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Review Article

SOLID LIPID NANOPARTICLES–A REVIEW

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ABSTRACT

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 varied sciences. Due to their unique size-dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics. The incorporation of drugs into nanocarriers offers a new prototype in drug delivery that could be used for several levels of drug targeting. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site-specific drug delivery and hence have attracted the wide attention of researchers. This review presents a broad treatment of solid lipid nanoparticles discussing their advantages, limitations, and their possible remedies. Different production methods which are suitable for large-scale production and applications of solid lipid nanoparticles are described. The characterization of solid lipid nanoparticles is generally carried out by photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry, etc.

Keywords: Solid lipid nanoparticles (SLN), Colloidal drug carriers, Homogenization, Scanning Electron Microscopy

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. Over the years, they have emerged as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. However, the scarcity of safe polymers with regulatory approval and their high cost have limited the widespread application of nanoparticles to clinical medicine [1].

To overcome these limitations of polymeric nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting the wide attention of formulators worldwide [2]. SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes, and polymeric nanoparticles). They are a new generation of submicron-sized lipid emulsions where the liquid lipid (oil) has been substituted by a solid lipid. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interfaces, and are attractive for their potential to improve the performance of pharmaceuticals, nutraceuticals and other materials [3].

Advantages of SLNs over polymeric nanoparticles

SLNs combine the advantages of polymeric nanoparticles, fat emulsions, and liposomes while simultaneously avoiding their disadvantages [4].

The advantages of SLNs include the following

☐ The nanoparticles and the SLNs particularly those in the range of120–200 nm are not taken up readily by the cells of the RES (Reticulo Endothelial System) and thus bypass liver and spleen filtration[9].

☐Controlled release of the incorporated drug can be achieved for up to several weeks [9-11]. Further, by coating with or attaching ligands to SLNs, there is an increased scope of drug targeting [12, 13].

☐SLN formulations stable for even three years has been developed. This is of paramount importance with respect to the other colloidal carrier systems [14, 15].

☐ Excellent reproducibility with a cost effective high-pressure homogenization method as the preparation procedure [8].

☐ The feasibility of incorporating both hydrophilic and hydrophobic drugs [5-7].

☐The carrier lipids are biodegradable and hence safe [16-18].

☐Avoidance of organic solvents [13].

☐Feasible large scale production and sterilization [9, 19].

☐ The possibility of controlled drug release and drug targeting [4, 6, 16-19].

☐Generally less toxic as compared to some polymeric nanoparticles because physiological and biocompatible lipids are used [5-6].

☐ Protecting the labile and sensitive drugs from chemical, photochemical or oxidative degradation, due to immobilization of drug molecules by solid lipids [7] and reduce drug leakage as commonly observed in liposomes.

Nanostructured lipid carriers (NLC)

NLC were introduced to overcome the potential difficulties with SLNs [20-22]. The goal was to increase the drug loading and prevent drug expulsion. This could be visualized in three ways. In the first model, spatially different lipids (like glycerides) composed of different fatty acids are mixed. The use of spatially different lipids leads to larger distances between the fatty acid chains of the glycerides and general imperfections in the crystal and thus provides more room for accommodation of guest molecules. The highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids (oils). This model is called imperfect type NLC. Drugs showing higher solubility in oils than in solid lipids can be dissolved in the oil and yet be protected from degradation by the surrounding solid lipids. These types of NLC are called multiple types NLC and are analogous to w/o/w emulsions since it is an oil-in-solid lipid-in-water dispersion. Since drug expulsion is caused by ongoing crystallization or transformation of the solid lipid, this can be prevented by the formation of a third type, the amorphous type NLC. Here the particles are solid, but crystallization upon cooling is avoided by mixing special lipids like hydroxyl octacosanol, hydroxyl stearate, and isopropyl myristate.

Lipid drug conjugates (LDC)

A major problem of SLNs is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Only

highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix [23]. In order to overcome this limitation, the so-called LDC nanoparticles with drug loading capacities of up to 33% have been developed [24]. An insoluble drug-lipid conjugate bulk is first prepared either by salt formation (e. g. with a fatty acid) or by covalent linking (e. g. to ester or ethers). The obtained LDC is then processed with an aqueous surfactant solution (such as Tweens) to a nanoparticle formulation using high-pressure homogenization (HPH). Such matrices may have potential application in brain targeting of Hydrophilic drugs in serious protozoal infections [25].

Preparation techniques for sln

Preparation of SLN by high-pressure homogenization

SLN are particles made from solid lipids with a mean photon correlation spectroscopy (PCS) diameter between approximately 50 and 1000 nm. In contrast to emulsions for parenteral nutrition which are normally stabilized by lecithin, the SLN can be stabilized by other surfactants or polymers and their mixtures. This is a technique well established on the large scale since the fifties and already available in the pharmaceutical industry. The two basic production methods for SLN are the hot homogenization technique and the cold homogenization technique [26, 27]. For both techniques, the drug is dissolved or solubilized in the lipid being melted at approximately 5±100C above its melting point. For the hot homogenization technique, the drug containing melt is dispersed under stirring in a hot aqueous surfactant solution of identical temperature. Then the obtained pre-emulsion is homogenized using a piston-gap homogenizer (e. g. Micron LAB40), the produced hot O/W nanoemulsion is cooled down to room temperature, the lipid recrystallizes and leads to solid lipid nanoparticles. Of course, care needs to be taken that recrystallization of the lipid occurs. Recrystallization can also be initiated by lyophilization.

SLN produced by microemulsion technique

Microemulsions are clear or slightly bluish solutions being composed of a lipophilic phase (e. g. lipid), a surfactant and in most cases also a co-surfactant and water. The term microemulsion is controversially discussed. Nowadays one considers microemulsions not as a real emulsion with very fine droplets but as a `critical solution'[28]. The microemulsions show properties of real macroemulsions (e. g. small particle sizes can be measured by laser light scattering) and simultaneously properties of a real solution (e. g. drugs possess a saturation solubility in a microemulsion and do not show a distribution coefficient as in macroemulsions). The addition of a microemulsion to water leads to precipitation of the lipid phase forming fine particles. This effect is exploited in the preparation method for SLN developed by Gasco. To form a microemulsion with a lipid being solid at room temperature, the microemulsion needs to be produced at a temperature above the melting point of the lipid. The lipid (fatty acids and/or glycerides) are melted, a mixture of water, co-surfactant(s) and the surfactant is heated to the same temperature as the lipid and added under mild stirring to the lipid melt. A transparent, thermodynamically stable system is formed when the compounds are mixed in the correct ratio for microemulsion formation. This microemulsion is then dispersed in a cold aqueous medium (380C±2) under mild mechanical mixing, thus ensuring that the small size of the particles is due to the precipitation and not mechanically induced by a stirring process [29, 30]. Surfactants and co-surfactants include lecithin, biliary salts, but also alcohols such as butanol [31]. Excipients such as butanol are less favorable with respect to regulatory aspects. From the technical point of view precipitation of the lipid particles in water is a dilution of the system that leads to a reduction of the solid content of the SLN dispersion. For some technological operations, it is highly desirable to have a high lipid solid content, e. g. 30%. An example is the transfer of the SLN dispersion to a dry product (e. g. tablet, pellet) by a granulation process. The SLN dispersion can be used as granulation fluid, but in the case of low particle content, too much water needs to be removed. Large scale production of SLN by the microemulsion technique also appears feasible and is at present under development at Vectorpharma (Trieste, Italy). The microemulsion is prepared in a large, temperature-controlled tank and then pumped from this tank into a cold water tank for the precipitation step [32]. Important process parameters during the scaling up are e. g. the temperatures of the microemulsion and the water, but also temperature follows in the water medium and the hydrodynamics of mixing which should change as little as possible during scaling up to maintain the same product characteristics.

SLN produced by hot homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and is similar to 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 (like silversion-type homogenizer). The quality of the pre-emulsion affects the quality of the final product to a great extent and it is desirable to obtain droplets in the size range of a few micrometers. High-pressure homogenization of the pre-emulsion is done above the lipid melting point. Usually, lower particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase, [33] although this might also accelerate the drug and carrier degradation. Better products are obtained after several passes through the high-pressure homogenizer (HPH), typically 3-5 passes. High-pressure processing always increases the temperature of the sample (approximately 10 ° at 500 bars) [34]. In most cases, 3-5 homogenization cycles at 500-1500 bar are sufficient. Increasing the homogenization leads to an increase of the particle size due to particle coalescence, this occurs because of the high kinetic energy of the particles.

SLN produced by cold homogenization

The cold homogenization process is carried out with the solid lipid and, therefore, is similar to milling of a suspension at elevated pressure. To ensure the solid state of the lipid during homogenization, effective temperature regulation is needed [35]. Cold homogenization has been developed to overcome the following problems of the hot homogenization technique such as Temperature-mediated accelerated degradation of the drug payload, Partitioning and hence loss of drug into the aqueous phase during homogenization, Uncertain polymorphic transitions of the lipid due to complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. The first preparatory step is the same as in the hot homogenization procedure and includes the solubilization or dispersion of the drug in the lipid melt. However, the subsequent steps differ. The drug containing melt is cooled rapidly (using dry ice or liquid nitrogen) to favor homogeneous drug distribution in the lipid matrix. In effect, the drug containing solid lipid is pulverized to microparticles by ball/mortar milling. Typical particle sizes attained are in the range 50-100 microns. Chilled processing further facilitated particle milling by increasing the lipid fragility. The SLNs are dispersed in a chilled emulsifier solution. The dispersion is subjected to high-pressure homogenization at or below room temperature with appropriate temperature control keeping in view the usual rise in temperature during high-pressure processing. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenized samples [36]. The method of cold homogenization minimizes the thermal exposure of the sample, but it does not avoid it due to the melting of the lipid/drug mixture in the initial step.

SLN produced by Ultra sonication or high-speed homogenization

SLN were also developed by high-speed stirring or sonication [37]. The most advantages are that equipment that are used here are very common in every lab. The problem of this method is broader particle size distribution ranging into micrometer range. This lead physical instability likes particle growth upon storage. Potential metal contamination due to ultrasonication is also a big problem in this method. So for making a stable formulation, studies have been performed by various research groups that high-speed stirring and ultrasonication are used combined and performed at high temperature.

Lipid nanopellets and lipospheres

The lipid nano-pellets for oral delivery developed by Speiser are produced by dispersing a melted lipid in a surfactant solution by

stirring or sonication. The obtained particle size is determined by the power density of the stirrer. In general,a mixture of nanoparticles and microparticles is obtained [38, 39]. To preferentially obtain nanoparticles, relatively high surfactant concentrations are employed (i.e. one moves towards solubilization of the lipid). However, during the production of lipid particles, the surfactant is also incorporated into the lipid phase, the more surfactant is present, the more it is incorporated leading to a reduced crystallinity of the lipid particles (unpublished data). Higher surfactant concentrations might be acceptable for oral administration, the route that nano-pellets were intended for according to the patent, [40] but might cause some problems for other administration routes such as intravenous. The lipospheres developed by Domb are `solid, water-insoluble microparticles that have a layer of phospholipids embedded on their surface. According to the patent claims, lipospheres comprise a core formed of a hydrophobic material solid at room temperature and a phospholipid coating surrounding the core. The average particle diameter is between 0.3 and 250 mm. The particles are prepared by melting the core material, adding phospholipid along with an aqueous medium and dispersing the melted material at increased temperature by mixing techniques, such as mechanical stirring or sonication. Cooling leads to solid lipospheres. The liposphere is restricted to one stabilizing material, which means the phospholipid layer. For SLN, it has been reported that suspensions stabilized only with phospholipid can tend to form semi-solid ointment-like gels [41]. Gel formation can be prevented by adding a co-emulsifier which is not covered by the liposphere patent. The SLN produced by our group are in most cases stabilized by binary or ternary surfactant mixtures providing optimal physical long-term stability.

Precipitated lipid particles

Solid lipid particles can also be produced by a precipitation method comparable to the production of polymeric nanoparticles by solvent evaporation. In contrast to SLN this method is characterized by the need for solvents. The glyceride is dissolved in an organic solvent (e. g. chloroform) and this solution is emulsified in an aqueous phase. After evaporation of the solvent, the lipid precipitates forming nanoparticles. A clear disadvantage is the need to use organic solvents. In addition, other problems arise similar to when scaling up production of polymeric nanoparticles on the basis of solvent evaporation. In contrast, SLN produced by high-pressure homogenization has the advantage of avoiding the use of solvents.

SLN prepared by solvent emulsification/evaporation

For the production of nanoparticle dispersions by precipitation in o/w emulsions [42], the lipophilic material is dissolved in a water-immiscible organic solvent (cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent nanoparticles, the dispersion is formed by precipitation of the lipid in the aqueous medium. The mean diameter of the obtained particles was 25 nm with cholesterol acetate as a model drug and lecithin/sodium glycocholate blend as an emulsifier. The reproducibility of the result was confirmed by Siekmann and Westesen, who produced the cholesterol acetate nanoparticles of mean size 29 nm [43].

SLN preparation by using supercritical fluid

This is a relatively new technique for SLN production and has the advantage of solvent-less processing [44, 45]. There are several variations in this platform technology for powder and nanoparticle preparation. SLN can be prepared by the rapid expansion of supercritical carbon dioxide solutions (RESS) method. Carbon dioxide (99.99%) was the good choice as a solvent for this method [44].

SLN produced by spray drying method

It's an alternative procedure to lyophilization in order to transform an aqueous SLN dispersion into a drug product. It's a cheaper method than lyophilization. This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle. Freitas and Mullera[45]recommends the use of lipid with melting point>70 0 for spray drying. The best result was obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in water or 20% trehalose in ethanol-water mixtures (10/90 v/v).

SLN produced by Double emulsion method

For the preparation of hydrophilic loaded SLN, a novel method based on solvent emulsification-evaporation has been used. Here the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of the external water phase of w/o/w double emulsion.

Characterization of sln quality and structure

Adequate and proper characterization of the SLNs is necessary for its quality control. However, characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters which need to be evaluated for the SLNs are, particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of additional colloidal structures (micelles, liposome, supercooled, melts, drug nanoparticles), time scale of distribution processes,drug content, *in vitro* drug release and surface morphology.

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).

Measurement of particle size and zeta potential [46]

Photon correlation spectroscopy (PCS) and 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) measures the fluctuation of the intensity of the scattered light which is caused by the particle movement. 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 microparticles. 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 millimeter range. The development of polarization intensity 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. For example, uncertainties may result from non-spherical particle shapes. Platelet structures commonly occur during lipid crystallization and have also been suggested in the SLN. Further, difficulties may arise both in PCS and LD measurements for samples which contain several populations of different size. Therefore, additional techniques might be useful. For example, light microscopy is recommended, although it is not sensitive to the nanometer size range. It gives a fast indication of the presence and character of microparticles (microparticles of unit form or microparticles consisting of aggregates of smaller particles). Electron microscopy provides, in contrast to PCS and LD, direct information on the particle shape. However, the investigator should pay special attention to possible artifacts which may be caused by the sample preparation. For example, solvent removal may cause modifications which will influence the particle shape. Zeta potential is an important product characteristic of SLNs since its high value is expected to lead to aggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zeta meter.

Static light scattering/Fraunhofer diffraction

Static light scattering (SLS) is an ensemble method in which the pattern of light scattered from a solution of particles is collected and fit fundamental electromagnetic equations in which size is the primary variable. The method is fast and rugged, but requires more

cleanliness than DLS, and advance knowledge of the particles' 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 nanoparticles.

Electron microscopy [47]

SEM and TEM provide a way to observe directly nanoparticles, physical characterization of nanoparticles with the former method being better for morphological examination. TEM has a smaller size limit of detection, 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) [48]

In this technique, a probe tip with atomic scale sharpness is restored 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 ultrahigh 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.

X-ray diffraction (X-ray powder 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 permitting the degree of crystallinity to be assessed. Another method that is a little different from its implementation with bulk materials, DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies [48].

Sterilization of SLNS

For intravenous and ocular administration SLN must be sterile. The high temperature reaches during sterilization by autoclaving presumably causes a hot o/w microemulsion to form in the autoclave, and probably modifies the size of the hot nanodroplets. On subsequent slow cooling, the SLN reformed, but some nanodroplets may coalesce, producing larger SLN than the initial ones. Since SLN are washed before sterilization, amounts of surfactant and cosurfactant present in the hot system are smaller, so that the nanodroplets may be not sufficiently stabilized. Options are therefore limited to aseptic manufacturing processes following sterilization of the starting materials (gamma ore-beam irradiation of the final dispersion) or exposure to ethylene oxide gas (EO). It should be monitored, especially when raw materials are of natural origin. It may be possible to lyophilize the SLN dispersion, and this lyophile can be irradiated or exposed to EO.

Schwarz found that lecithin is a suitable surfactant for steam sterilization because only a minor increase in particle size was observed. Experiments conducted by Freitas indicated that lowering of the lipid content (to 2%) and surface modification of the glass vials prevent the particle increase to a large extent and avoid gelation. Additionally, it was observed by Freitas that purging with nitrogen showed a protective effect during sterilization. That observation suggests that chemical reactions could contribute to particle destabilization. Y-irradiation could be an alternative method to steam sterilization for temperature sensitive samples.

Lyophilization is a promising way to increase the chemical and physical stability over extended periods of time. Lyophilization had been required to achieve long-term stability for a product containing hydrolysable drugs or a suitable product for per-oral administration. Transformation into the solid state would prevent the Oswald ripening and avoid hydrolytic reactions. In the case of freeze drying of the product, all the lipid matrices used, form larger solid lipid nanoparticles with a wider size distribution due to the presence of aggregates between the nanoparticles. The conditions of the freeze drying process and the removal of water promote the aggregation among SLNs. An adequate amount of cryoprotectant can protect the aggregation of solid lipid nanoparticles during the freeze drying process [49].

Oral lipid-based formulations [50]

Among the benefits which oral lipid-based formulations can provide are included: Improvement and reduction in the variability of GI absorption of poorly water-soluble, lipophilic drugs. Possible reduction in, or elimination of, a number of development and processing steps (salt selection or identification of a stable crystalline form of the drug, coating, taste masking, and reduced need for containment and clean-up requirements during manufacture of highly potent or cytotoxic drug products). Reduction or elimination of positive food effect. The relative ease of manufacture using the readily available equipment. Different types of oral lipid-based formulation are like, single-component lipid solutions, self-emulsifying formulations, and self-emulsifying solid dispersion formulations and melt pelletization. It has been revealed that the most frequently chosen excipients for preparing oral lipid-based formulations were dietary oils composed of medium (coconut or palm seed oil) or long-chain triglycerides (corn, olive, peanut, rapeseed, sesame, or soybean oils, including hydrogenated soybean or vegetable oils), lipid soluble solvents (polyethylene glycol 400, ethanol, propylene glycol, glycerin), and various pharmaceutically acceptable surfactants (Cremophor; EL, RH40 or RH60; polysorbate 20 or 80; D-α-tocopherol polyethylene glycol 1000 succinate (TPGS;); Span 20; various Labrafils, Labrasol;, and Gelucires;). These formulations, which took the form of either bulk oral solutions or liquid-filled hard or soft gelatin capsules, were applied in instances where conventional approaches (solid wet or dry granulation, or water-miscible solution in a capsule) did not provide sufficient bioavailability, or in instances in which the drug substance itself was an oil (dronabinol, ethyl icosane Tate, Indomethacin farnesyl, teprenone, and tocopherol nicotinate). The total daily drug dose administered in these formulations, which range in complexity from simple solutions of the drug in a dietary oil up to multi-excipient, self-emulsifying drug delivery systems (SEDDS), range from less than 0.25 μg to greater than 2000 mg. The amount of drug contained in a unit-dose capsule product ranges from 0.25 μg to 500 mg and for oral solution products, from 1 μg/ml to 100 mg/ml. The total amount of lipid excipient administered in a single dose of a capsule formulation ranges from 0.5 to 5 g, but can range from as low as 0.1 ml to as high as 20 ml for oral solution products. Some of these products tolerate room temperature storage for only brief periods of time and require long-term storage at 2-8 ° due to chemical and/or physical stability issues. Routes of Administration and their Biodistribution The *in vivo* fate of the solid lipid nanoparticles will depend mainly on the administration route and distribution process (adsorption of biological material on the particle surface and desorption of SLN components into the biological surrounding). SLN are composed of physiological or physiologically related lipids or waxes. Therefore, pathways for transportation and metabolism are present in the body which may contribute to a large extent to the *in vivo* fate of the carrier. Probably the most important enzymes of SLN degradation are lipases, which are present in various organs and tissues. Lipases split the ester linkage and form partial glycerides or glycerol and free fatty acids. Most lipases require activation by an oil/water interface, which opens the catalytic center (lid opening). *In vitro* experiment indicates that solid lipid nanoparticles show different degradation velocities by the lipolytic enzyme pancreatic lipase as a function of their composition (lipid matrix, stabilizing surfactant) [51].

Peroral administration

Peroral administration forms of SLN may include aqueous dispersions or SLN-loaded traditional dosage forms such as tablets, pellets or capsules. The microclimate of the stomach favors particle aggregation due to the acidity and high ionic strength. It can be expected; that food will have a large impact on SLN performance. However, no experimental data have been publishing on this issue to our knowledge. The question concerning the influence of the gastric and pancreatic lipases on SLN degradation *in vivo* remains open, too. Unfortunately, only a few *in vivo* studies have been performed yet.

Parenteral administration

SLN have been administered intravenously to animals. Pharmacokinetic studies of doxorubicin incorporated into SLN showed higher blood levels in comparison to a commercial drug solution after i. v. injection in rats. Regarding distribution, SLN were found to have higher drug concentrations in lung, spleen, and brain, while the solution led to more distribution into liver and kidneys [52]. Yang *et al.* reported on the pharmacokinetics and body distribution of camptothecin after i. v. injection in mice. In comparison to a drug solution, SLN was found to give much higher AUC/dose and mean residence times (MRT) especially in the brain, heart and reticuloendothelial cells containing organs. The highest AUC ratio of SLN to drug solution among the tested organs was found in the brain [52, 53].

Transdermal Administration

The smallest particle sizes are observed for SLN dispersions with low lipid content (up to 5%). Both the low concentration of the dispersed lipid and the low viscosity are disadvantageous for dermal administration. 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 semisolid, gel-like systems, which might be acceptable for direct application on the skin [54].

Applications

Solid lipid Nanoparticles possesses a better stability and ease of upgradability to production scale as compared to liposomes. This property may be very important for many modes of targeting. SLNs form the basis of colloidal drug delivery systems, which are biodegradable and capable of being stored for at least one year. They can deliver drugs to the liver *in vivo* and *in vitro* to cells which are actively phagocytic. There are several potential applications of SLNs some of which are given below:

SLNs as gene vector carrier

SLN can be used in the gene vector formulation [55]. In one work, the gene transfer was optimized by incorporation of a diametric HIV-1 HAT peptide (TAT 2) into SLN gene vector. There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids [56]. The lipid-nucleic acid nanoparticles were prepared from a liquid nanophase containing water and a water miscible organic solvent where both lipid and DNA are separately dissolved by removing the organic solvent, stable and homogeneously sized lipid-nucleic acid nanoparticle (70-100 nm) were formed. It's called genospheres. It is targeted specific by insertion of an antibody-lipo polymer conjugated in the particle.

SLNs for topical use

SLNs and NLCs have been used for topical application [57] for various drugs such as imidazole antifungals [58] tropolide, [59] anticancer, [60] vitamin A, [61] isotretinoin, [62] ketoconazole, [63] DNA, [64] flurbiprofen [65] and glucocorticoids [66]. The penetration of podophyllotoxin-SLN into stratum corneum along with skin surface lead to the epidermal targeting [59, 65]. By using glyceryl behenate, vitamin A-loaded nanoparticles can be prepared. The methods are useful for the improvement of penetration with the sustained release [61]. The isotretinoin-loaded lipid nanoparticles were formulated for topical delivery of the drug. The soyabean lecithin and Tween 80 are used for the hot homogenization method for this. The methodology is useful because of the increase of accumulative uptake of isotretinoin in skin [62]. Production of the flurbiprofen-loaded SLN gel for topical application offers potential advantages of delivering the drug directly to the site of action, which will produce higher tissue concentrations. Polyacrylamide, glycerol, and water were used for the preparation of this type of SLN gel [64].

SLNs as cosmeceuticals

The SLNs have been applied in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers [66]. The *in vivo* study showed that skin hydration will be increased by 31% after 4 w* by the addition of 4% SLN to a conventional cream [67]. SLN and NLCs have proved to be controlled release innovative occlusive topicals [68]. Better localization has been achieved for vitamin A in upper layers of skin with glyceryl behenate SLNs compared to conventional formulations [69].

SLNs for potential agriculture application

Essential oil extracted from Artemisia arboreseens L when incorporated in SLN were able to reduce the rapid evaporation compared with emulsions and the systems have been used in agriculture as a suitable carrier of ecologically safe pesticides [70]. The SLN were prepared here by using compritol 888 ATO as lipid and poloxamer 188 or Miranol Ultra C32 as a surfactant.

SLNs as a targeted carrier for anticancer drug to solid tumors

SLNs have been reported to be useful as drug carriers to treat neoplasms [71]. Tamoxifen, an anticancer drug incorporated in SLN to prolong the release of drug after i. v. administration in breast cancer and to enhance the permeability and retention effect [72]. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate [73] and camptothecin [74].

SLNs in breast cancer and lymph node metastases

Mitoxantrone-loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug [75]. Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs [76]. In the methodology, the Dox was complexed with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system is enhanced its efficacy and reduced breast cancer cells.

Oral SLNs in antitubercular chemotherapy

Antitubercular drugs such as rifampicin, isonizide, pyrazinamide-loaded SLN systems, were able to decrease the dosing frequency and improve patient compliance [77]. By using the emulsion solvent diffusion technique this antitubercular drug loaded solid lipid nanoparticles are prepared. The nebulization in an animal by incorporating the above drug in SLN also reported for improving the bioavailability of the drug [78].

Stealth nanoparticles

These provide a novel and unique drug-delivery system they evade quick clearance by the immune system. Theoretically, such nanoparticles can target specific cells. Studies with antibody labeled stealth lipobodies have shown increased delivery to the target tissue inaccessible sites. Stealth SLNs have been successfully tested in animal models with marker molecules and drugs [79].

Solid lipid nanoparticles for ultrasonic drug and gene delivery

Drug delivery research employing micelles and nanoparticles has expanded in recent years. Of particular interest is the use of these nanovehicles that deliver high concentrations of cytotoxic drugs to diseased tissues selectively, thus reducing the agent's side effects on the rest of the body. Ultrasound, traditionally used in diagnostic medicine, is finding a place in drug delivery in connection with these nanoparticles. In addition to their non-invasive nature and the fact that they can be focused on targeted tissues, acoustic waves have been credited with releasing pharmacological agents from nanocarriers, as well as rendering cell membranes more permeable.

Ultrasonic drug delivery from micelles usually employs polyether block copolymers and has been found effective *in vivo* for treating tumors. Ultrasound releases drug from micelles, most probably via shear stress and shock waves from the collapse of cavitation bubbles. Liquid emulsions and solid nanoparticles are used with ultrasound to deliver genes *in vitro* and *in vivo*. The small packaging allows nanoparticles to extravagate into tumor tissues. Ultrasonic drug and gene delivery from nanocarriers has tremendous potential because of the wide variety of drugs and genes that could be delivered to targeted tissues by fairly non-invasive means [72].

SLN applications for improved delivery of antiretroviral drugs to the brain

Human immunodeficiency virus (HIV) can gain access to the central nervous system during the early course of primary infection. Once in the brain compartment the virus actively replicates to form an independent viral reservoir, resulting in debilitating neurological complications, latent infection, and drug resistance. Current antiretroviral drugs (ARVs) often fail to reduce the HIV viral load effectively in the brain. This, in part, is due to the poor transport of many ARVs, in particular, protease inhibitors, across the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSBF). Studies have shown that nanocarriers including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLN) and micelles can increase the local drug concentration gradients, facilitate drug transport into the brain via endocytotic pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites. By delivering ARVs with nanocarriers, a significant increase in the drug bioavailability to the brain is expected to be achieved. Recent studies show that the specificity and efficiency of ARVs delivery can be further enhanced by using nanocarriers with specific brain targeting, cell penetrating ligands or ABC-transporters inhibitors. Future research should focus on achieving brain delivery of ARVs in a safe, efficient, and yet cost-effective manner [80].

SLN as potential new adjuvant for vaccines

Adjuvants are used in vaccination to enhance the immune response. The safer new subunit vaccines are less effective in immunization and. Therefore, effective adjuvants are required [81]. 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 [82, 83].

SLN applied to the treatment of malaria

Despite the fact that we live in an era of advanced technology and innovation, infectious diseases, like malaria, continue to be one of the greatest health challenges worldwide. The main drawbacks of conventional malaria chemotherapy are the development of multiple drug resistance and the nonspecific targeting to intracellular parasites, resulting in high dose requirements and subsequent intolerable toxicity. Nanosized carriers have been receiving special attention with the aim of minimizing the side effects of drug therapy, such as poor bioavailability and the selectivity of drugs. Several nanosized delivery systems have already proved their effectiveness in animal models for the treatment and prophylaxis of malaria. A number of strategies to deliver antimalarials using nanocarriers and the mechanisms that facilitate their targeting to Plasmodium spp-infected cells are discussed in this review. Taking into account the peculiarities of malaria parasites, the focus is placed particularly on lipid-based (e. g., liposomes, solid lipid nanoparticles and nano and microemulsions) and polymer-based nanocarriers (nanocapsules and nanospheres) [84].

CONCLUSION

In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept; the idea that drugs reaches the right site in the body, at the right time, at the right concentration. It should not exert side effects, either on its way to the therapeutic target, or at the target site, nor during the clearance process. The SLNs have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is aptly achieved with SLNs. They are relatively young drug delivery systems, having received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of SLNs in the future.

CONFLICT OF INTERESTS

Hereby the authors of this article declare no conflict of interest

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