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RECENT PROSPECTIVE ON SOLID LIPID NANOPARTICLES AND ITS APPLICATION- 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 and research. Due to their unique size dependence properties, lipid nanoparticles offer possibility to develop new therapeutics. SLNs introduced at the beginning of the 1990s represents an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro and nanoparticles as they have advantages like controlled drug release and targeted drug delivery with increased stability. SLN are administrated by various route such as oral, parenteral, rectal, respiratory, nasal, topical and ocular have been proposed for the delivery of SLNs. The present review paper highlight on various advantages, disadvantages, various production methods, drug incorporation model, factor affecting loading capacity of drug in lipid, Analytical techniques for characterization of SLNs like photon correlation spectroscopy, electron microscopy, atomic force microscopy, dynamic light scattering [DLS], differential scanning calorimetry [DSC], static light scattering, acoustic method and nuclear magnetic resonance [NMR] are discussed along with application of SLNs.

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INTRODUCTION

The field of Novel Drug Delivery System is emerging at an exponential rate with the deep understanding gained in diversified fields of Biotechnology, Biomedical Engineering and Nanotechnology. [1] Nanotechnology is the most promising technology that is used today. It can be applied to almost all spheres of life, ranging from electronic storage systems, pharmaceutical, biotechnology. [2] In nanoparticulate drug delivery systems [DDS] have attracted a lot of attention because of their size-dependent properties. Among the array of nanoparticles being currently investigated by pharmaceutical scientists, lipid nanoparticles have taken the lead because of obvious advantages of higher degree of biocompatibility and versatility also lipid nanoparticles offer the possibility to develop new therapeutics that could be used for secondary and tertiary level of drug targeting. Hence, lipid nanoparticles hold great promise for reaching the goal of controlled and site specific drug delivery and have attracted wide attention of researchers. The most frequent role of lipid-based formulations has traditionally been to improve the solubility of sparingly water soluble drugs especially Biopharmaceutics Classification System [BCS] Classes II & IV drugs. [3] Increasing interest in lipid-based delivery systems is due to following reasons like. [4, 5]

- Versatility of lipidic excipients.
- Formulation versatility and the choice of different drug delivery systems.
- Low risk profile.
- Enhanced oral bioavailability and reduced plasma profile variability.
- Enhanced permeation of these systems when used topically.
- Formation of vesicular system which is passive, non-invasive and is available for immediate commercialization.
- Better characterization of lipidic contents.
- High market attractiveness for products with proprietary technology.
- Improved ability to address the key issues of technology transfer and manufacture scale-up.
- Ability to control and target drug release.
- Can improve stability of pharmaceuticals.
- The feasibility of carrying both lipophilic and hydrophilic drugs.
- Lipids used are biodegradable, and as such they have excellent biocompatibility, are non-toxic, non-allergenic and non-irritating.
- Can be formulated by water-based technologies and thus can avoid organic solvents.
- Easy to scale-up and sterilize.
- Lipids are less expensive than polymeric/surfactant based carriers.
- They are easy to validate.
- Classification of Lipid nanoparticles.
- Lipid nanoparticles are classified into Solid lipid nanoparticles [SLN], Nano-structured lipid carriers [NLC], Lipid drug conjugate [LDC].

In the following years, extensive work and experiments with solid lipids resulted in the invention of lipid base solid particles in the submicron range by the groups of Westesen, Müller and Gasco. This system called Solid Lipid Nanoparticles [SLN] is defined as drug carrier in the submicron size range made of biocompatible and biodegradable lipids solid at room and body temperature. [6,7] Also Solid lipid nanoparticles [SLN] introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals. [8, 9]

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles.

There are many reasons for the increasing interest in lipid based system as-

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipoid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up.

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid shown on Fig. 1. They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable as shown in Fig. 2.

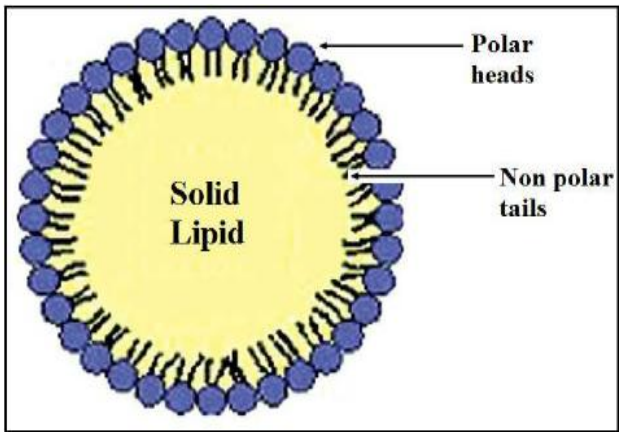

Figure 1 **Structure of SLN.**

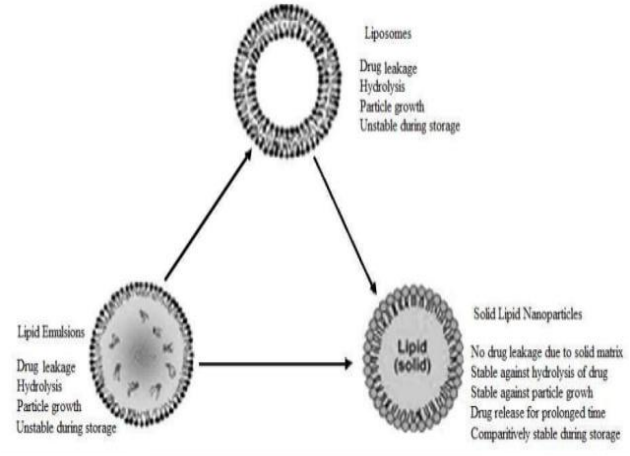

Figure 2 **Advantage of SLN over Emulsion and Liposome.**

The schematic representation of different particulate drug carriers such as emulsions and liposomes and their advantages are compared with SLNs in Fig. 2. SLNs combine all the advantages of polymeric nanoparticles, fat emulsions and liposomes. List of excipients used in SLN Preparation are as shown in table 1

It has been claimed that SLN combine the advantages and avoid the disadvantages of other colloidal carriers.

Table 1 List of excipients used in SLN preparation [10,12]

Lipid	Surfactant
Triglycerides	Phospholipids
Tricaprin	Soy lecithin [LipoidÒ S 75, LipoidÒ S 100]
Trilaurin	Egg lecithin [Lipoid E 80]
Trimyristin [Dynasan 114]	Phosphatidylcholine [Epikuron 170, Epikuron 200]
Tripalmitin [Dynasan 116]	Ethylene oxide/propylene oxide copolymers Poloxamer 188
Tristearin [Dynasan 118]	
Hydrogenated coco-glycerides [SoftisanÒ 142] Hard fat types WitepsolÒ W 35	Poloxamer 182
	Poloxamer 407
WitepsolÒ H 35	Poloxamine 908
WitepsolÒ H 45	Sorbitan ethylene oxide/propylene oxide copolymers
WitepsolÒ E 85	Polysorbate 20
Acyl glycerols	Polysorbate 60
Glyceryl monostearate [ImwitorÒ900]	Polysorbate 80
Glyceryl distearate[Precirol]	Alkylaryl polyether alcohol polymers
Glyceryl monooleate[Peceol]	Tyloxapol
Glyceryl behenate [CompritolÒ 888 ATO]	Bile salts Sodium cholate
Glyceryl palmitostearate [PrecirolÒ ATO 5]	Sodium glycocholate
Waxes Cetyl palmitate	Sodium taurocholate
Fatty Acids Stearic acid	Sodium taurodeoxycholate
Palmitic acid	Alcohols
Decanoic acid	Ethanol
Behenic acid	ButanoL
Acidan N12	Butyric acid
Cyclic complexes	Dioctyl sodium sulfosuccinate
Cyclodextrin	Monooctylphosphoric acid sodium
Para-acyl-calix-arenes	

Aims of solid lipid nanoparticles [10]

Advantages

- Possibility of controlled drug release and drug targeting.
- Increased drug stability
- High drug payload.
- Incorporation of lipophilic and hydrophilic drugs.
- No biotoxicity of the carrier
- Avoidance of organic solvents.
- No problems with respect to large scale production and sterilization.
- Increased Bioavailability of entrapped bioactive compounds.

Disadvantages [11]

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

General requirement for preparation of Solid lipid nanoparticles

The general excipients used in any SLN formulation are solid lipids, emulsifiers, co-emulsifiers and water. The term lipid is used here in a broader sense and includes triglycerides [e.g. Tristearin], partial glycerides [e.g. Imwitor], fatty acids [e.g. stearic acid], and steroids [e.g. cholesterol] and waxes [e.g. Cetyl palmitate]. All classes of emulsifiers [with respect to charge and molecular weight] have been used to stabilize the lipid dispersion. It has been found that the combination of emulsifiers might prevent particle agglomeration more efficiently [10].

Influence of various excipients used on product quality

Influence of the lipid

In hot homogenization it can be seen that average particle size of SLN dispersion is increasing with higher melting lipids and this is because of higher viscosity of dispersed phase. Some peculiar parameters are specific for every lipid like lipid crystallization, lipid hydrophilicity and shape of lipid crystals. Chemically most lipids are mixtures of various compounds so their composition can very from different suppliers and also from batch to batch but these small differences affect the quality of SLNs to a great extent [e.g. by changing the zeta potential, retarding crystallization processes etc.]Increasing the lipid content over 5%-10% result in larger particles and broader particle size distribution in most cases [10, 13]

Influence of emulsifier

Choice of emulsifier has a great impact on quality of SLN. Reduction in surface tension and particle partitioning during homogenization is facilitated by increasing the emulsifier concentration. Reduction in particle size leads to increased surface area.
During SLN preparation the primary dispersion must contain excessive emulsifier to rapidly cover the new surfaces formed during High Pressure Homogenization; otherwise it will lead to agglomeration of uncovered new lipid surfaces. The time taken for redistribution of emulsifier between new particle surfaces and micelles is different for different types of surfactants. It has been studied that Low Molecular Weight surfactants will take less time for redistribution and High Molecular Weight will take longer time for redistribution. The addition of some co-emulsifying agent like Sodium Glycocholate further decreases the particle size [10].

Methods of Preparation of solid lipid nanoparticles [1, 14, 15, 16]

SLNs are prepared from lipid, emulsifier and water/solvent by using different methods and are discussed below. Methods of preparation of solid lipid nanoparticles

1. High pressure homogenization
   a. Hot homogenization
   b. Cold homogenization
2. Ultrasonication/high speed homogenization
   a. Probe ultrasonication
   b. Bath ultrasonication
3. Solvent evaporation method
4. Solvent emulsification-diffusion method
5. Supercritical fluid method
6. Microemulsion based method
7. Spray drying method
8. Double emulsion method
9. Precipitation technique
10. Film-ultrasound dispersion

High shear homogenization technique [HPT]:

High shear homogenization techniques were initially used for the production of solid lipid nanodispersions. [17]. It is a reliable and powerful technique, which is used for the production of SLNs. High pressure homogenizers push a liquid with high pressure [100–2000 bar] through a narrow gap [in the range of a few microns]. The fluid accelerates on a very short distance to very high velocity [over 1000 km/h]. Very high shear stress and cavitation forces disrupt the particles down to the submicron range. Generally 5-10% lipid content is used but up to 40% lipid content has also been investigated [18,19].
Two general approaches of HPH are hot homogenization and cold homogenization; work on the same concept of mixing the drug in bulk of lipid melt [20, 21]

Hot homogenization:

Hot homogenization is carried out at temperatures above the melting point of the lipid and therefore regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase [same temperature] is obtained by high-shear mixing device. HPH of the pre-emulsion is carried out at temperatures above the melting point of the lipid. In general, higher temperatures result in lower particle sizes due to the decreased viscosity of the inner phase. However, high temperatures increase the degradation rate of the drug and the carrier. Increasing the homogenization pressure or the number of cycles often results in an increase of the particle size due to high kinetic energy of the particles. [22, 23, 24]

Cold homogenization

Cold homogenization has been developed to overcome various problems associated with hot homogenization such as: Temperature-induced drug degradation, drug distribution into the aqueous phase during homogenization, Complexity of the crystallization step of the nanoemulsion leading to several modifications and/or super cooled melts. In this technique the drug containing lipid melt is cooled, the solid lipid ground to lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution yielding a presuspension. Then this pre-suspension is homogenized at or below room temperature, the gravitation force is strong enough to break the lipid microparticles directly to solid lipid nanoparticles. [22, 23, 24,25]. Fig 3 gives schematic representation of SLN Preparation by hot and cold homogenization.

➢ **Advantages**
- Low capital cost.
- Customary at lab scale.

➢ **Disadvantages**
- Energy intensive process.
- Polydisperse distributions.
- Unproven scalability.

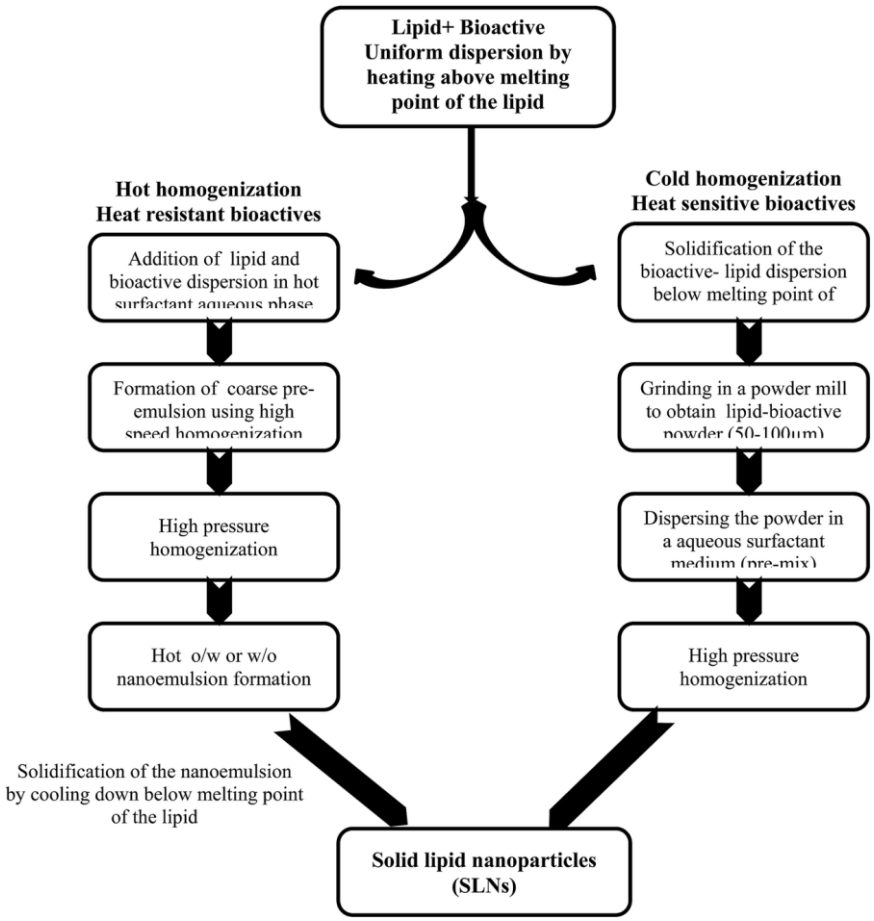

Figure 3 **Schematic representation of SLN preparation by hot and cold homogenization.**

Ultrasonication/high speed homogenization :-

SLNs were successfully prepared by an ultrasonic and high speed homogenization method to improve the oral bioavailability of the poorly water-soluble drug. SLNs are prepared by ultrasonication or high speed homogenization techniques to achieve smaller particle size, combination of both ultrasonication and high speed homogenization is required. [26, 27] 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 [8]. Then they obtained SLN is stored at 4ºC. To increase the stability of the formulation, was lyophilized by a lyophilizer to obtain freeze-dried powder and sometime mannitol [5%] was added into SLNs as cryoprotector.

Advantages
- Reduced shear stress.

Disadvantages
- Potential metal contamination.
- Physical instability like particle growth upon storage.

Solvent evaporation method

In solvent emulsification evaporation technique, the hydrophobic drug and lipophilic material 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. [28, 29] To improve the efficiency of fine emulsification, the coarse emulsion was immediately passed through the micro fluidizer. 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 big advantage of this method is the avoidance of any thermal stress, which makes it appropriate for the incorporation of highly thermolabile drugs. Fig. 4 shows flow chart of solvent evaporation technique

Disadvantage

Use of organic solvent which may interact with drug molecules and limited the solubility of the lipid in the organic solvent.

Solvent emulsification-diffusion technique

SLNs can also be produced by solvent emulsification-diffusion technique. The mean particle size depends upon lipid concentration in the organic phase and the emulsifier used. Particles with average diameters of 30-100 nm can be obtained by this technique. Avoidance of heat during the preparation is the most important advantage of this technique. Here, the lipid matrix is dissolved in water-immiscible organic solvent followed by emulsification in an aqueous phase. The solvent is evaporated under reduced pressure resulting in nanoparticles dispersion formed by precipitation of the lipid in aqueous medium [30, 31]. Fig. 5 gives schematic representation of emulsification diffusion method.

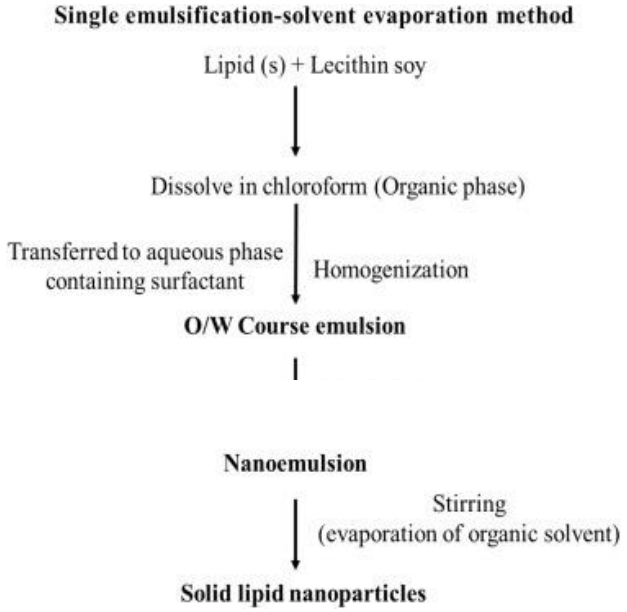

Figure 4 Solvent evaporation technique.

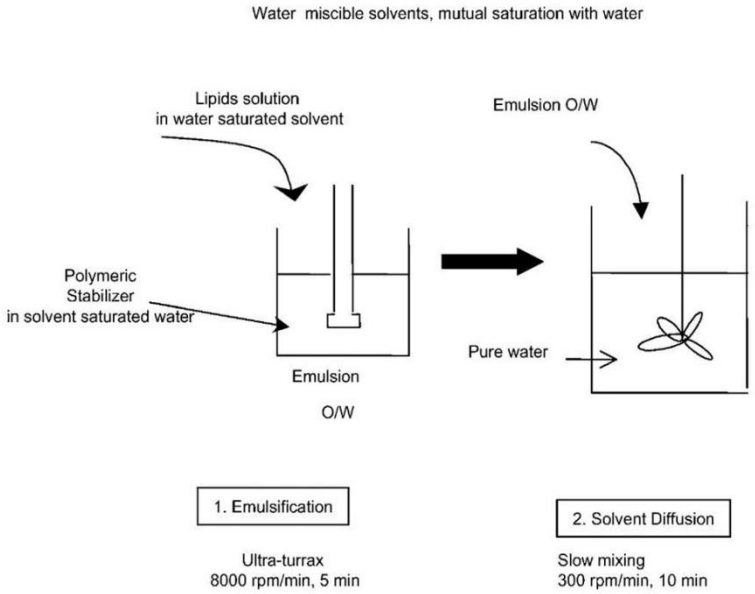

Figure 5 Systematic representation for emulsification diffusion method.

Supercritical fluid method

The supercritical fluid technology is a new technique and has advantage of solvent less processing [32].This is an alternative method of preparing SLNs by particles from gas saturated solutions [PGSS].

Advantages [33, 34]

- Avoid the use of solvents.
- Particles are obtained as a dry powder, instead of suspensions.
- Mild pressure and temperature conditions. Carbon dioxide solution is the good choice as a solvent for this method.[35]

Microemulsion based method

Gasco and co-workers develop a new technique for production of SLNs based on the dilution of micro emulsions. [36] As microemulsions are two-phase systems composed of an inner and outer phase [e.g. o/w microemulsions]. They are made by stirring an optically transparent mixture at 65-70°C which is typically composed of a low melting fatty acid [e.g. stearic acid], an emulsifier [e.g. polysorbate 20, polysorbate 60, soy phosphatidylcholine and taurodeoxycholic acid sodium salt], co-emulsifiers [e.g. butanol, sodium mono octyl phosphate] and water. The hot microemulsion is dispersed in cold water [2-3°C] under stirring. [37, 38] 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.

Spray drying method

It is an alternative technique to lyophilization in order to transform an aqueous SLN dispersion into a drug product. This is a cost-effective method than lyophilization and recommends the use of lipid with melting point >70°C. This method causes particle aggregation due to high temperature shear forces and partial melting of the particle. According to Freitas and Mullera [1998] best results were obtained with SLN concentration of 1% in a solution of trehalose in water or 20% trehalose in ethanol water mixtures [10/90 v/v] [39,40]

Double emulsion method

Here the drug is encapsulated with a stabilizer to prevent the partitioning of drug in to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. [39, 41]

Precipitation technique

Solid lipid nanoparticles can also be produced by a precipitation method which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent [e.g. chloroform] and the solution will be emulsified in an aqueous phase. After evaporation of the organic solvent the lipid will be precipitated forming nanoparticles. [39]

Film-ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. Using the ultrasound with the probe to diffuser at last, the SLN with the little and uniform particle size is formed [39]

Drug incorporation models of SLN [42]

Type I or homogenous matrix model

The SLN Type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLN are produced by the cold homogenation method. A lipid blend can be produced containing the active in a molecularly dispersed form. After solidification of this blend, it is ground in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

Type II or drug enriched shell model

It is achieved when SLN are produced by the hot technique, and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w Nanoemulsion the lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model is the incorporation of coenzyme

Type III or drug enriched core model

Core model can take place when the active ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reduce the solubility of the active in the melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core.

Factors affecting loading capacity of a drug in lipid are:

1. Solubility of drug in lipid melt.
2. Miscibility of drug melt and lipid melt.
3. Chemical and physical structure of solid matrix lipid.
4. Polymorphic state of lipid material.

The condition to obtain an adequate loading capacity is a sufficiently high solubility of the drug in the lipid melt. Usually, the solubility must be higher in the melted state than that essential in the solid state because the solubility reduces when the melt cools and might even be lesser in the solid lipid. The presence of mono- and di-glycerides in the lipid used as the matrix material also promotes drug solubilization. The chemical nature of the lipid is also important because lipids which form highly crystalline particles with a perfect lattice [e.g. monoacid triglycerides] lead to drug expulsion [43]. In broad the conversion is slower for long chain than for short chain triglycerides. A finest SLN carrier can be formed in a controlled way when a definite fraction of ß'-form can be created and preserved during the storage time. By doing this ordinary SLN carrier transforms to an intellectual drug delivery system by having a built-in triggering mechanism to set off transformation from ß'- to ß-forms and accordingly controlled drug release. [44]

Determination of incorporated drug: It is of primary importance to determine the sum of drug incorporated in SLN, since it influences the release characteristics. The degree of encapsulation can be assessed ultimately by determining the quantity of drug remaining in supernatant after centrifugation of SLN suspension or otherwise by dissolution of the sediment in a suitable solvent and subsequent analysis. Standard analytical techniques such as spectrophotometry, high performance liquid chromatography, or liquid scintillation counting can be used to assay the drug. [45]

Characterization of SLN

Measurement of particle size and zeta potential [46, 47]

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

Photon Correlation Spectroscopy [PCS]

It is an established method which is based on dynamic scattering of laser light due to Brownian motion of particles in solution/suspension. This method is suitable for the measurement of particles in the range of 3 nm to 3 mm. The PCS device consists of laser source, a sample cell [temperature controlled] and a detector. Photomultiplier is used as detector to detect the scattered light. The PCS diameter is based on the intensity of the light scattering from the particles.

Electron Microscopy

Scanning Electron Microscopy [SEM] and Transmission Electron Microscopy [TEM] are used to measure the overall shape and morphology of lipid nanoparticles. It permits the determination of particle size and distributions. SEM uses electrons transmitted from the surface of the sample while TEM uses electrons transmitted through the sample.

Atomic Force Microscopy [AFM]

It is an advanced microscopic technique which is applied as a new tool to image the original unchanged shape and surface properties of the particles. AFM measures the force acting between surface of the sample and the tip of the probe, when the probe is kept in close proximity to the sample which results in a spatial resolution of up to 0.01 nm for imaging.

Dynamic Light Scattering [DLS]

DLS or quasi-elastic light scattering records the variation in the intensity of scattered light on the microsecond time scale. This variation results from interference of light scattered by individual particles under the influence of Brownian motion and is quantified by compilation of an autocorrelation function. This function is fit to an exponential, or some combination or modification thereof, with the corresponding decay constant[s] being related to the diffusion coefficient. The advantages of the process are the speed of analysis, lack of requisite calibration, and sensitivity to submicrometer particles. [48, 49, 50]

Differential Scanning Calorimetry [DSC] and X-Ray Diffraction [XRD]

Among the large number of analytical techniques engaged for that purpose, DSC and XRD play an 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 X-ray/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. [51]

Static light scattering [SLS]/fraunhofer diffraction

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

Acoustic methods

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

Nuclear magnetic resonance [NMR] [52]

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

In vitro and ex vivo methods for the assessment of drug release from SLN [48, 49, 53]

A large number of drugs including very hydrophilic molecules have been postulated to be incorporated into SLN. Various methods used to study the in vitro release of the drug are: − Side by side diffusion cells with artificial or biological membrane. Dialysis bag diffusion technique. Reverse dialysis bag technique. Agitation followed by ultracentrifugation or centrifugal ultrafiltration.

In vitro drug release [48, 54]

In vitro drug release could be achieved using dialysis tubing. The solid lipid nanoparticle dispersion is placed in pre - washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analysed for the drug content using a suitable analytical method [1, 54].

Administration routes of SLNs:

- Oral administration
- Parenteral administration
- Rectal administration
- Nasal administration
- Respiratory delivery
- Topical application
- Ocular administration

Oral administration

Controlled release behaviour of SLNs enables the bypass of gastric and intestinal degradation of the encapsulated drug, and their possible uptake and transport through the intestinal mucosa. However, the assessment of the stability of colloidal carriers in GI fluids is essential in order to predict their suitability for oral administration. [48, 55, 56]

Parenteral administration

SLNs are very appropriate for systemic delivery because they consist of physiologically well-tolerated ingredients and have fine storage capabilities after lyophilization. Cationic SLN has been confirmed to attach genes directly via electrostatic interactions, and to have probable benefits in targeted gene therapy in treatment of cancer. The charge of particles can also be modulated via the composition, thus allowing binding of oppositely charged molecules [57-58]. Moreover, coating of SLN with PEG increases steadiness and plasma half life of SLN in order to decline phagocytic uptake, and therefore improves the biovailability of drugs. Wissing et al [59] intensively reviewed parenteral use of SLN. Peptide and protein drugs are usually obtainable for parenteral use in the market. SLN products of several pharmaceutical companies can be given as follows: cationic SLN for gene transfer namely TransoPlexR was produced by VansolinTM and ZysolinTM trade names [www.alpharx.com]. They are very efficient in treatment of life-threatening contagious disease such as pneumonia. SkyePharma [UK] has formulations of nanoparticulate technology which includes SLNs and nanosuspensions under preclinical development [61]

Rectal administration

When rapid pharmacological effect is required, in some circumstances, parenteral or rectal administration is preferred. This route is used for paediatric patients due to easy application. [48, 55, 62]

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. [63] Epirubicin-loaded SLNs were effectively prepared as an inhalable formulation for treatment of lung cancer. Furthermore the drug concentration in lungs after inhalation of epirubicin-loaded SLNs was much higher than that after administration of epirubicin solution. [64] Assessment of inhaled radio-labelled SLN biodistribution has been described and the data showed an important and significant uptake of the radio-labelled SLN into the lymphatics after inhalation. [65] Recently, antitubercular drugs [rifampicin, isoniazid and pyrazinamide] were incorporated into various formulations of solid lipid particles and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery. [66]

Nasal administration

Nasal route is preferred due to its fast absorption and rapid onset of drug action, avoiding degradation of labile drugs in the GIT and insufficient transport across epithelial cell layers. [48, 55, 36, 54]

Topical administration

SLN are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids.

Ocular administration

Biocompatibility and muco-adhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. [48, 55, 67, 68]

Applications

SLNs as gene vector carrier:

Cationic solid lipid nanoparticles have established themselves during the past decades. They can well bind DNA directly via ionic interaction and intervene gene transfection. SLN can be used in the gene vector formulation. [69] There are several recent reports of SLN carrying genetic/peptide materials such as DNA, plasmid DNA and other nucleic acids. [70] 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. [71] 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. [72]

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 allowing autoclave 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.[73]

Solid Lipid Nanoparticles for Topical Use:

SLNs used for topical application for various drug such as anticancer, [74] vitamin-A [75] isotretinoin, flurbiprofen. [76] Using glyceryl behenate, vitamin A-loaded nanoparticles can be prepared. This method is useful for the improvement of penetration with sustained release. The isotretinoin loaded lipid nanoparticles were formulated for topical delivery of drug. Production of the flurbiprofen-loaded SLN gel for topical application offer a potential advantage of delivering the drug directly to the site of action, which will produce higher tissue concentrations.

Solid lipid nanoparticles in cancer chemotherapy:

From the last two decades several chemotherapeutic agents have been encapsulated in SLN and their in-vitro and in-vivo efficacy have been evaluated. Outcomes of these studies have been shown to improve the efficacy of chemotherapeutic drugs, simultaneously reduction in side effects associated with them. Improved stability of drugs, encapsulation of chemotherapeutic agents of diversified physicochemical properties, enhanced drug efficacy, improved pharmacokinetics and less in-vitro toxicity are the important features of SLN which make them a suitable carrier for delivering chemotherapeutic drugs. Several obstacles frequently encountered with anticancer compounds, such as normal tissue toxicity, poor specificity and stability and a high incidence of drug resistant tumor cells, are at least partially overcome by delivering them using SLN. The rapid removal of colloidal particles by the macrophages of the RES is a major obstacle to targeting tissues elsewhere in the body, such as bone marrow and solid tumors. [77, 78, 79]

SLN in breast cancer and lymph node metastases:

Mitoxantrone SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of the drug. Solid lipid nanoparticles for delivering peptides and proteins [80]

SLN as targeted carrier for anticancer drug to solid tumour:

SLN have been to be useful as drug carriers. Tamoxifen is an anticancer drug incorporated in SLN to prolong the release of drug after IV administration in breast cancer. Tumor targeting has been achieved with SLN loaded with drugs like methotrexate and camptothecin. [81, 79]

Solid lipid particulate systems such as solid lipid nanoparticles [SLN], lipid microparticles [LM] and lipospheres have been sought as alternative carriers for therapeutic peptides, proteins and antigens.

CONCLUSION

SLN as colloidal drug carrier combined many advantages of transitional colloidal system like polymeric nanoparticles, fat emulsion, liposomes. Due to various advantages like ease incorporation of both lipophilic and hydrophilic drug, well tolerated physiological lipid, improved stability by surfactant, large scale production is possible, and avoidance of organic solvent. Drug having low solubility are potential candidates for SLN as these access through lymphatic system to systemic circulation which avoid extensive first pass metabolism. By using SLN, site specific and sustained release effect of drug can better achieved. Therefore, SLN are most promising candidate in future in case of targeting, controlled release, loading capacity of both drug, and improving stability of drug.

ABBREVIATIONS

DDS : Drug Delivery System
BCS : Biopharmaceutical Classification System
SLN : Solid-Lipid Nanoparticles
NLC : Nano-structure Lipid Carrier
LPD : Lipid Drug Conjugate
HPT : High Shear Homogenization Technique
PSC : Photon Correlation Spectroscopy
LD : Laser Diffraction
ZP : Zeta Potential
SEM : Scanning Electron Microscopy
TEM : Transmission Electron Microscopy
AFM : Atomic Force Microscopy
DLS : Dynamic Light Scattering
DSC : Differential Scanning Calorimetry
X-RD : X-Ray Diffraction
SLS : Static Light Scattering
NMR : Nuclear Magnetic Resonance
pDNA : Plasmid DNA

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Conflict of Interest

The authors do not report any conflict of interest.

REFERENCES

1. Nadkar S, Lokhande C. Current Trends in Novel Drug Delivery- An OTC Perspective. Pharma Times 2010; 42 Suppl 4 :17-23.
2. Kang YS, Risbud S, Rabolt JF, Stroeve P. Synthesis and Characterization of nanometer-size Fe3O4 and γFe2O3 Particles. Chem Mater. 1996; 8:2209–11
3. Northern Lipids Inc. [2008] Lipid Based Drug Formulation. http://www.northernlipids.com/ourfacilities.htm. [Accessed 17 FEB 2017].
4. Anthony A. Attama, Mumuni A. Momoh and Philip F. Builders: Lipid Nanoparticulate Drug Delivery Systems: A Revolution in Dosage Form Design and Development.
5. Soumya S, Doney A, Sabitha M. Current Trends In Lipid Based Delivery Systems And Its Applications In Drug Delivery.
6. Siekmann B, Westesen K. Submicron-sized parenteral carrier systems based on solid lipids. Pharm. Pharmacol. Lett 1992;1[3] 123-126.
7. Gasco MR. U.S. Patent No. 5,250,236. Washington, DC: U.S. Patent and Trademark Office, 1993. http://www.google.bg/patents?hl=en&lr=&vid=USPAT5250236&id=MU4nAAAAEBAJ&oi=f nd&dq=Method+for+producing+solid+lipid+microspheres+having+a+narrow+size+distribu tion&printsec=abstract [accessed 16 Jan 2017].
8. Houli L, Xiaobin Z, Yukun M, Guangxi Z, Ling B. J. Cont. Release,2009, 133: 238-244.
9. Melike U, Gulgun Y, Int. J. Nanomedicine, 2007; 2[3]: 289-300.
10. Mehnert W, Mader K. Solid lipid nanoparticles-Production, characterization and applications. Advanced Drug Delivery Reviews 2001; 47:165–196.
11. Ekambaram P, Sathali AH, Priyanka K. Solid Lipid Nanoparticles: A Review. Scientific Reviews and Chemical. Communication 2012; 2 (1): 80-102.
12. Jannin V, Musakhanian J, Marchaud D. Approaches for the development of solid and semi-solid lipid-based formulations. Advanced Drug Delivery Reviews 2008; 60: 734–746.
13. Chakraborty S, Shukla D, Mishra B, Singh S. Lipid – An emerging platform for oral delivery of drugs with poor bioavailability. European Journal of Pharmaceutics and Biopharmaceutics 2009; 73:1–15.
14. Antonio J, Eliana Souto. Adv. Drug Delivery Rev. 2007; 59: 478-490.
15. Vyas S, and Khar R. Controlled Drug Delivery - Concepts and Advances, First Edition, Vallabh Prakashan. 2002: 38-50.
16. Wolfgang M. Karsten M. Adv. Drug. Deliv. Rev. 2007; 47: 165-196.
17. Domb AJ. United States Patent, US 188837; 1993.
18. Lippacher A, Muller R, Mader K. Investigation on the viscoelastic properties of lipid based colloidal drug carriers. Int J Pharm. 2007; 196: 227-230.
19. Muller R, Mehnert W, Lucks J, Schwarz C, Muhlen A, Weyhers H, Freitas C, Ruhl D. Solid lipid nanoparticles [SLN] - An alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm,. 1995; 41: 62-69
20. Muhlen A and Mehnert W. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. Pharmazie. 1998; 53: 552-555.
21. Lander R, Manger W, Scouloudis M, Davis AKC and Lee A. Gaulin homogenization: a mechanistic study. Biotech- nol. Prog,2000; 16:80-85.
22. Krishna S, Amareshwar P, Chakravarty P. Formulation of solid lipid nanoparticles and their applications. CPR 2011; 1[2], 197-203.
23. Ahlin P, Kristl J, Kobar S. Optimization of procedure parameters and physical stability of solid lipid nanoparticles in dispersion. Acta Pharm. 1998; 48, 257-67.
24. Jahnke S. The theory of high pressure homogenization, in: Muller R, Benita S, Bohm B. editors. Emulsions and nanosuspensions for the formulation of poorly soluble drugs, Stuttgart Medpharm Scientific Publishers. 1998; 77-2005.
25. Siekmann B, Westesen K. Investigations on solid lipid nanoparticles prepared by precipitation in o/w emulsions. Eur J Pharm Biopharm. 1996; 43, 104-9.
26. Gasco M. Method for producing solid lipid microspheres having narrow size distribution. United State Patent. USS 188837. 1993.
27. Elldem T, Speiser P, Hineal A. Optimization of spray-dried and congealed lipid microparticles and characterization of their surface morphology by scanning electron microscopy. Pharm Res. 1991; 8, 47-54.
28. C Jin, L Bai, H Wu, F Tian, G Guo., Biomaterials. 2007; 28, 3724–30.
29. CP Tan, M Nakajima, Food Chemistry. 2005; 92, 661–71.
30. Muller R, Mader K., Gohla S. Solid Lipid Nanoparticles for Controlled Drug Delivery- A Review of the State of the art. Eur J Pharm Bio Pharm. 2000; 50[1], 161-177.
31. Trotta, M., Debernardi, F., Caputo, O. Preparation of Solid Lipid Nanoparticles by a solvent emulsification-diffusion technique. Int J Pharm. 2003; 257, 153-160.

32. Chen Y, Jin R, Zhou Y, Zeng J, Zhang H, Feng Q. Zhongguo Zhong Yao Za Zhi 2006; 31, 376-9.
33. Kaiser C, Rompp H, Schmidt P. Pharmaceutical applications of supercritical carbon dioxide. Pharmazie. 56, 2001; 907-926.
34. Gosselin P, Thibert R, Preda M, Macmullen J. Polymeric properties of micronized carbamazepine produced by RESS. Int J Pharm, 252, 2003; 225-233.
35. Gasco M. Method for producing solid lipid microspheres having a narrow size distribution. United States Patent, USS 188837, 1993.
36. Gasco M. United State Patent.US 188837, 1993.
37. Boltri L, Canal T, Esposito PA and Carli F. Lipid nanoparticles: evaluation of some critical formulation parameters. Proc Intern Symp. Control Release Bioact Mater, 20, 1993: 346-347.
38. Muchow M, Maincent P and Muller RH. Lipid nanoparticles with a solid matrix [SLN, NLC, LDC] for oral drug delivery. Drug Development and Industrial Pharmacy. 34, 2008: 1394-1405.
39. Krishna S, Amareshwar P, Chakravarty P. Formulation of solid lipid nanoparticles and their applications. CPR 2011; 1[2]: 197-203.
40. De Labouret A, Thioune O, Fesii H, Devissaguet J, Puiseieux F. Application of an original process for obtaining colloidal dispersion of some coating polymers. Preparation, Characterization, industrial scaling up. Drug Develop Ind Pharm. 1995; 21: 229-4.
41. Ghada A, Rania H. Diazepam-Loaded Solid Lipid Nanoparticles: Design and Characterization AAPS Pharm. Sci. Tech. 2009, 10[1].
42. Melike U, Gulgun Y, Int. J. Nanomedicine. 2007; 2[3]: 289-300
43. Westesen K, Siekmann B, Koch M. Int. J. Pharm. 1993; 93: 189–99.
44. Jenning V, Gohla S. J. Microencapsul, 18, 2001: 149– 158.
45. Magenheim B, Levy M, Benita S. Int. J. Pharm. 94, 1993: 115–123.
46. Rathapon A, Iver L, Sunee S, and Kiat R, Uracha R, Garnpimol C. Ritthidej, Pharm. Res. 2007; 24[6]: 1098 – 1107
47. Suresh G, Kopparam M, Vobalaboina V, Vemula S. AAPS Pharm. Sci. Tech., 8[1], Article 24 [2007].
48. Ekambaram P, Abdul A, Priyanka K. solid lipid nanoparticles: a review. Sci. Revs. Chem. Commun., 2012; 2[1]: 80-102.
49. Yung C, Hung H. Chen, Int. J. Pharm. 2009; 365: 206-213.
50. Robhash K, Keon W, Kanga, Hoo K. Choi. Preparation and characterization of solid lipid nanoparticles loaded with doxorubicin Eur. J. Pharm. Sci. 2009; 37[3-4]: 508-513.
51. Heike B, Tobias U. Advanced Drug Delivery Reviews. 2007; 59: 379–402.
52. Yung C, and Hung H. Chen, Int. J. Pharm. 2009; 365: 206-213.
53. Yi F, DaWei C, Li X, Xiu L. Jing Qin. Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability. J. Cont. Release. 2006; 114: 53–59.
54. Lippacher A. Fluessigund halbfeste SLN Dispersion Application, Ph.D. thesis, Free University of Berlin 2001.
55. Melike U, Gulgun Y. Importance of solid lipid nanoparticles [SLN] in various administration routes and future perspectives Int J Nanomedicine. 2007; 2[3]: 289-300.
56. Zara G, Cavalli R, Fundaro A`, Bargoni A, Caputo O, Gasco M. Pharmacokinetics of doxorubicin incorporated in solid lipid nanospheres [SLN]. Pharm. Res. 1999: 281-286.
57. Olbrich C, Bakowski U, Lehr CM, J Control Release, 2001;77: 345–55.
58. Pedersen N, Hansen S, Heydenreich AV, Eur J Pharm Biopharm, 2006; 62: 155–62.
59. Wissing S, Kayser O, Muller R, Adv Drug Deliv Rev, 2004; 56: 1257–72.
60. Powers M. Nanobiotech News, 2005; 3: 45.
61. Kanto J. Int J Clin Pharmacol, 1975; 12: 419–26.
62. Santos M, Mehnert W, Schaller M. Drug targeting by solid lipid nanoparticles for dermal use. J Drug Target. 2002, 10, 489-95.
63. Agu R, Ugwoke M, Armand M. Respir Res, 2001; 2: 198–209.
64. Hu L, Jia Y. WenDing., Pharmazie, 2010; 65: 585-7.
65. Videira M, Botelho M, Santos A, J Drug Target, 2002; 10: 607–13.
66. Pandey R, Khuller G. Tuberculosis, 2005; 85: 227–34.
67. Gupta P, Pandit J, Kumar A, Swaroop P, Gupta S. Pharmaceutical nanotechnology novel nanoemulsion –High energy emulsification preparation, evaluation and application. T. Ph. Res. 2010: 117-138
68. Sven G. Solid lipid nanoparticles [SLN] for controlled drug delivery – a review of the state of the art Eur. J. Pharm. Biopharm. 2000; 50: 161177.
69. Rudolph C, Schillinger U, Ortiz A, Tabatt K, Plank C, Muller R, Pharmaceutic Res 2004; 21: 1662-9.
70. Hayes M, Drummond D, Kirpotin D. Gene Ther, 2006; 13: 646-51.
71. Vighi E, Ruozi B, Montanari M, Battini R, Leo E. Int J Pharm, 2010; 389: 254-61.
72. Yu W, Liu C, Liu Y, Zhang N, Xu W. Pharm Res. 2010; 27: 1584-96.
73. Seyfoddin A, Shaw J, Al-Kassas R. Drug Deliv, 2010; 17: 467-89.
74. Pandey R, Sharma S, Khuller G. Oral SLN Based antitubercular chemotherapy, Tuberculosis 2005; Edi 85: 415-420.
75. Chen H, Chang X, Du D, Liu W, Liu J. Podophyllotoxin- loaded solid lipid nanoparticles for epidermal targeting. Journal of Control Release 110, 2006, 296-306. Solid lipid nanoparticle: a review 44
76. Santos Mehnert W, Schaller M. Drug targeting by solid lipid nanoparticles for dermal use. Journal Drug Target, 10, 2002, 489-495.

77. Qing Z, Aihua Y, Yanwei X, Houli L, Zhimei S, Fengliang C, Guangxi Z. Int. J. Pharm., 2009; 372: 191 – 198.
78. Paliwal R, Rai S, Vaidya B, Khatri K, Amit K, Goyal. Nanomedicine, Nanotechnology, Biology and Medicine, 2009; 52: 184-191.
79. Bin L, Xionga S, Hong Y, Xiao-Dong Y, Ruo- Bing C. Eur. J. Pharmaceutical Sci.2006; 28[1-2]: 86-95.
80. Karsten M. 187-212.
81. Sven G. Eur. J. Pharm. Biopharm., 50, 161-177 [2000].