1:50 using a specially developed thermostated syringe with gentle stirring . The composition of microemulsion determines the dilution process. The SLN preparations were washed three times with distilled water and filtered using a membrane (e.g. Diaflo YM 100) having cut off 100,000 Dalton in order to remove any unwanted bigger lipid particles . The excess water was removed either by ultra-filtration or by lyophilisation in order to increase the particle concentration**.**In the microemulsion, drugs are partitioned partly in the internal oil phase and partly at the interphase between internal and continuous phase, depending on their lipophilicity. When SLNs are formed by a quick quenching of the microemulsion, the presence of the droplet structure of the microemulsion does not allow the drug molecules to nucleate and form the crystal lattice, and consequently the drug molecules remain dispersed in the lipid matrix of the SLNs in an amorphous state .The major parameters during scaling up are temperature gradient (the temperature difference between lipid melting and emulsion process), the pH value and the water content. High temperature gradients facilitate rapid lipid crystallization and prevent aggregation. The removal of excess water from the prepared SLN dispersion is a difficult task with regard to the particle size and high concentrations of surfactants and co surfactants which are necessary for formulating purposes.

3.3. 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 that is emulsified in an aqueous phase using high speed homogenizer.To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the microfluidizer. Thereafter, the organic solvent was evaporated by mechanical stirring at room temperature and reduced pressure (e.g. rotary evaporator) leaving lipid precipitates of SLNs. 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 thermolabile 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

3.4. 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 thermodynamic equilibrium of both liquid . When heating is required 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.

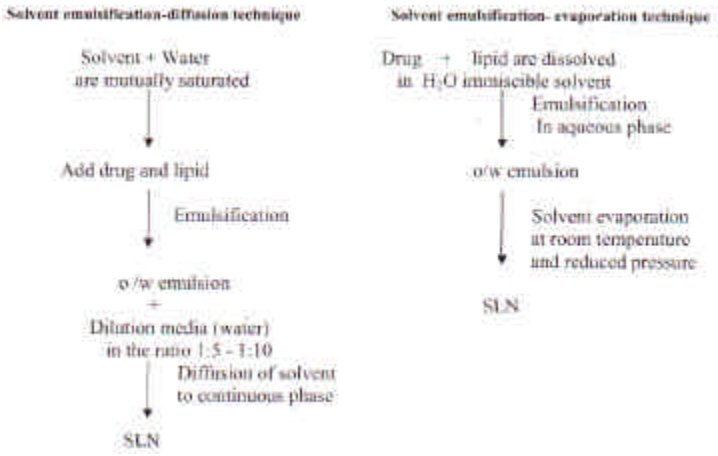

Fig. 4.Solvent emulsification-diffusion technique

3.5 .Melting dispersion method (Hot melt encapsulation method)

The melting dispersion method was as follows, in first step, drug and solid lipid were melted in an organic solvent regarded as oil phase and simultaneously water phase was also heated to same temperature as oil phase. Then in second step, the oil phase added in to a small volume of water phase and the resulting emulsion was stirred at higher rpm for few hrs. At last it was cooled down to room temperature to give SLNs. 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 ultrasonication method.

3.6. High shear homogenization and/or Ultrasonication technique

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 recrystallization 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 the 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 .

Advantages of this technique are widespread and easy to handle. It is a simple, available and effective method to produce SLNs without organic solvents; but it also having the limitation that, it require an extra step of filtration of formed SLN emulsion in order to remove impurity materials (e. g. metal) produced during ultrasonication and is often compromised by the presence of microparticles .

3.7. Double emulsion technique

In double emulsion technique the drug (mainly hydrophilic drugs) was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (e.g. PVA). 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 the incorporation of a lipid -PEG derivative. Sterical stabilization significantly improved the resistance of these colloidal systems in the gastrointestinal fluids. This technique is mainly used to encapsulate hydrophilic drug (peptides). A major drawback of this technique is the formation of high percentage of microparticles. Sodium cromoglycate containing SLN was tried to be prepared by this technique but the produced colloidal system gave the average particle of micrometer range. Insulin loaded SLN was prepared by a novel reverse micelle-double emulsion technique, using sodium cholate-phosphatidylcholine based mixed micelle.

3.8. Membrane contactor technique

It is a novel technique to prepare the SLN. 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 ZrO2 layer on an AlO2-TiO2 support) allowing the formation of small droplets as indicated in **Fig.5**. The aqueous phase was stirred continuously and circulates tangentially inside the membrane module, and sweeps away the droplets being formed at the pore outlets. SLNs were formed by the cooling of the preparation at the room temperature. Here both the phases were placed in the thermostated bath to maintain the required temperature and nitrogen was used to create the pressure for the liquid phase.

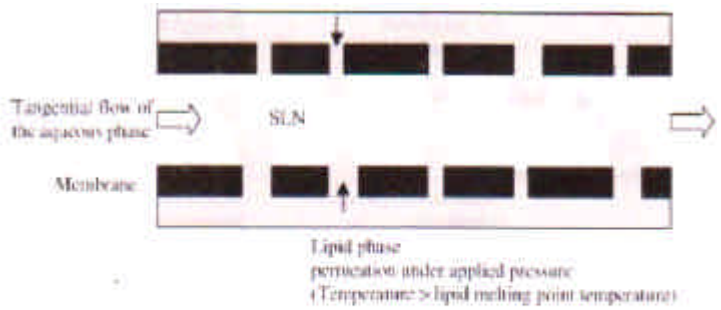

Fig. 5. Schematic drawing of the membrane contactor for the SLN preparation

The membrane contactor method is also used for the preparation of polymeric nanoparticles, by methods involving a polymerization of dispersed monomers (interfacial polymerization method) or a dispersion of preformed polymers (nanoprecipitation method). The advantages of this process of SLN preparation using a membrane contactor are shown to be its facility of use, the control of the SLN size by an appropriate choice of process parameters and its scaling up ability. Vitamin-E loaded SLN was prepared by this technique.

3.9. Solvent injection technique[17]

Solvent injection technique is a novel approach to prepare SLN, which has following advantages over other production methods like use of pharmacologically acceptable organic solvent, easy handling and fast production process without technically sophisticated equipment. It is based on lipid precipitation from the dissolved lipid in solution. In this technique, the solid lipid was dissolved in water-miscible solvent (e.g. ethanol, acetone, isopropanol) or a water-miscible solvent mixture. Then this lipid solvent mixture was injected through an injection needle in to stirred aqueous phase with or without surfactant. The resulted dispersion was then filtered with a filter paper in order to remove any excess lipid. The presence of emulsifier within the aqueous phase helps to produce lipid droplets at the site of injection and stabilize SLN until solvent diffusion was complete by reducing the surface tension between water and solvent resulting in solvent.

3.10. Supercritical fluid technology

This is a novel technique which recently applied for the production of SLNs. A fluid is qualified as supercritical when its pressure and temperature exceed their respective critical value. Above the critical temperature, it is not possible to liquefy a gas by increasing the pressure. The supercritical fluid has unique thermophysical properties. As the pressure is raised, the density of the gas increases without significant increase in viscosity while the ability of the fluid to dissolve compounds also increases. A gas may have little to no ability to dissolve a compound under ambient condition can completely dissolve the compound under high pressure in supercritical range. Therefore, its solvation power is altered by careful control of changes in temperature and pressure. Many gases like, CO_2, ammonia, ethane, $CHClF_2$ and CH_2FCF_3 were tried, but CO_2 is the best option for SCF technique because, it is generally regarded as safe, easily accessible critical point [31.5ºC, 75.8 bar), does not causes the oxidation of drug material, leaves no traces behind after the process, is inexpensive, noninflammable, environmentally acceptable an easy to recycle or to dispose off. Most of the time solubility enhancers (e.g. ethanol) are used to increase the solubility of less soluble solvent (e.g. water) in the SCF phase or this technique generally use organic solvents (e.g. DMSO, DMFA) because they are fully miscible in SCF-CO2. This technology comprises several processes for nanoparticles production such as rapid expansion of supercritical solution (RESS), particles from gas saturated solution(PGSS), gas/supercritical antisolvent (GAS/SAS), aerosol solvent extraction solvent (ASES), solution enhanced dispersion by supercritical fluid (SEDS),supercritical fluid extraction of emulsions (SFEE). Mainly SAS and PGSS were used for SLN preparation.

3.10.1.GAS/SAS

In this process SCF acts as antisolvent for processing solid that are insoluble in SCF. It exploits the ability of SCF to dissolve in organic solvent and reduce the solvation power of solid in solution, thus causing the solid to precipitate. At first, the near critical or supercritical fluid was introduced in a vessel containing an organic solvent in which the solid material to be crystallized was dissolved which causes the intimate mixing of the fluid and liquid resulting in liquid expansion and particle precipitation. A clear disadvantage of this technique is the lack of control on the particle formation. A modification of SAS technique was used to prepare lysozyme spherical nanoparticles, which combines both the atomization and anti-solvent process, by using water/ethanol solution.

3.10.2.PGSS

In this process, the SCF was dissolved in liquid substrate, or a solution of substrate in solvent, or a suspension of substrate in solvent followed by a rapid depressurization of this mixture through a nozzle causing the formation of SLN. The great advantage of this process is that it produces particles of great variety of substance that need not be soluble in SCF-CO2. Limitations are, care must be taken for thermolabile solute and the final product may contain microparticles. Insulin nanoparticles are produced by this process, in which the solvent used, was DMSO and the lipid mixture (tristearin, phosphatidylcholine, dioctylsulfo succinate) were atomized to produce insulin SLN (<500nm).

4. STABILITY OF SOLID LIPID NANOPARTICLE FORMULATIONS[11,13,14]

For intravenous and ocular administration solid lipid nanoparticles must be sterile. The high temperature reached during sterilization by autoclaving presumably causes a hot o/w microemulsion to form in the autoclave, and probably modifies the size of hot nanodroplets. On subsequent slow cooling, the solid lipid nanoparticles reformed, but some nanodroplets may coalesce, producing larger solid lipid nanoparticles than the initial ones.

4.1.Influence of the lipid on stability of solid lipid nanoparticle formulations

The average particle size has been increasing with increasing lipid-melting tem-

perature for both high-pressure homogenization and high shear homogenization. This is due to the increased viscosity of dispersed phase.

4.2.Influence of the emulsifier on stability of solid lipid nanoparticle formulations

A higher concentration of the emulsifier reduces the surface tension of the particles and facilitates the particle partition during homogenization process. Increase in the surface tension decreases the particle size. However the use of rapidly distributing surfactants like SDS is not recommended as their ability to cover surfaces and reduce surface tension is often combined with properties of water solubility and toxicity.

5. ROUTES OF ADMINISTRATION[29]

Solid lipid nanoparticles are used to prepare drugs for different routes of administration . The various routes are

1. Transdermal administration
2. Parenteral administration
3. Per oral administration
4. Lung administration

5.1. Transdermal administration

The smallest particle sizes are observed for solid lipid nanoparticle dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantages for dermal administration. Due to their small particle size solid lipid nanoparticles possess both adhesive and occlusive properties. This is due to the fact that solid lipid nanoparticles form an intact film upon drying and thus decreases water evaporation from the skin. In most cases, the incorporation of the SLN dispersion in an ointment or gel is necessary in order to achieve a formulation which can be administered to the skin. The incorporation step implies a further reduction of the lipid content of the SLN dispersion resulting in semi solid, gel-like systems, which might be acceptable for direct application on the skin. It has been found that solid lipid nanoparticles have UV reflecting properties. These observations open the possibility of the development of solid lipid nanoparticles based UV protective systems. Solid lipid nanoparticles have been found to modulate the drug release into the skin and to improve drug delivery to particular skin layers in vivo. After applying on the skin, the loss of water causes change in lipid modification and SLN structure.

5.2. Parenteral administration

The parenteral administration for solid lipid nanoparticles ranges from intra articular to intravenous administration. Pharmacokinetic studies of doxorubicin incorporated into SLN showed higher blood levels in comparision to a commercial drug solution after i.v injection in rats. Regarding distribution, solid lipid nanoparticles were found to have higher drug concentrations in lung, spleen and brain, while the solution led to more distribution into liver and kidney.

5.3. Per oral administration

Per oral administration forms of solid lipid nanoparticles may include aqueous dispersions or solid lipid nanoparticle-loaded traditional dosage forms such as tablets, pellets or capsules. The microclimate of the stomach favours particle aggregation due to the acidity and high ionic strength. It can expected, that food will have a large impact on solid lipid nanoparticle performance, however no experimental data have been published on this issue to our knowledge. The question concerning the influence of the gastric and pancreatic lipases on solid lipid nanoparticle degradation in vivo remains open, too unfortunately; only few in vivo studies have been performed yet.

5.4. Lung administration

Solid lipid nanoparticles are prepared in powder form, which can be used to be an inhalation to the target site. The main advantage in this route is we can control the release curve.

6. Pharmaceutical Applications of Solid Lipid Nanoparticles [29,30]

6.1.Topical application

Similar to liposomes they are composed of well tolerated excipients and due to their small particle size they possess adhesive properties leading to film formation on the skin. Moreover they ensure increased penetration of drug into the epidermis by close contact with the stratum corneum. However the drug free nanoparticles can be used to improve occlusive properties. An additional advantage of these formulations is regarding their product registration for pharmaceuticals as well as for cosmetics.

Liposomes are extremely difficult to be quantified whereas quantitative analysis of SLNs in creams is very straight forward and simple. Many cream bases do not exhibit a melting peak below 100°C, which signifies the content of SLNs in a cream can be quantified by their melting peak determined by DSC. This unique property of SLNs opens new markets for topical products containing colloidal carriers for active ingredients. SLNs forms adhesive film on the skin however, previously it was assumed that SLNs would be forming films of densely packed spheres, however, recent studies suggested that under the pressure of application the spheres form a coherent film. Such a lipid film formation will be able to restore a damaged protective lipid film on the skin. Application of the conventional SLN-free cream only slightly changed the structure.

SLNs are found to be more suitable for hydrophilic peptide drugs too. Further solid lipid nanoparticles are used as the topical carrier for epidermal targeting of podophyllotoxin (POD).

6.2.Oral administration

Solid lipid nanoparticles might be an interesting carrier system for per oral administration of poorly water soluble drugs with low per oral bioavailability. Oral administration of SLNs is possible as aqueous dispersion or in a traditional dosage form i.e. tablets, pellets, capsules or powders in sachets. The poor absorption of certain drugs can be related to their poor wettability, so that incorporation of drugs into solid lipid nanoparticles provides completely wettable carriers. The lipid particles undergo digestion similarly to food lipids. Due to high dispersivity of solid lipid nanoparticles, they exhibit a high specific surface area for enzymatic attack by intestinal lipases.This enzymatic degradation of the lipids leads to release of incorporated drugs in molecularly dispersed form. The bile salts facilitate their solubilization in the intestine and subsequent absorption. For the production of tablets the aqueous SLNs dispersion can be used instead of a granulation fluid in the granulation process. Alternatively SLNs can be converted to a powdered form (e.g. by spray-drying) and added to the tableting powder mixture.

6.3.Lymphatic transport carrier

Over 65% of commercially available drugs are formulated for oral administration. However, one of the major factors limiting the effectiveness of orally administered drugs is poor absorption from gastro-intestinal tract or extensive pre-systemic clearance through hepatic first-pass metabolism. For poorly water-soluble drugs, the slow dissolution rates in the primarily aqueous contents of the gastro-intestinal tract shows a significant barrier to absorption. One strategy for improving the absorption of these drugs involves administration in a lipid based delivery system, which presents the drug to the gastro-intestinal tract in a solubilised form, thus eliminating poor aqueous solubility, and slows dissolution as barriers to absorption. The gastro-intestinal lymphatic system is a specific transport pathway through which dietary lipids, fat soluble vitamins, and water in-soluble peptide type molecules can gain access to systemic circulation. Drugs transported by way of gastro-intestinal lymphatic system, bypass the liver and avoid potential hepatic first-pass metabolism. Lymphatic drug transport may promote drug incorporation into the body's lipid handling system, thus offering the potential to manipulate the drug residence time and drug distribution within the body. For a maximum bioavailability enhancing effect, the drug should be closely associated with the lipid. This means that when the lipid is degraded to surface active compounds, the drug should be simultaneously be solubilized. The drug should be preferentially dissolved (molecularly dispersed) in the lipid to be digested. Movements of the gastrointestinal tract in combination with the presence of surface active compounds such as bile salts transfer oils and fat in general to a coarse emulsion. The emulsion droplets are then degraded. Degradation and subsequent solubilization of drugs is faster, in case the droplets are finer, preferentially in the nanometer size range and not microdroplets. Both principles, close association of the drug with the lipid and ultrafine dispersion in the nanometer range are realized in the SLN delivery systems.

6.4.Pulmonary Administration

SLNs have been proved to possess a high tolerability that may lead drug target-

ing to lung macrophages. Particles in the lungs are easily accessed by lung macrophages that suggest the use of the SLNs system for treating infections of the mononuclear phagocytic system (MPS). It is difficult to reach to particular parasites such as mycobacterium with a normal course treatment. Within the MPS macrophages, liver and spleen macrophages are more accessible than the parasites in the lung macrophages. SLNs (200 nm) as a carrier of drugs to the lungs, through alveolar airways to the lymphatic system thus minimizing MPS uptake and increasing the concentration at the tumor site.

6.5.SLNs as potential new adjuvant for vaccines

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

Degradation can be slowed down even more when using sterically stabilizing surfactants that hinder the anchoring of enzyme complexes. SLNs have been tested as adjuvant in sheep the two unoptimized SLN formulations exhibited 43% and 73% of the immune response (antibody titer) of FIA investigated as standard. These data are promising and currently the SLNs are being optimized regarding their surface properties to give a maximum immune response.

6.6.Solid lipid nanoparticles (SLNs) as targeting carriers

The extremely small particle size of solid lipid nanoparticles, which are less than 50 nm, might be beneficial with respect to drug targeting. Small carrier size generally favors reduced uptake by the reticuloendothelial system. Moreover after intravenously administration particles smaller than the fenestration of the endothelial wall i.e. below 150 nm might be able to leave the vascular compartment, through these fenestrae in the sinusoids of the liver spleen and bone marrow or at the location where the basal membrane of the endothelium is damaged; for example, at the site of inflammation or in tumor tissues. Drug targeting might also be possible by surface modification of solid lipid nanoparticles.

6.7. Brain targeting through SLNs

SLNs can improve the ability of the drug to penetrate through the blood-brain barrier and is a promising drug targeting system for the treatment of central nervous system disorders. SLNs are mainly composed of biocompatible and biodegradable lipids and show a very good tolerability *in vivo*. SLN increases the solubility and makes the drug lipophilic .Due to this the drug can able to penetrate the blood brain barrier easily for targeting the brain disorder with increased bioavailability.

6.8. Liver targeting through SLNs

SLNs are an attractive carrier system to polymeric nanoparticles, increasing attention from different groups. For more than a decade the antineoplastic agent 5-flourouracil (5-FU) has been used in the treatment of various solid tumors such as cancers of stomach, liver, intestine and so on. However 5-FU may cause the various side effects such as gastrointestinal tract reaction, bone marrow depression, leucopenia or cytopenia. In this context the use of SLNs could be to target the drug to the intended sites. This would result in increase in the therapeutic index by decreasing the dose of the drug and also the side effects caused by the drug. The surface properties of SLNs can also be modified to alter the pharmacokinetic behavior of the incorporated drug. This can be done by using the amphiphilic solvation enhancer PE-PEG. Both SLN and SLN-PE-PEG incorporation of 3'-Azido-3'-deoxythmidine palpitate (AZT-P) significantly decreased the urinary excretion of (AZT-P) but increased the localization of (AZT-P) in liver. Higher levels were obtained after i.v. injection of (AZT-P). Similarly 5-FU has poor liposoluble properties and it dissolves readily in aqueous media. Synthesis of a more lipophilic prodrug is an effective method for lipophobic drugs to form stable SLNs. To enhance the liver targeting and reduce the side effects of 5-FU, it was acylated by stearyl chloride to form N- stearyl-5-FU (5-FuS). Thus stable SLNs were produced through combination of 5-FU with long chain fatty acids, which is a physiologically acceptable and biodegradable excipients. After i.v injection of 5-FU-SLN it was easily uptaken by organs containing reticuloendothelial cells, especially in the liver. In order to improve the efficiency of 5-FU for treating liver cancer, 5-FU-SLN is a promising drug targeting system and may also allow a reduction in drug dose and decrease in side effects as well as systemic toxicity. Results showed that 5-FU-SLN was rapidly eliminated from the circulating blood and mostly recovered from the liver. Thus in tested organs, about 70% of the total amount of the drug was concentrated in liver.

6.9.Application of SLNs in cancer chemotherapy

Cancer is characterized by the formation of abnormal tissues known as neoplasm. Developed basically due to change in the way cells proliferate and differentiate. The effectiveness of cancer therapy in various solid tumors depends upon adequate delivery of therapeutic agent to tumor cells. Inadequate delivery of drugs to tumor cells leads to re growth of tumor cells and even result in development of resistant cells.Several drug delivery systems were introduced namely liposomes, microparticles, supramolecular bio-vectors, polymeric conjugates and nano-particulates to facilitate effective chemotherapy with the anti-cancer agents. The introduction of doxorubicin long circulating liposome in the market for cancer therapy has brought a renewed interest in the field of targeted drug delivery to cancer.Due to drawback of these carrier systems such as physical instability, difficulties in scale-up, lack of specific tumor targeting and cytotoxicity of the polymers; research groups have focused on nanoparticles prepared using lipid matrices which can be a beneficial system to deliver anticancer drug to cancer tissues through enhanced permeability and retention effect.

7. Evaluation of SLN

- Particle size and Zeta potential using
  - PCS-Photon Correlation Microscopy
  - TEM-Transmission Electron Microscopy
  - SEM-Scanning Electron Microscopy
  - AFM-Atomic Force Microscopy
  - STM-Scanning-tunneling Microscopy
  - FFEM-Freez Fracture Electron Microscopy
  - LD-Laser Diffraction
- Surface morphology by Scanning Electron microscopy
- Polymorphism and crystallinity by Powder X-ray Diffraction (XRD)
- Degree of crystallinity by Differential Scanning Calorimetry (DSC)
- Drug content
- Drug Entrapment efficiency(%)
- *Invitro* drug release studies
- *Invivo* animal studies

CONCLUSION

SLN is a carrier system that possesses the potential to develop as the new generation of the carrier systems after the liposomes. They have good perspectives to be developed and marketed very successfully. The promising results of SLN prove their potential as versatile carrier systems for application in cosmetic and pharmaceutical formulations. Solid lipid nanotechnology represents a new and exciting frontier for pharmaceutical dosage form design to increase bioavailability and patient compliance. Because of their distinct advantages, such as small size, high solubility, Chemical protection of labile incorporated compound, use of biodegradable physiological lipids, wide application spectrum, improved bioavailability of poorly water- soluble molecules, site specific delivery of drugs, enhanced penetration of drugs SLNs seem to be the prototype of an ideal carrier for Class III and Class IV drugs.

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