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SOLID LIPID NANOPARTICLES - FUTURE TECHNOLOGY: A BRIEF 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 ability to incorporate drugs into nanocarriers offers a new prototype in drug delivery that could be used for secondary and tertiary levels of drug targeting. This broad review includes advantages, disadvantages, preparation methods, administration routes and applications of solid lipid nanoparticles. Analytical techniques for characterization of SLNs like Coexistence of several colloidal species , dynamic light scattering, atomic force microscopy, differential scanning calorimetry, X-ray diffraction, nuclear magnetic resonance and electron spin resonance are discussed. Hence, solid lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and hence have attracted wide attention of researchers.

KEY WORDS: Solid lipid nanoparticles, Colloidal carriers, drug targeting.

INTRODUCTION

Many of the recent formulation approaches utilize Nanotechnology that is the preparation of Nanosized structures containing the API.[1] Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), is the study and use of structures roughly in the size range of 1 to 100 nm. The overall goal of nanotechnology is the same as that of medicine: to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using controlled and targeted drug delivery approach.[2] Some of the important

Drug Delivery System developed using Nanotechnology principles are- Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion, Nanocrystals.[3]

Nanomaterials differ significantly from other materials due to the following two major principal factors: the increased surface area and quantum effects. These factors can enhance properties such as reactivity, strength, electrical characteristics, and in vivo behavior.[4-5] Now a days nanotechnology, as applied to medicine, brought significant advances in the diagnosis and treatment of disease. The desired applications in medicine include drug delivery, nutraceuticals, both in vitro and in vivo diagnostics and production of improved biocompatible materials.[6-9] Nanoparticles are emerging as a class of therapeutics for cancer and can show improved efficacy, while simultaneously decreasing side effects, owing to properties such as more targeted localization in tumors and active cellular uptake.[10] The solid lipid nanoparticles are submicron colloidal carriers (50-1000 nm) which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. SLNs as a colloidal drug carrier combines the advantages of polymeric nanoparticles, fat emulsions and liposomes simultaneously and avoiding some of their disadvantages. SLNs were invented at the beginning of 1990s and are produced either by high-pressure homogenization or by microemulsion technique and are considered to be the most effective lipid based colloidal carriers. Owing to their solid particle matrix, they can protect incorporated ingredients against chemical degradation and allow modification of release of the active compounds .[11-12] 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.[1] In SLNs as compared to other colloidal carriers liquid lipid is replaced by solid lipid. The use of solid lipid as a matrix material for drug delivery is well known from lipid pellets for oral drug delivery (eg. Mucosolvan® retard capsules).[13] The term lipid in a broad sense includes triglycerides, partial glycerides, fatty acids, hard fats & waxes. A clear advantage of SLN is the fact that the lipid matrix is made from physiological lipids which decreases the danger of acute and chronic toxicity.[14] The use of solid lipid instead of liquid lipid is beneficial as it has been shown to increase control over the release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients.

History and concept of SLN's,[15-16]

Nanosized drug delivery systems have been developed to overcome one or several of the following problems;

- Low or highly variables drug concentrations after per oral administration due to poor absorption, rapid metabolism and elimination.
- Poor drug solubility which includes i.v injections of aqueous drug solutions.
- Drug distribution to other tissue combined with high toxicity. (eg: Cancer drugs).

Several systems, including micelles, liposomes, polymer nanoparticles, nanoemulsions, solid dispersion and nanocapsules have been developed. A promising strategy to overcome these problems involves the development of suitable drug carrier system like solid lipid nanoparticles**.**

Aims of SLNs.[17-19]

- Possibility of controlled drug release
- Possibility of controlled drug release and drug targeting
- Increased drug stability and high drug payload
- Incorporation of lipophilic and hydrophilic drugs feasible
- No biotoxicity of the carrier
- Avoidance of organic solvents
- No problems with respect to large scale production and sterilization

Principles of drug release from SLN

Drug release is affected by particle size, where tiny particles have larger surface area, therefore, the majority of the drug associated would be at or close to the particle surface, leading to quick drug release. Whereas, larger particles have bulky cores which permit more drug to be encapsulated and gradually diffuse out. It is a challenge to formulate nanoparticles with the smallest size possible and with maximum stability. The common ideology of drug release from lipid nanoparticles is as follows.[20-21] There is an opposite association between drug release and the partition coefficient of the drug.

– Larger surface area due to smaller particle size in nanometric range gives high drug release.
– When the drug is homogenously dispersed in the lipid matrix, slower drug release can be achieved. It depends on type of drug entrapment model of SLN.

Advantages of SLNs.[16-18]

- Small size and relatively narrow size distribution which provide biological opportunities for sitespecific drug delivery by SLNs.

- Controlled release of active drug over a long period can be achieved.
- Protection of incorporated drug against chemical degradation.
- Possible sterilization by autoclaving or gamma irradiation and subjected to commercial sterilization procedures.
- SLNs can be lyophilized as well as spray dried.
- No toxic metabolites are produced.

Disadvantages.[19,22]

- ✓ Need to remove too much water in tablet / pellet production
- ✓ Dosing problems, relatively high water content of the dispersions (70-99.9%)
- ✓ Physical stability of aqueous solution, gel formation, particle aggregation
- ✓ Poor drug loading capacity, drug expulsion after polymeric transition during storage.
- ✓ The low capacity to load hydrophilic drugs due to partitioning effects during the production Process.

Method of preparations of SLNs

A. High pressure homogenization.

1. Hot homogenization.
2. Cold homogenization.

B. Microemulsion.

C. Emulsification solvent diffusion.

D. Solvent emulsification/ evaporation technique.

E. Double emulsion (w/o/w) solvent evaporation method.

F. Lipid extrusion.

G. Solvent injection method.

H. High shear homogenization.

High pressure homogenization.[23]

HPH is suitable method for preparation of SLN, NLC, and LDC and can be performed at elevated temperature (hot HPH technique) or at or below room temperature (cold HPH technique). The particle size is decreased by cavitations' and turbulences. Basically, there are two approaches for SLN production by high pressure homogenization, hot and cold homogenization techniques.

Hot Homogenization

Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high-shear mixing device (Ultra-Turrax). The quality of the final product is affected by the quality of pre-emulsion to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures also accelerate the degradation rate of the drug and the carrier. The homogenization step can be repeated several times. It should always be kept in mind, that high pressure homogenization increases the temperature of the sample (approximately 10°C for 500 bar). In most cases, 3–5 homogenization cycles at 500–1500 bar are sufficient. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to particle coalescence which occurs as a result high kinetic energy of the particles. The primary product is a nanoemulsion due to the liquid state of the lipid which on cooling at room temperature leads to solid particles. Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a super cooled melt for several months.[2,13,24,25]

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.[26] 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 homogenous drug distribution in the lipid matrix. In effect, the drug containing solid lipid is pulverized to micropaticles 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.[27] 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.

Micro emulsion based SLN preparations

Gasco and co-workers developed SLN preparation techniques which are based on the dilution of microemulsions.[27] They are made by stirring an optically transparent mixture at 65-700 which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (sodium monooctylphosphate) and water. The hot microemulsion is dispersed in cold water (2-30) under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. The dilution process is critically determined by the composition of the microemulsion. According to the literature.[28,29] the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle sizes. With respect to the similarities of the production procedure of polymer nanoparticles described by French scientists.[36] different mechanisms might be considered. Fessi produced polymer particles by dilution of polymer solutions in water. According to De Labouret *et al.*,[30] the particle size is critically determined by the velocity of the distribution processes. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The hydrophilic co-solvents of the microemulsion might play a similar role in the formation of lipid nanoparticles as the acetone for the formation of polymer nanoparticles.[30]

Solvent emulsification diffusion method

The particles with average diameters of 30-100 nm can be obtained by this technique. Voidance of heat during the preparation is the most important advantage of this technique. In this technique lipid is, are generally dissolved in the organic phase in water bath at50 °C and

used an acidic aqueous phase in order to adjust the zeta potential to form coacervation of SLN, and then easy separation by centrifugation. The SLN suspension was quickly produced. The entire dispersed system can then be centrifuged and re-suspended in distilled water.[24, 31,32,33]

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).[24]

Double emulsion based method

Warm w/o/w double microemulsions can be prepared in two steps. Firstly, w/o microemulsion is prepared by adding an aqueous solution containing drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature slightly above the melting point of lipid to obtain a clear system. In the second step, formed w/o microemulsion is added to a mixture of water, surfactant and co-surfactant to obtain a clear w/o/w system. SLNs can be obtained by dispersing the warm micro double emulsions in cold then washed with dispersion medium by ultra filtration system. Multiple emulsions have inherent instabilities due to coalescence of the internal aqueous droplets within the oil phase, coalescence of the oil droplets, and rupture of the layer on the surface of the internal droplets. In case of SLNs production, they have to be stable for few minutes, the time between the preparations of the clear double microemulsions and its quenching in cold aqueous medium, which is possible to achieve.[24, 34]

Influence of the lipids

Using the hot homogenization, it has been found that the average particle size of SLN dispersions is increasing with higher melting lipids. However, other critical parameters for nanoparticle formation will be different for the different lipids. The examples include the velocity of lipid crystallization, the lipid hydrophilicity (influence on self-emulsifying properties and the shape of the lipid crystals (and therefore the surface area).Further, increasing the lipid content over 5-10% resulted in larger particles (including microparticles) and broader particle size distribution in most cases.

Solvent injection technique

It 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 (eg. ethanol, acetone, isopropanol) or a water miscible solvent mixture. Then this lipid solvent mixture was injected through an injection needle into stirred aqueous phase with or without surfactant. The resultant 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.[24,35,36,37]

High shear homogenization

High shear homogenization technique were initially used for the production of solid lipid Nanodispersions.[38,39] Both methods are widespread and easy to handle. However, dispersion quality is often compromised by the presence of micro particles. High-speed homogenization method is used to produce SLN by melt emulsification.[40] Olbrich *et al*. investigated the influence of different process parameters, including emulsification time, stirring rate and cooling condition on the particle size and zeta potential. Lipids used in this study included trimyristin, tripalmitin, a mixture of mono, di and triglycerides (Witepsol W35, Witepsol H35) with glycerol behenate and poloxamer 188 used as steric stabilizers (0.5% w/w). For Witepsol W35 dispersions the best SLN quality was obtained after stirring for 8 min at 20,000 rpm followed by cooling 10 min and stirring at 5000 rpm at a room temp. In contrast, the best conditions for Dynasan116 dispersions were a 10-min emulsification at 25,000 rpm and 5 min of cooling at 5,000 rpm in cool water (≈160).[41] Higher stirring rates did not significantly change the particle size, but slightly improved the poly dispersity index.

Supercritical fluid method

This is a relatively new technique for SLN production and has the advantage of solvent-less processing. 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.[24]

Table 1: Shows list of excipients used in SLN preparation.[25,42]

LIPIDS	SURFACTANTS
Triglycerides	**Phospholipids**
Tricaprin	Soy lecithin (Lipoid S 75, Lipoid S 100)
Trilaurin	Egg lecithin (Lipoid E 80)
Trimyristin (Dynasan 114)	Phosphatidylcholine (Epikuron170, Epikuron 200)
Tripalmitin (Dynasan 116)	**Ethylene oxide/propylene oxide copolymers**
Tristearin (Dynasan 118)	Poloxamer 188
Hydrogenated coco-glycerides (SoftisanÒ 142)	Poloxamer 182
Hard fat types	Poloxamer 407
WitepsolÒ W 35	Poloxamine 908
WitepsolÒ H 35	**Sorbitan ethylene oxide/propylene oxide copolymers**
WitepsolÒ H 45	Polysorbate 20
WitepsolÒ E 85	Polysorbate 60
Acyl glycerols	Polysorbate 80
Glyceryl monostearate (ImwitorÒ900)	**Alkylaryl polyether alcohol polymers**
Glyceryl distearate(Precirol)	Tyloxapol
Glyceryl monooleate(Peceol)	**Bile salts**
Glyceryl behenate (CompritolÒ 888 ATO)	Sodium cholate
Glyceryl palmitostearate (PrecirolÒ ATO 5)	Sodium glycocholate
Waxes	Sodium taurocholate
Cetyl palmitate	Sodium taurodeoxycholate
Fatty Acids	**Alcohols**
Stearic acid	Ethanol
Palmitic acid	ButanoL
Decanoic acid	Butyric acid
Behenic acid	Dioctyl sodium sulfosuccinate
Acidan N12	Monooctylphosphoric acid sodium
Cyclic complexes	
Cyclodextrin	
para-acyl-calix-arenes	

CHARACTERIZATION OF SLNs

Adequate and proper characterization of the SLNs is necessary for its quality control. However, characte-rization 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 impor-tant parameters evaluated for the SLNs include particle size, size distribution kinetics (zeta poten-tial), degree of crystallintity and lipid modification (polymorphism), coexistence of additional colloidal structures (miscelles, liposome, super cooled melts, drug nanoparticles), entrapment efficiency, time scale of distribution processes, in-vitro drug release and surface morphology.

Measurement of particle size and zeta potential.[43]

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 deaggregation of particles in the absence of other complicating factors such as steric stabilizers or hydrophilic surface appendages. It is usually measured by zetameter.

Coexistence of several colloidal species

The presence of several colloidal species is an important point to consider. Stabilizing agents are not localized exclusively on the lipid surface, but also in the aqueous phase. Therefore, micelle forming surfactant molecules (e.g. SDS) will be present in three different forms, namely: (i) on the lipid surface; (ii) as micelle; and (iii) as surfactant monomer. Only the detection of the presence of several colloidal species is not sufficient to describe the structure of colloidal lipid dispersions, because dynamic phenomena are very important for drug stability and drug release. Therefore, the kinetics of distribution processes has to be considered. Unstable drugs will hydrolyze rapidly in contact with water and, therefore, the distribution equilibrium of the drug between the different environments will be distorted. Carrier systems will be protective only if they prevent the redistribution of the drug. Increasing the matrix viscosity will decrease the diffusion coefficient of the drug inside the carrier and, therefore, SLN are expected to be superior to lipid nanoemulsions. However, drug stabilization is a very challenging task for colloidal drug carriers, because of the very high surface area and the short diffusion pathways.[25]

Entrapment efficiency

The entrapment efficiency of the drug is determined by measuring the concentration of free drug in the dispersion medium. Ultracentrifugation was carried out using Centrisart, which consist of filter membrane (molecular weight cutoff 20,000 Da) at the base of the sample recovery chamber. The SLNs along with encapsulated drug remain in the outer chamber and aqueous phase moves into the sample recovery chamber. The amount of the drug present in the aqueous phase is determined by HPLC or UV spectrophotometer.[44]

In-vitro drug release

The SLNs dispersion is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed in an appropriate dissolution medium at room temperature, the samples are withdrawn at suitable intervals from the dissolution medium, centrifuged and analyzed for drug content using a appropriate analytical method. This method however suffers from the disadvantage of a lack of direct dilution of the SLNs by the dissolution medium. The drug release of camptothecin SLN using a dynamic dialysis method in phosphate buffered saline has been reported. 45 Secondly, in reverse dialysis technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN

dispersion. The direct dilution of the SLNs is attainable with this process; however the fast release cannot be quantified with this technique.[46]

Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD)

Among the large number of analytical techniques engaged for that purpose, DSC and XRD play a important role because they are able to afford structural information on the dispersed particles. DSC and XRD are renowned typical techniques in the area of pharmaceutics and since data evaluation from these methods is usually straightforward. In addition to XRD, the associated techniques of small angle X-ray and neutron scattering can give very attractive added information on the structure of the systems. Most popular applications are the identification of crystal structures, particle sizes and shapes as well as quantitative phase analysis and determination of crystallinity indices. Structural modifications of materials are accompanied by heat exchanges, e.g., uptake of heat during melting or emission of heat during crystallization. DSC is planned to measure these heat exchanges at some stage in controlled temperature programs and allows to draw conclusions on the structural properties of a sample. DSC and Xray/ neutron diffraction and scattering techniques are crucial tools for SLN characterization and offer many possibilities to gain information on the properties of the dispersed particles.[47]

Nuclear Magnetic Resonance (NMR) and Electron Spin Resonance (ESR)

NMR and ESR are dominant tools for investigating dynamic phenomena of nanocompartments in colloidal drug delivery systems. Due to the different chemical shifts it is likely to feature the NMR signals to particular molecules or their segments. Simple NMR spectroscopy allows an simple and rapid detection of supercooled melts due to the low line widths of the lipid protons (84). This technique is based on the different proton relaxation times in the liquid and solid state. Protons in the liquid state provide sharp signals with high signal amplitudes, whilesolid protons give weak and broad NMR signals under these conditions.

It also allows for the characterization of liquid nanocompartments in recently developed lipid particles, which are made from blends of solid and liquid lipids.[48] The great prospective of NMR with its mixture of different approaches has scarcely been used in the SLN field, although it will provide unique insights into the structure and dynamics of SLN dispersions. ESR allows the straight, repeatable and noninvasive characterization of the distribution of the spin probe among the aqueous and the lipid phase. Investigational results reveal that storage-

induced crystallization of SLN leads to an exclusion of the probe out of the lipid into the aqueous phase.[49] Using an ascorbic acid reduction assay it is likely to observe the time scale of the replace between the aqueous and the lipid phase. The progress of low-frequency ESR allows noninvasive measurements on small mammals.

ROUTES OF ADMINISTRATION

Oral administration

Significant parameters have been broadly overlooked in the design of new and wellorganized colloidal drug carrier systems for oral use: I) their firmness upon contact with gastrointestinal (GI) fluids since they are poised of biodegredable materials and particle size in nanorange maximizes the surface area for enzymatic degradation.[50] II) particle aggregation due to environmental circumstances of the GI tract leading decline in the interaction capability of particles with the intestinal mucosa.[51] Controlled release behaviour of these systems bypass the gastric and enables intestinal degradation of the encapsulated drug.[52] and their possible transport through the intestinal mucosa.[53] However, the estimation of the stability of colloidal carriers in GI fluids is necessary in order to calculate their appropriateness for oral administration. The machines used for large-scale production often yield an even better product quality than the lab-scale types.[54-55] The adhesive properties of nanoparticles are reported to increase bioavailability and reduce or minimize erratic absorption.[56] SLN powders or granulates can be placed into capsules, compressed into tablets or integrated into pellets. The conversion of the liquid dispersion into a dry product by lyophilization or spray-drying is useful or often necessary.[57] Antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were entrapped into polyvinyl alcohol coated SLN and following a single oral administration to mice, therapeutic drug concentrations were maintained in the plasma for 8 days and in the organs (lungs, liver and spleen) for 10 days. Suitable adsorbent was employed with free flowing characteristics for improving the physical properties and stability of solid lipid nanoparticles for oral administration. The adsorbent technology would be useful in imparting additional features to the SLNs for pharmaceutical application which would simplify the handling of formulations by patients, ease the process of capsule filling at industrial scale, and can considerably improve the shelf life of the manufactured goods for a longer period of time as compared to liquid formulations.[58] Various companies are paying attention in solid lipid nanotechnology for oral drug delivery. Pharmatec (Italy) developed a cyclosporine SLN formulation for oral administration.[59] Avoidance of high plasma peak and low variability in plasma profile were provided in this case. AlphaRx have also rifampicin-

loaded SLN under preclinical phase (RifamsolinTM). Rifampicin used in treatment of tuberculosis, requires long-term treatment due to poor cellular antibiotic penetration.

Nasal administration

Approaches such as prodrug derivatization and formulation development have been employed to improve drug absorption through the nasal mucosa. SLN has been anticipated as substitute transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups.[60,61] Nasal administration was a capable alternative noninvasive route of administration due to rapid onset of drug action, avoiding degradation of labile drugs in the GI tract and insufficient transport across epithelial cell layers.[62] Tobio et al successful reported that the function of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecules.[63]

Respiratory delivery

The respiratory delivery of SLN is a novel and forthcoming area of research. Lymphatic drainage acts significant role in the uptake of particulates in the respiratory system. The lungs avoid first pass effects by offering a high surface area for drug absorption. Rapid drug absorption by aerosolization of drugs occurs since the walls of alveoli in the deep lung are extremely thin.[64]

Topical application

SLNs are very attractive colloidal drug delivery systems for skin applications due to their various advantageous effects on skin. They are well suitable for use on inflamed or damaged skin because they are based on non-toxic and non-irritant lipids.[65] SLNs and NLC have been studied with compounds such as vitamin E,[66] tocopherol acetate.[67] retinol.[68] ascorbyl palmitate.[69-70] clotrimazole, triptolide.[71] and a nonsteroidal antiandrogen RU 58841.[72] for topical application. Morphine, morphine-loaded and unloaded SLNs accelerated reepithelialization; acceleration of wound closure, low cytotoxicity and irritation as well as possible prolonged morphine release makes SLN an interesting approach for innovative wound management.[73]

APPLICATIONS

Solid lipid nanoparticles for ocular drug delivery

Ocular drug delivery remains demanding because of the composite nature and structure of the eye. It is a necessary to develop novel drug delivery carriers capable of increasing ocular

absorption and decreasing both local and systemic cytotoxicity. SLNs are especially useful in ocular drug delivery as they can improve the corneal absorption of drugs and progress the ocular bioavailability of both hydrophilic and lipophilic drugs. SLNs have another benefit of allowingautoclave sterilization, a essential step towards formulation of ocular preparations. Special consideration has been given to the nature of lipids and surfactants commonly used for SLN production .[74]

SLNs as gene vector carrier

Cationic solid lipid nanoparticles have established themselves during the past decades. Theycan well bind DNA directly via ionic interaction and intervene gene transfection. SLN can be used in the gene vector formulation.[75] There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids.[76] Cationic solid lipid nanoparticles are promising nonviral gene delivery carriers suitable for systemic administration. The relationship between the composition of cationic SLN and their ability to condense plasmid DNA (pDNA) and to transfer it in neuroblastoma cells were investigated.[77] The lipid nucliec 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-nuclic acid nanoparticle (70-100 nm) were formed. It's called genospheres. Mannan-modified DNA-loaded vehicles have great potential for targeted gene delivery.[78]

Stealth nanoparticles

Stealth nanoparticles provide a novel and unique drug-delivery system which can target specific cells. Stealth SLNs have been effectively tested in animal models with marker molecules and drugs. Stealth Tashinone IIA-loaded solid lipid nanoparticles have been prepared by ananoprecipitation/solvent diffusion method in which Poloxamer 188 was used as a stealthagent. Rhodamine B was successfully incorporated into nanoparticles as a fluorescent marker to view and compare the phagocytic uptake of nanopreticles.[79] Antibody labelled stealth lipobodies have shown increased delivery to the target tissue in accessible sites.[80]

SLNs in anti tubercular chemotherapy

Another prominent example of SLNs-based drug delivery is pulmonary delivery of antimicrobials to treat tuberculosis, a serious lung infection caused by *Mycobacterium tuberculosis*. Antitubercular drugs such as rifampicin, isoniazide, pyrazinamide-loaded SLN

systems, were able to decrease the dosing frequency and improve patient compliance.[81] This antitubercular drug loaded solid lipid nanoparticles were prepared by using the emulsion solvent diffusion technique.

SLNs in breast cancer

Photodegradation and low bioavailability are chief hurdles for the therapeutic use of curcumin. Transferrin mediated SLNs were formulated to increase photostability and enhance its anticancer activity against MCF-7 breast cancer cells. The anticancer activity of curcumin is enhanced with transferrin-mediated SLNs compared to curcumin solubilized surfactant solution and apoptosis is the mechanism underlying the cytotoxicity [82]. Mitoxantrone-loaded SLNs local injectionswere formulated to reduce the toxicity and improve the safety and bioavailability of drug.[83]

Efficacy of doxorubicin has been reported to be enhanced by incorporation in SLNs. Doxorubicin was complexed with soybean-oil-based anionic polymer and dispersed collectively with a lipid in water to form doxorubicin loaded solid lipid nanoparticles. The system has improved its efficacy and reduced breast cancer cells.

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 labelled stealth lipobodies have shown increased delivery to the target tissue in accessible sites.

Stealth SLNs have been successfully tested in animal models with marker molecules and drugs.[84]

SLNs as cosmeceuticals

Cosmeceuticals is rising as the major application target of these carriers. Carrier systems like SLNs and NLC were formulated with a point of view to meet manufacturing needs like scale up, qualification and validation, simple technology, low cost etc.[85] The SLNs have been functional in the preparation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers.[86] Many features of SLNs are advantageous for dermal application of cosmetic products have been reported, e.g. occlusive properties, increase in skin hydration, modified release, increase of skin penetration and avoidance of systemic

uptake. The first two cosmetic products containing lipid nanoparticles were introduced to the market in 2005. Within 3 years after the introduction, of about 30 cosmetic products containing lipid nanoarticles are in the market these days.[87]

Table 2: A summary of different drugs incorporated in SLNs for different activities.

Activity	Drug	Reference
Cancer	Doxorubicin, Paclitaxel, Camptothecin, Methotrexate,	88, 89, 90,91, 92
Tuberculosis	Rifampicin, Isoniazid	81
Antifungal	Clotrimazole, Ketoconazole	93,94
Immunosuppressant	Cyclosporin-A	95
Sunscreen	Oxybenzone, Tocopherol acetate	96,67
Antipsycotic	Risperidone, Clozapine	97,44
Antiretroviral	Zidovudine, Saquinqvir	98,99
NSAID	Flurbiprofen	100
Antioxidant	Vitamin-A	101
Antidiabetic	Insulin	102, 103
Anti-parkinsonism	Apomorphine	104

CONCLUSION

Lipid nanoparticle drug delivery technology presents considerable opportunities for improving medical therapeutics, but the technology's potential remains unrealized. The review has focused on the variety of aspects of SLNs and their applicability in the encapsulation of various drugs. In recent years, number of research works has been successfully carried out in this area. It would result in a simultaneous improvement in the quality, efficacy, and safety profile of drugs.

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