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RESEARCH ARTICLE

A REVIEW ON CURRENT STATE OF ART ON SOLID LIPID NANOPARTICLES AS AN ALTERNATIVE ORAL DELIVERY VEHICLE FOR POORLY SOLUBLE DRUGS

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ABSTRACT

Poor aqueous solubility, hepatic first-pass metabolism, presence of barriers and enzymes might be hamper the oral absorption of the majority of new chemical entities. Solid lipid nanoparticles (SLNs) can be an attractive for oral drug delivery vehicle as they grip tremendous possible to improve the oral bioavailability of drugs, associated reduction of drug toxicity and stability of drug in both GIT and plasma. SLNs are in submicron size range and are made of biocompatible and biodegradable materials capable of incorporating both lipophilic and hydrophilic drugs. SLNs are also considered as substitute to other colloidal drug systems and also used controlled systems and targeted delivery. This review provides the summary on the development of SLNs of poorly water soluble drugs for improved oral delivery. Further, special focus will be made on the current status of pharmacokinetic and pharmacodynamic studies reported on SLNs.

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INTRODUCTION

Administration by the oral route remains most prevalentway of drug delivery. Despite the popularity and versatility of the oral route, significant problems remain. Not all drug molecules possess the physical, chemical or biological characteristics necessary for the successful therapy by oral route. Problems such as poor solubility or chemical stability in the location of the gastrointestinal tract, poor permeability over the biological membranes or compassion to metabolism are well known to result in the refusal of potential drug candidates as oral applied products. Lipid based drug delivery systems have been proposed as a means of by-passing some of more resistant chemical or physical barriers associated with poorly absorbed drugs (Andrew and William, 1997). Hence, various alternative drug delivery systems are developed to enhance the oral BA of these drugs. The delivery systems include; enhancement of solubility through solid dispersions (Ettireeddy*et al.,* 2017), complexation with cyclodextrins (Palem*et al.,* 2016), liquisolid compacts (Arun*et al.,* 2015); increase the stability and prolonged residence time through floating systems (Dudhipala *et al*., 2011; Reddy *et al.,* 2016), increase the mucoadhesive property (Bomma*et al.,* 2016); lipid based delivery systems for by passing metabolism with solid lipid nanoparticles (Narendar and Kishan, 2015), transfersomes (Pitta *et al.,* 2018), nanostructured lipid carriers (Reddy *et al.,* 2018) and micronization for reducing particle size using nanosuspensions (Nagaraj *et al*., 2017; Butreddy*et al.,* 2018). These potential drug delivery systems include the more conventional forms such as emulsions and microemulsions, as well as more recent ones such as liposomes, microspheres, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).

Colloidal carrier systems also protect sensitive drugs against the degradation in biological fluids. They offer protection of patient against gastric irritation and can also be the candidate for prolonged drug action due to sustained release. Colloidal particles as drug carriers are also promising candidates for drug targeting. Colloidal carrier systems are mostly based on compositions similar to the physiological structures exhibit greater biological acceptance. Also, lipids are easily metabolized to nontoxic metabolites. Colloidal systems using biodegradable polymers have also been extensively investigated and proved to be ideal candidates for per oral drug administration. Nevertheless, the major problem with the administration of colloidal particles is this interaction with the reticulo endothelial system (RES). This system consists of phagocytic cells which remove foreign particles from the blood stream rapidly and effectively.

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This lead to the development of techniques to 'mask' the colloids with hydrophilic macromolecules (Heiati *et al*., 1998).

Solid lipid nanoparticles (SLNs): Solid lipid nanoparticles (SLNs) are emerging as alternative carriers to colloidal drug systems, for controlled systems and targeted delivery. These are in submicron size range (50-1000nm) and are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs. SLNs combine the advantage of different colloidal carriers, for instance, like emulsions and liposomes, these are physiologically acceptable and like polymeric nanoparticles, controlled release of drug from lipid matrix can be anticipated (Müller *et al*., 1996; Mehnert and Mader, 2001; Gohla *et al*., 2001).

Additional advantages include lack of coalescence after reaching to room temperature (following their preparation or during their storage) and better physical stability. Since mobility of incorporated drug molecule is drastically reduced in solid lipid nanoparticles, there would not be any appreciable drug leakage from particles. In recent years, much work has been focused in the development of SLNs as delivery systems for anticancer drugs, peptides, genetic material, cosmetic, *etc.* (Hu *et al*., 2004; Olbrich *et al*., 2001; Wissing *et al*., 2003). SLNs are particles made from solid lipids (i.e., lipids solid at room temperature and also at body temperature) and stabilized by surfactant(s). By definition, the lipids can be highly purified triglycerides, complex glyceride mixtures or even waxes. Through the work of various research groups, the SLN carrier system has been characterized intensively. The US patent, granted in 1993 contained claims on different production methods of SLN.

Great progress has been made in the treatment of a variety of diseases by using drug delivery systems including solid lipid nanoparticles (SLN). SLNs are colloidal carriers developed in the last decade as an alternative system to the existing traditional carriers (emulsions, liposomes and polymeric nanoparticles). SLN are colloidal drug carrier systems (Mühlen *et al*., 1998; Müller and Keck 2004; Castelli *et al*., 2005; Mehnert and Mäder 2012). They are very much like nanoemulsions, differing in lipid nature. The liquid lipid used in emulsions is replaced by a lipid solid at room temperature in SLN including high-melting point glycerides or waxes (Schwarz *et al*., 1994; Manjunath and Venkateswarlu 2005). Controlled drug delivery, enhancement of bioavailability of entrapped drugs via modification of dissolution rate (Schwarz, 1999; Demirel*et al*., 2001) and/or improvement of tissue distribution and targeting of drugs (Göppert and Müller, 2005) by using SLN have been reported.

Structure of solid lipid nanoparticles: SLNs consist of a core of solid lipid with the bioactives being a part of the lipid matrix (Figure 1). The particle is stabilized by a surfactant layer, which may consist of a single surfactant, but typically is composed of a mixture of surfactants. In general, the use of crystallized lipids instead of liquid lipids has been shown to increase control over release and stability of incorporated bioactives. This is because mobility of bioactives can be controlled by controlling the physical state of the lipid matrix **(**Jochen Weiss *et al*., 2008).

Advantages of Sln

The advantages of SLNs include the following:

- The nanoparticles and the SLNs particularly those in the range of 120–200 nm are not taken up readily by the cells of the RES (Reticulo Endothelial System) and thus bypass liver and spleen filtration (Müller RH *et al*., 2000).
- Controlled release of the incorporated drug can be achieved for upto several weeks (Müller RH *et al*., 1995; Muhlen AZ *et al*., 1998). Further, by coating with or attaching ligands to SLNs, there is an increased scope of drug targeting (Allen DD *et al*., 2003; Dingler A *et al*., 1998).
- SLN formulations stable for three years have been developed. This is of paramount importance with respect to the other colloidal carrier systems (Diederichs and Müller, 1994; Freitas and Müller, 1998; Ho Lun *et al*., 2007).
- Excellent reproducibility with a cost effective high pressure homogenization method as the preparation procedure (Gohla *et al*., 2001).
- The feasibility of incorporating both hydrophilic and hydrophobic drugs (Rohit and Indu, 2013)
- The carrier lipids are biodegradable and hence safe (Siekmann *et al*., 1992; Yang S *et al*., 1999).
- Avoidance of organic solvents (Mohammad M. Mojahedian *et al*., 2013).
- Various application routes (Uner and Yamen, 2007)
- Increasing attention has also been paid to the coating of SLN to provide receptor mediated drug and gene delivery in recent years (Kakizawa and Kataoka, 2002; Garcia-Garcia *et al*., 2005). Coating of colloidal carriers has been demonstrated to improve stability of the particles and to enhance transmucosal transport of the associated compounds following either nasal (Vila *et al*., 2004), oral (Jani *et al*., 1990) or ocular administration (De Campos *et al*., 2001).
- Topical treatment of skin diseases has the advantage that high drug levels can be achieved at the site of disease and systemic side effects can be reduced, when compared to oral or parenteral drug administration. Drugs under investigations for dermal application using lipid nanoparticles at the present are for instance glucocorticoids, retinoids, non-steroidal anti-inflammatory drugs, COX-II inhibitors and antimycotics (Sanket *et al*., 2011).
- Stability of SLNs can be increased against microbial organisms by adding preservatives where the SLNs were prepared with natural lipids and not undergone aseptic manufacturing process.
- Another clear advantage of SLNs compared to polymeric nanoparticles is the availability of large-scale production units. To summarize, especially with regard to industrial production aspects, SLNs have the chance to be exploited as delivery system in commercial products.

Disadvantagesof SLN

- During storage, drug may expel after polymeric transition.
- High water content of dispersions.
- Need to remove too much water in tablet / pellet production

Limitations of SLN

- Pay-load for a number of drugs is too low.
- Drug expulsion during storage.
- High water content of SLN dispersions.

Factors to be considered in the formulation of SLN

Common ingredients used in the formulation of SLN are lipids (matrix materials), emulsifiers, co-emulsifiers and water. Charge modifiers, stealthing agents and homing devices are also used to meet the requirements of stability and targeting aspects.

Selection of lipids: The rationale behind choosing lipid materials for developing oral pharmaceutical dosage forms had been reviewed recently. Lipid matrices used for the production of SLNs for i.v. administration should have the following appropriate properties (R.H. Müller *et al*., 2000).

- They are capable of producing small size particles (in the nanometer size range) with a simultaneous low content of micro particles (>5μm).
- They possess sufficient loading capacity for lipophilic and possible also hydrophilic drugs.
- They should be stable in aqueous dispersions on long term storage, or alternatively they can be lyophilized or spray dried.
- They should not leave any toxic residues from the production process (e.g., solvents).
- They must be biodegradable.

Various lipids (matrix materials) used for the production of solid lipid nanoparticles are tristearin, tripalmitin or cetylpalmitate. Lipids of less ordered crystal lattices favour successful drug inclusion, as is observed in case of glyceryl monostearate and glyceryl behenate SLN compared to SLN prepared using highly ordered crystal packing bees wax, cetylpalmitate. However, their long term stabilities were quite different. Within glycerides, the best physical stability was obtained for tripalmitate, followed by tribehenin and is due to the presence of 15% of monoglycerides in tribehenin which possess the surfactant properties. On the other hand, glycerymonostearate is extremely unstable and considerable particle growth takes place within a few days and is attributed to the presence of 50% of monoglycerides in glyceryl monostearate which are responsible for their physical destabilization (Jenning *et al*., 2000). Important point to be considered in the selection of drug carrier system is its loading capacity and also the intended use, for instance complex glycerides like hard fats are not suited for controlled release applications because these particles melt at body temperature (Jenning *et al*., 2000a). Lipophilicity of the glyceride increases as the chain length of hydrocarbon increases. Therefore, lipophilic drugs are better soluble in lipid melts of longer fatty acid chain lengths.

Selection of emulsifier: Emulsifier should be non-toxic, compatible with other excipients, capable of producing desired size with minimum amount used and also provide adequate stability to the SLN by covering the surface of nanoparticles. From literature, it is evident that the type and amount of emulsifier, method of preparation, influence the size of the particles and also their stability. The amount of the emulsifier should be optimum to cover the surface of the nanoparticles. Lesser amounts of emulsifier result in particle aggregation and lead to increase in particle size. However, use of excess amount of emulsifier is avoided to prevent decrease in entrapment efficiency, burst release as observed in case of release studies of SLN and also toxic effects associated with surfactants (Müller *et al*., 2000). The combined use of two or more emulsifying agents appears to produce mixed surfactant films at the interface.

Selection of co-emulsifier: Phospholipids used in the formulation of SLNs are neither soluble in continuous phase nor do they form highly dynamic micelles. The excess phospholipid molecules form small, predominantly unilamellar vesicles during homogenization process. Phospholipid molecules bound to vesicles, however, exhibit only a limited mobility. Therefore, they are not able to immediately cover the newly created interfaces during recrystallization. Due to the low mobility of the phospholipid molecules, sudden lack of emulsifier on the surface of the particle leads to particle aggregation and increase in the particle size of SLN. To avoid this, co-emulsifiers are employed. They stabilize the colloidally dispersed state of recrystallizing triglycerides. These water soluble emulsifiers are able to form micelles. Polymer molecules are able to diffuse to the particle surface in a much shorter time than do vesicles. However, it is not recommended to use rapid distributing surfactants like sodium lauryl sulphate due to their toxic effects (Manjunath and Venkateshwarlu, 2005).

Preparation methods of solid lipid nanoparticles: Apart from the ingredients used for the preparation of SLNs, the method of preparation also greatly influences particle size, drug loading capacity, stability of the drug, etc. The techniques that could be employed for generating solid lipid nanoparticles are

- High pressure homogenization (Muller and Runge 1998; Jores *et al*., 2004; Uner *et al*., 2005b)
- Hot homogenization (Siekmann and Westesen, 1994)
- Cold homogenization (for thermo labile drugs)
- Microemulsion technique (Gasco1993;Cavalli *et al*., 1997; Cavalli *et al*., 1999; Igartua *et al*., 2002).
- Solventemulsification technique (Sjostrom and Bergenstah, 1992;Shahgaldian *et al*., 2003)
- Solventemulsifiation- diffusion technique (Quintanar-Guerrero *et al*., 2005; Hu *et al*., 2005)
- Solvent injection (Schubert and Muller-Goyman, 2003).
- Double emulsion technique (for encapsulatinghydrophilicdrugs) (Morel *et al*., 1998;Cortesi *et al*., 2002).
- Homogenization followed by Ultrasonication(Mei *et al*., 2003; Song and Liu, 2005).
- Membrane contactor as a new reported technique for SLN production (Charcosset *et al* 2005).

High pressure homogenization (Hot and Cold)

High pressure homogenization (HPH) has emerged as a reliable and powerful technique for the preparation of SLN. Homogenizers of different sizes are commercially available from several manufacturers. The high pressure homogenization technique has been demonstrated to be the most effective technique due to some advantages such as narrow particle size distribution of the product with a low content of microparticles (> 5 μm is requested for iv injections), higher particle content in thedispersions, avoidance of organic solvents, acceptability

of the homogenization equipment by the regulatory authorities (even for parenteral products), scale-up feasibility and the availability of homogenization lines in industry (Muller and Runge, 1998; Gohla and Dingler 2001; Mehnert andMader, 2001). Depending on the size of production-scale homogenizers, a wide production range can be possible (Muller and Keck 2004; Wissing *et al* 2004). There aretwo general approaches within the homogenization technique, the hot and the cold homogenization. In both cases, a preparatory step involves the drug incorporation into the bulk lipid by dissolving or dispersing the drug in the lipid melt.

Hot homogenization technique: 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. 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 pre-emulsion affects the quality of the final product to a large extent and it is desirable to obtain droplets in the size range of a few micrometers. 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 may also increase the degradation rate of the drug and 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 of the high kinetic energy of the particles.

The primary product of the hot homogenization is a nanoemulsion due to the liquid state of the lipid. Solid particles are expected to be formed by the following cooling of the sample to room temperature or to temperatures below (MehnertandMader, 2001). Due to the small particle size and the presence of emulsifiers, lipid crystallization may be highly retarded and the sample may remain as a supercooled melt for several months. The hot homogenization technique is also suitable for drugs showing some temperature sensitivity because the exposure to an increased temperature is relatively short. In case of highly temperature-sensitive compounds the cold homogenization technique can be applied. A camptothecin loaded SLN suspension consisted of 0.1% (w/w) camptothecin, 2.0% (w/w) stearic acid, 1.5% (w/w) soybean lecithin and 0.5% (w/w) polyoxyethylene–polyoxypropylene copolymer (Poloxamer 188) was prepared by high pressure homogenization (Yang S *et al*., 1999a & 1999b).

Cold homogenization technique: In contrast, the cold homogenization is carried out with the solid lipid and represents, therefore, a high pressure milling of a suspension. Effective temperature control and regulation is needed in order to ensure the un-molten state of the lipid due to the increase in temperature during homogenization. Cold homogenization has been developed to overcome the following three problems of the hot homogenization technique:

- 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 supercooled melts

The first preparatory step is the same as in the hot homogenization procedure and includes the solubilization or dispersing of the drug in the melt of thebulk lipid. However, the following steps are different. The drug containing melt is rapidly cooled (e.g.by means of dry ice or liquid nitrogen). The highcooling rate favors a homogenous distribution of the drug within the lipid matrix. The solid, drug containing lipid is milled to microparticles. Typicalparticle sizes obtained by means of ball or mortarmilling are in the range of 50–100 microns. Lowtemperatures increase the fragility of the lipid andfavor, therefore, particle comminution. The solidlipid microparticles are dispersed in a chilled emulsifier solution. The pre-suspension is subjected tohigh pressure homogenization at or below roomtemperature. In general, compared to hot homogenization, larger particle sizes and a broader sizedistribution are observed in cold homogenized samples (MehnertabdMader, 2001). The method of cold homogenizationminimizes the thermal exposure of the sample, but itdoes not avoid it due to the melting of the lipid /drug-mixture in the initial step. Vancomycin B (VB)-loaded SLNs were prepared by cold homogenization technique (Jian You *et al*., 2007). For comparison,SLNs were also prepared by solvent diffusion method. Higher drug entrapment efficiency (close to 80%) of VB-loaded SLNs were obtained by cold homogenization technique, which was higher than that of SLNs produced by solvent diffusion method (only about 50%).However, exposure of the drug to temperature cannot be completely avoided due to solubilization of the drug in molten lipid and also temperature generated during homogenization process.

Microemulsion method: 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 (Gasco*et al*., 2003; R.H. Müller *et al*., 2000). Considering incorporation of shear and temperature-sensitive compounds such as DNA, albumin and erythropoietin, the HPH is not suitable and therefore, other preparation techniques; such as precipitation from microemulsion have been developed. Microemulsions are thermodynamically stable colloid mixtures of two immiscible solvents stabilized by an adsorbed surfactant film at the liquid–liquid interface. They can be prepared spontaneously by mixing surfactant, co surfactant, oil and water. Thus, no energy is required to prepare microemulsion, and the simplest representation of the structure of microemulsion is the droplet model with small droplet diameter, generally below 100 nm. Synthesis of nanoparticles in microemulsions is an area of considerable current interest (Mehnert and Mader, 2012). 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) is molten, 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 (2-3^{o}C) under mild mechanical mixing, thus ensuring that the small size of the particles is due to the precipitation.

Table 1. Various SLNs formulations studied by different researcher to improve the oral bioavailability of drugs

Drug	Purpose	Inference	Ref
Adefovirdipivoxil	Poor oral BA	Improved oral BA	Dodiya S *et al*., 2013
Andrographolide	poor aqueous solubility and instability, poor BA	Enhanced bioavailability and stability	Yang *et al*., 2013
Andrographolide	poor aqueous solubility	Enhanced bioavailability and improved antitumor activity.	Rabea *et al*., 2014
Arteether	Poor oral BA	Improved oral BA	Pankaj *et al*., 2014
Bioactive food (carotenoids, omega-3 fatty acids, phytosterols)	Highly lipophilic, limited solubility (poor BA), chemical instability, binding with food	Improve stability, BA, no binding with food	Weiss *et al*., 2008
Baicalin	Poor BA	Enhanced bioavailability	Hao *et al*.,2012
Candesartan cilexetil	Hepatic first pass Metabolism and poor BA	Improved BA	Narendar &Kishan, 2014
Camptothecin	Poor solubility, acid liability	Improved stability and sustained release effect	Yang *et al*., 1999
Capecitabine	Poor stability and BA	Improved BA and tumor targeting	Narendar and Govardhan, 2018
Clozapine	first-pass metabolism, poor BA	Increased BA, high distribution to brain and RE cells	Manjunath and Venkateswarlu, 2014
Cyclosporine A	Poor solubility and limited absorption window, firstpass metabolism, P-gp efflux	Improved BA, less Mvariation in plasma conc.	Muller RH *et al*., 2006; Muller RH *et al*., 2008
Cryptotanshinone	Poorly water soluble	Increases the solubilization capacity, changes metabolism behavior, improved oral BA	Hu LD *et al*., 2013
Cantharidin	insolubility, toxicity and short half-life	Improved BA	Yun-Jie *et al*., 2013
Carvedilol	Poor oral BA	Improved BA	Sanjula *et al*., 2009; Vinay Kumar *et al*., 2012
Curcumin	Poor oral BA	Improved BA	Vandita *et al*., 2011
Fenofibrate	Poor soluble, low oral BA	Improved BA	Hanafy *et al*., 2007
Felodipine	Poor soluble, low oral BA	Improved BA	Usha *et al*., 2017
Idarubicin	Poor BA	Improved BA, modifies the PK and tissue distribution	Zara *et al*., 2002
Insulin	GIT unstability, poor BA	Improved stability and BA	Zhang *et al*., 2006
Lacidipine	Poor oral BA	Improved oral BA	Sandeep *et al*., 2017
Lovastatin	Hepatic first pass metabolism	Avoid first pass metabolism, improved BA	Suresh *et al*., 2007
Lopinavir	Hepatic first pass metabolism and P-gp efflux	improved BA by avoid first pass metabolism	Aji *et al*., 2011
Methotrexate	Low oral BA	improved BA	Paliwal *et al*., 2009
Nimodipine	Poor oral BA	Enhanced bioavailability	Chalikwar *et al*., 2012
Nisoldipine	Poor solubility and first-pass metabolism, poor BA	Improved BA	Narendar and Kishan, 2015
Nisoldipine	Poor BA	Improved BA	Narendar *et al*., 2018
Nitrendipine	Poor BA, poorly solubility, high firstpass metabolism	Improved BA	Manjunath and Venkateswarlu, 2006; Vinay Kumar *et al*., 2007
Ofloxacin	Improve the pharmacological activity	Enhanced the pharmacological activity	Xie *et al*., 2011
Olanzapine	Poorly solubility, high firstpass metabolism	Enhanced relative bioavailability	Sood *et al*., 2013
Olmesartanmedoxomil	Poor BA	Improved BA	Arun *et al*., 2018
Peptides/proteins	GIT unstability, poor permeability	Improved stability and permeability	Rao, 2007; Almeida *et al*., 1997
Puerarin	Poor solubility, short half life	Improved BA	Luo *et al*., 2011
Quercetine	Absorption mechanism and oral delivery carrier	SLNs are carrier to enhance the absorption	HouLi *et al*., 2009
quetiapine fumarate	first-pass metabolism	Improved BA	Arjun and Kishan, 2013
Rifampicin, Isoniazid and Pyrazinamide	Acid degradation, low BA	Improved BA and stability, Reducing dosing frequency	Pandey *et al*., 2005
Rosuvastatin calcium	Poor solubility and first-pass metabolism, poor BA	Improved BA	Suvarna *et al*., 2015
Rosuvastatin calcium	Poor BA	Improved BA	Narendar and Kishan, 2017
Raloxifene hydrochloride	Poor solubility and first-pass metabolism	Bioavailability enhanced	Anand *et al*., 2013
Raloxifene hydrochloride	Poor and variability in	Improved and minimize in BA	Nekkanti *et al*., 2013
Simvastatin	extensive hepatic first-pass metabolism p-gp efflux	Improved BA	Tiwari *et al*., 2011
Tobramycin	Poor oral BA, high side effects	Improved BA, sustained drug release, lymphatic Targeting	Cavalli *et al*., 2003
Triptolide	Drug-induced hepatotoxicity, Problem in solubility	Increase BA, controlled release, decrease toxicity with protective effect	Mei *et al*., 2005
Vinpocetine	Poor aqueous solubility and extensive firstpass metabolism	Improved oral BA by increased saturatedsolubility and reduced metabolism	Luo *et al*., 2006
Zaleplone	Poor BA	ImrovedbA	Narendar and Karthik, 2017

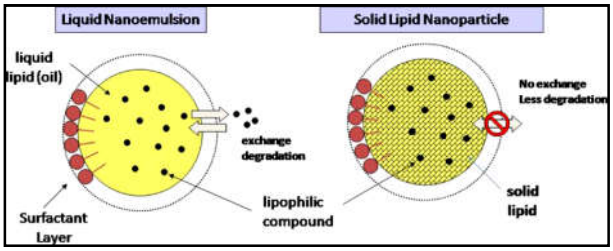

Figure 1. Structure of liquid nanoemulsions (left) and solid lipid nanoparticles (right) stabilized by a surfactant layer carrying a lipophilic bioactive

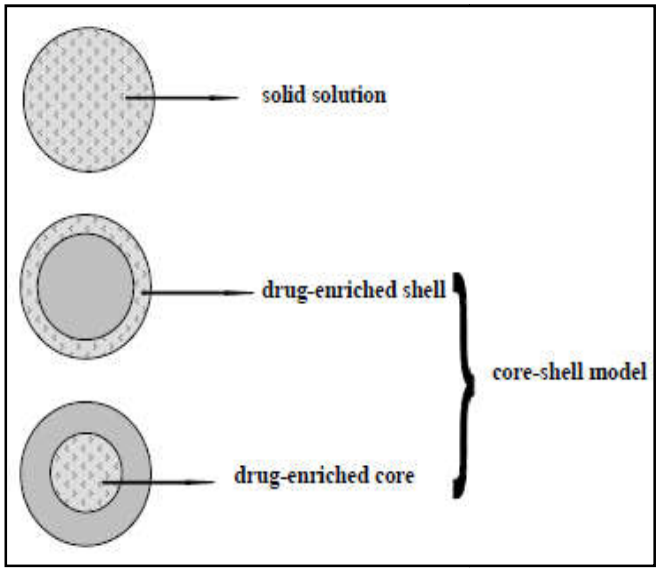

Figure 2. Models of drug incorporation into SLN

Volume ratios of the hot microemulsion to cold water are in the range of 1:25 and 1:50. Rapid recrystallization of oil droplet on dispersion in cold aqueous medium produces SLNs. Surfactants and co-surfactants include lecithin, bile salts, but also alcohols such as butanol. Excipients such as butanol are less favourable with respect to regulatory aspects (Müller *et al*., 2000).

Solvent emulsification method: SLNs have been produced by solvent emulsification technique by Siekmann (Siekmann*et al*., 1992). Lipid matrix is dissolved in water immiscible organic solvent (chloroform or cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticle dispersion is formed due to the precipitation of the lipid in the aqueous medium (Sjostrom and Bergenstahl *et al*., 1992). The advantage of this procedure over the cold homogenization process described before is the avoidance of any thermal stress. Residues of organic solvents used in this method create toxicity problems and is the major disadvantage of this method.

Solvent diffusion method: The first step in the production of lipid nanoparticles by the solvent diffusion technique is to prepare a solvent in water emulsion with a partially water miscible solvent containing the lipid. Low toxic, water miscible solvents such as benzyl alcohol or butyl lactate were used. Upon transferring a transient oil-in-water emulsion into water and continuous stirring, droplets of dispersed phase solidify as lipid nanoparticles due to diffusion of the organic solvent.

Further, the suspension is purified by ultrafiltration and almost 99.8% of benzylalcohol is eliminated (Müller R H *et al*., 2000; Manjunath and Venkateshwarlu, 2005).

Double emulsion method: Recently, a novel method based on solvent emulsification–evaporation for the preparation of SLN loaded with hydrophilic drugs has been introduced. Here, the hydrophilic drug is encapsulated along with a stabilizer to prevent drug partitioning to the external water phase during solvent evaporation in the internal water phase of a w/o/w double emulsion (Sanket *et al*., 2011). In double emulsion technique, the drug was dissolved in aqueous solution, and then was emulsified in melted lipid. This primary emulsion was stabilized by adding stabilizer (e.g. gelatin, poloxamer-407). Then this stabilized primary emulsion was dispersed in aqueous phase containing hydrophilic emulsifier (Zimmermann *et al*., 2000). Thereafter, the double emulsion was stirred and was isolated by filtration. Double emulsion technique avoids the necessity to melt the lipid for the preparation of peptide-loaded lipid nanoparticles and the surface of the nanoparticles could be modified in order to sterically stabilize them by means of the incorporation of a lipid/-PEG derivative. Sterical stabilization significantly improved the resistance of these colloidal systems in the gastrointestinal fluids. This technique is mainly used to encapsulate hydrophilic drug (peptides). A major drawback of this technique is the formation of high percentage of microparticles. SLNs loaded with insulin-mixed micelles (Ins-MMs) were prepared by a novel reverse micelle-double emulsion method, in which sodium cholate and soybean phosphatidylcholine were employed to improve the lipid solubility of insulin, and the mixture of stearic acid and palmitic acid were employed to prepare insulin loaded solid lipid nanoparticles. Some of the formulation parameters were optimized to obtain high quality nanoparticles. The particle size, zeta potential, entrapment efficiency (EE %) and drug loading capacity (DL %) were 114.7±4.68 nm, −51.36±2.04mV, 97.78±0.37% and 18.92±0.07%, respectively (Liu *et al*., 2007).

Homogenization followed by Ultra sonication: It is a simple, sensitive and reproducible method used to prepare SLNs. In brief, drug, lipid, and emulsifier were dissolved in a common solvent and evaporated under reduced temperature to obtain solvent free drug dissolved or dispersed lipid phase. Drug loaded lipid melt was homogenized with hot aqueous surfactant in solution using homogenizer to get coarse emulsion. The coarse emulsion so obtained was ultrasonicated using ultrasonicator to obtain nanoemulsion. SLNs are formed upon cooling to room temperature. SLNs of clozapine were prepared by this method to obtain the nanoparticles in the size range of 60-380 nm (Venkateshwarlu and Manjunath, 2004).

Solvent injection method: The basic principle for the formation of SLNs is similar to the solvent diffusion method. However, SLNs are prepared by rapidly injecting a solution of solid lipids in water miscible solvents into water. Mixture of water miscible solvents can be used to solubilize solid lipids. Normally used solvents in this method are acetone, ethanol, isopropanol, and methanol (Schubert *et al*., 2003).

Other methods

Supercritical fluid: This is new technique for preparation of SLN giving the advantage of solventless processing. SLN can

be produced by the rapid expansion of supercritical carbon dioxide solutions. Carbon dioxide with 99.99% is good solvent for preparation of SLN by this method (Sanket *et al*., 2011).

Membrane contactor method: This is a new method of preparation of SLN using a membrane contactor. The lipid phase is pressed, at a temperature above the melting point of the lipid, through the membrane pores allowing the formation of small droplets and the aqueous phase circulates inside the membrane module, and sweeps away the droplets forming at the pore outlets. SLNs are formed by the following cooling of the preparation to room temperature. In this method different process parameters (aqueous phase and lipid phase temperatures, aqueous phase cross-flow velocity and lipid phase pressure, membrane pore size) influence the size of SLNs (Charcosset *et al*., 2006).

Co-flowing microchannel technique : Zhang *et al*. research group investigated a new method of production of SLNs in a co-flowing microchannel. The microchannel system assembled with inner and outer capillaries. A lipid-solvent phase obtained by dissolving lipid in a water-miscible solvent is injected into the inner capillary, while an aqueous phase with surfactant is injected into the outer capillary at the same time. When these two fluids meet in the outer capillary, the solvent in the lipid phase diffuses rapidly into the aqueous phase, resulting in the local supersaturation of lipid and finally formation of SLNs. This is a simple and easy approach to produce SLNs with small diameters and slight narrow size distribution (Zhang *et al*., 2008). The particle diameter was influenced by several factors, the velocities of the lipid-solvent and the aqueous phases, the lipid concentration and the surfactant concentration.

Secondary production steps

Sterilization: Sterilization of SLNs is most important especially if SLNs are to be administered by parenteral and pulmonary routes. The common methods available for sterilization of pharmaceutical dosage forms are autoclaving, filtration, γ- irradiation and aseptic production. For parenteral administration, SLN dispersions must be sterile. The mean particle diameter of SLNs is often more than 200 nm, so sterile filtration is not possible in these cases. Autoclaving the finished dispersion is not practical as the lipids melt at temperatures used to terminally heat-sterilize pharmaceutical products, and the molten lipid droplets coalesce as there is no applied shear to prevent this. Options are therefore limited to aseptic manufacturing processes following sterilization of the starting materials (gamma irradiation of the final dispersion) or exposure to ethylene oxide gas (EO). Bacterial endotoxins in raw materials need to 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. Among all these methods of sterilization, the most popular and convenient method is sterilization by autoclaving at 121^{o}C for at least 15 min. Cavalli *et al*., 1997 studied the influence of autoclaving on sizes of SLNs. The high temperatures reached during autoclaving causes formation of a hot o/w nanoemulsion. On subsequent slow cooling of the system, SLNs are reformed but some nanodroplets merge to form a larger SLN than the initial. It was observed that there was an increase in the average diameter of SLNs, with slight change in polydispersity index following autoclaving but the particles still being in the colloidal range. Thus, SLNs sterilized by autoclaving can still maintain their almost spherical shape without any significant increase in size or distribution, which was indeed confirmed by transmission electron microscopy (TEM) analysis. SLNs stabilized with sterically stabilizing polymers such as poloxamer series cannot be autoclaved at 121^{o}C. Polymer adsorption layer seems to be partially collapsed and leads to particle aggregation. This can be avoided by reducing autoclaving temperature, and simultaneously prolonging the autoclaving time (Müller *et al*., 2000).

Lyophilization: Aqueous dispersions of SLNs may not be stable physically for a long period of time; moreover, drug release properties may be altered on storage. To avoid these problems, it is necessary to convert such aqueous dispersions into dry product by lyophilization or spray drying. Various types and concentrations of cryoprotectants (e.g., glucose, mannose and trehalose) are tested and trehalose proved most effective in preventing particle growth during freezing and thawing and in freeze-drying process (Shahgaldian *et al*., 2003). Lyophilization changes the properties of the surfactant layer due to removal of water and increases the particle concentration which favors particle aggregation (Mehnert and Mader, 2001). Change in the particle size during lyophilization could be minimized by optimizing the lyophilization process parameters such as freezing velocity and redispersion method.
Spray-Drying. This is an alternative method to lyophilization to convert aqueous dispersion of SLNs into dry product. During spray-drying of SLNs, elevated temperatures and shear forces increase the kinetic energy, leading to frequent particle collision. General drawback of this method is risk of melting of SLNs prepared with lipids of lower melting point, during spray drying. This problem can be avoided using higher melting point lipids (e.g., tribehenin 72^{o}C). The influence of temperature could be reduced by addition of carbohydrates, which form a layer around the particles and prevent the coalescence of molten lipid droplets (Müller *et al*., 1995; Freitas and Müller, 1998).

Characterization of solid lipid nanoparticles: Several parameters which have to be considered in characterization are as follows:

Measurement Particle size and distribution: Size of nanoparticles can be determined by several methods such as photon-correlation spectrometry (PCS), Laser Diffraction (LD), Transmission Electron Microscopy (TEM), Scanning electron microscopy (SEM), SEM combined with energy-dispersive X-ray spectrometry and scanned probe microscopy. Among these methods, most widely used methods are PCS and electron microscopy (SEM, TEM) methods.

Photon Correlation Spectroscopy (PCS): PCS method determines the hydrodynamic diameter of the nanoparticles. This technique is based on dynamic laser light scattering due to Brownian movement of particles in dispersion medium. PCS measures the fluctuation of the intensity of scattered light, which is caused by the particle movement. This method is suitable for the measurement of particles in the size range of few nanometers to 3 μm. Photon correlation spectroscopy (PCS) is also known as dynamic light scattering. The PCS device consists of a light source, a temperature-controlled sample cell, and a photomultiplier for detection of the scattered light (Mehnert and Mader, 2001).

Laser Diffraction (LD): This method is based on the dependency 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. It is highly recommended to use PCS and LD simultaneously. It is noted, that both methods are not measuring particle sizes. Rather, they detect light scattering effects which are used to calculate particle sizes (Mehnert and Mader, 2001).

Measurement of shape and morphology

Transmission Electron Microscopy (TEM): TEM determines the particle size with or without staining. TEM uses electrons transmitted through the specimen to determine the overall shape and morphology and both particle size as well as distribution. TEM allows visualization of nanoparticles after freeze fracturing and freeze substitution. Thus, it allows observation of their interior. Because this method is laborious and time-consuming, it is not useful for routine measurements (Manjunath and Venkateshwarlu, 2005).

Scanning Electron Microscopy (SEM): SEM uses electrons transmitted from the specimen to determine the overall shape and morphology and both particle size as well as distribution. SEM has high resolution and the sample preparation is relatively easy. SEM imaging has no source–sample contacts and imaging is carried out in high vacuum and samples require pre-treatment (Manjunath and Venkateshwarlu, 2005).

Atomic Force Microscopy (AFM): It is another advanced microscopic technique used for characterization of nanoparticles. This is a new tool to image the original unaltered shape and surface properties of the particles. In this technique, the force acting between the surface and probing tip results in a spatial resolution up to 0.01 nm for imaging. Sample preparation is simple, as no vacuum is needed during operation and that the sample does not need not be conductive. Hence, it allows the analysis of hydrated and solvent containing samples (Manjunath and Venkateshwarlu, 2005).

Measurement of zeta potential: The measurement of the zeta potential allows predictions about the storage stability of colloidal dispersions. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. However, this rule cannot strictly be applied for systems which contain steric stabilizers, because the adsorption of steric stabilizers will decrease the zeta potential due to the shift in the shear plane of the particle (Mehnert and Mader, 2001).

Measurement of entrapment efficiency (EE %): The entrapment efficiency of the system can be determined by measuring the concentration of free drug in the dispersion medium (Venkateswarlu&Manjunath, 2004). To separate dispersion medium, ultrafiltration can be employed using Centrisort separators. This consists of filter membrane (molecular weight cut-off 20,000 Daltons) at the base of the sample recovery chamber. The sample is placed in the outer chamber and sample recovery chamber is placed on top of the sample and subjected for centrifugation. The SLN along with the encapsulated drug remain in the outer chamber and aqueous phase moves into the sample recovery chamber through filter membrane. Analyzing drug concentration in aqueous phase gives entrapment efficiency.

Drug incorporation models of SLN: The prerequisite for a sufficient loading capacity is the high solubility of the drug in the lipid melt. Factors affecting loading capacity of a drug in lipid are (Müller *et al*., 2000):

- Solubility of drug in molten lipid,
- Miscibility of drug melt and lipid melt,
- Chemical and physical structure of solid lipid matrix,
- Polymorphic state of lipid material.
- There are basically three different models for the incorporation of active ingredients into SLN (Figure 2).
- Solid solution model (Homogeneous matrix model)
- Drug-enriched shell model
- Drug-enriched core model

Solid solution model

A homogeneous matrix with molecularly dispersed drug or drug being present in amorphous clusters is thought to be mainly obtained when applying the cold homogenization method and when incorporating very lipophilic drugs in SLN with the hot homogenization method. In the cold homogenization method, the bulk lipid contains the dissolved drug in molecularly dispersed form, mechanical breaking by high pressure homogenization leads to nanoparticles having the homogeneous matrix structure. The same will happen when the oil droplet produced by the hot homogenization method is being cooled, crystallize and no phase separation between lipid and drug occurs during this cooling process. This model is assumed to be valid for incorporation of, e.g., the drug prednisolone, which showed release from 1 day up to weeks (Müller *et al*., 2002).

Drug-enriched shell model: An outer shell enriched with active compound can be obtained when phase separation occurs during the cooling process from the liquid oil droplet to the formation of a solid lipid nanoparticle. The lipid can precipitate first forming a practically compound-free lipid core. At the same time, the concentration of active compound in the remaining liquid lipid increases continuously during the forming process of the lipid core. Finally, the compound-enriched shell crystallizes. This model is assumed, for example, for coenzyme Q10, the enrichment leads to a very fast release. A fast release can be highly desired when application of SLN to the skin should increase the drug penetration, especially when using the occlusive effect of SLN at the same time (Heiati *et al*.,1997).

Drug-enriched core model: A core enriched with active compound can be formed when the opposite occurs, which means the active compound starts precipitating first and the shell will have distinctly less drug.This leads to a membrane controlled release governed by the Fick law of diffusion (Müller *et al*., 2000).The three models presented each represent the ideal type. Of course, there can also be mixed types which can be considered as a fourth model. The structure of SLN obtained is a function of the formulation composition (lipid, active compound, and surfactant) and of the production conditions (hot vs. cold homogenization).

Principles of drug release from SLN: The general principles of drug release from lipid nanoparticles are as follows(Muhlen *et al*., 1998; Muhlen and Mehnert, 1998; Venkateswarlu and Manjunath, 2004; Uner, 2006);

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

The particle size that affects drug release rate directly depends on various parameters such as composition of SLN formulation (such as surfactant/surfactant mixture, amount of drug incorporated, structural properties of lipid and drug), production methods and conditions (such as time, production temperature, equipment, sterilization and lyophilization). All those parameters have been extensively investigated and data have been reported in the literature for years (Siekmann and Westesen, 1992; Cavalli *et al*., 1997; Freitas and Muller, 1998; Liedtke *et al*., 2000; Mehnert and Mader, 2001; Hou *et al*., 2003; Schubert *et al*., 2006). Additionally, surface modifiers to reduce phagocytic uptake such as polyethylene oxide and PEG may change the particle size.

Possible problems in sln preparation and sln performance: Solid lipid nanoparticles offer several advantages compared to other systems (easy scaling up, avoidance of organic solvents). However, less attention has been paid to the detailed and appropriate investigation of the limitations of this carrier system. Points to consider include high pressure-induced drug degradation, the coexistence of different lipid modifications and different colloidal species, the low drug-loading capacity and the kinetics of distribution processes (Mehnert and Mader, 2001).

High pressure-induced drug degradation: HPH has been shown to decrease the molecular weight of polymers. High shear stress has been assumed to be the major cause and evidence of free radical formation was reported. Cavitation can be suppressed by the application of back pressure without significant changes of the homogenization efficiency (Lander *et al*., 2000). The molecular weight and the general molecular structure are the most important parameters for predicting the drug degradation. High molecular weight compounds and long chain molecules are more sensitive than low molecular weight drugs or molecules with a spherical shape. For example, it was found that HPH causes degradation of DNA and albumin. According to the data in the literature, it can be stated that HPH-induced drug degradation will not be a serious problem for the majority of the drugs. However, HPH might be not suitable for the processing of shear sensitive compounds (DNA, albumin, and erythropoietin).

Lipid crystallization and drug incorporation: Lipid crystallization is an important point for the performance of the SLN carriers. The relation between lipid modification and drug incorporation has been investigated for decades. The characterization of lipid modifications is well established. Methods are mainly based on X-ray and DSC measurements. However, most of the data have been extracted from investigations on bulk lipids. The behavior of SLN might differ considerably due to the very small size of the particles and the high amount of surfactant molecules which are necessary to stabilize the colloidal lipid dispersion. Therefore, surface-related phenomena and lipid–surfactant interactions may contribute to a great extent to the properties of the lipid particle. The following four key aspects should be considered in the discussion of drug incorporation into SLN:

- The existence of super cooled melts (Westesen and Bunjes, 1995)
- The presence of several lipid modifications (Unruh *et al*., 1999; Jenning *et al*., 2000)
- The shape of lipid nanodispersions (Siekmann and Westesen,1994)
- Gelation phenomena (Graham *et al*., 1977).

Importance of SLN in various administration routes: The oral route is the most preferred route of administration of drugs. Use of SLNs can be an attractive option for oral drug delivery vehicles as they hold tremendous potential to improve the oral BA of drugs, concomitant reduction of drug toxicity and stability of drug in both GIT and plasma (Table 1).

Oral administration: Oral administration of SLN is possible as aqueous dispersion or alternatively after transformation into a traditional dosage form, i.e., tablets, pellets, capsules or powders in sachets. For the production of tablets, the aqueous SLN dispersion can be used instead of a granulation fluid in the granulation process. Alternatively, SLN can be transferred to a powder (e.g., by spray-drying) and added to the tabletting powder mixture.

For the production of pellets, the SLN dispersion can be used as wetting agent in the extrusion process. SLN powders can be used for the filling of hard gelatine capsules. Sachets are also possible using spraydried or lyophilized powders. For cost reasons spray drying might be the preferred method for transferring SLN dispersions into powders. The use of submicron-size particular systems in oral drug delivery, especially peptide drugs, has attracted considerable pharmaceutical interest. Controlled release behavior of these systems is reported to enable the bypass of gastric and intestinal degradation of the encapsulated drug (Damgé *et al*., 1990) 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. The adhesive properties of nanoparticles are reported to increase bioavailability and reduce or minimize erratic absorption (Ponchel *et al*., 1997). Absorption of nanoparticles occurs through mucosa of the intestine by several mechanisms, namely through the Peyer's patches, by intracellular uptake or by the paracellular pathway.

Various companies are interested in solid lipid nanotechnology for oral drug delivery. Pharmatec (Italy) developed a cyclosporine SLN formulation for oral administration (Radtke and Müller, 2001). 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 is mainly used to treat tuberculosis, which requires long-term treatment due to poor cellular antibiotic penetration. AlphaRx aims to deliver this drug inside the human cell, to increase its efficacy and as a result to increase patient compliance.

Parenteral administration: Basically SLN can be used for all parenteral applications suitable for polymeric nanoparticles. This ranges from intra articular to intravenous administration. Studies using intravenously administered SLN have been

performed by various groups. The i.v. administered SLN led to higher and prolonged plasma levels of Paclitaxel (Müller *et al*., 2000). When injected intravenously, SLNs are sufficiently small to circulate in the microvascular system and prevent macrophage uptake in case of hydrophilic coating. Therefore, SLNs have been suggested for viral and non-viral gene delivery. Cationic SLN has been demonstrated to bind genes directly via electrostatic interactions, and to have potential benefits in targeted gene therapy in treatment of cancer. Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is often constrained by the inability of potent drugs to pass blood brain barrier (BBB), which is formed by the endothelium of the brain vessels, the basal membrane and neurological cells. Hydrophilic coating of colloids improves the transport of these through BBB and tissue distribution (Kreuter, 2001). Fundaro *et al*., 2000 investigated that doxorubicin was determined at a detectable concentration in the brain only after administration of stealth SLN. SkyePharma (UK) have formulations of nanoparticulate technology which includes nanosuspensions and solid lipid nanoparticles under preclinical development (Powers, 2005).

Topical application: SLN and NLC 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. Researchers have reported intensively on the topical application of SLNs. During the last few years, SLN and NLC have been studied with active compounds such as vitamin E tocopherol acetate, retinol, ascorbyl palmitate, clotrimazole, triptolide, phodophyllotoxin and a nonsteroidal antiandrogen RU 58841 for topical application. SLNs showed occlusive properties as a result of film formation on the skin, which reduces transdermal water loss. Increase of water content in the skin reduces the symptoms of atopic eczema and also improves the appearance of healthy human skin. Occlusion also favors the drug penetration into the skin (Manjunath and Venkateshwarlu, 2005). A completely new, recently investigating area of use of SLN in sun-protective creams. Side effects of molecular sunscreens (UV-blockers) are penetration into the skin and consequently irritation (Wissing and Müller, 2001) Particulate sunscreens like titanium dioxide were also found to possibly penetrate into the skin. This can be avoided or minimized by entrapping molecular and particulate sunscreens into the SLN matrix. Surprisingly, it was found that the SLN themselves have also a sun protective effect. Due to their particulate character they are protective due to scattering of UV-light (similar to titanium dioxide). In addition, it was found that molecular sunscreens and SLN in combination show a synergistic effect (Müller *et al*., 2000).

Ocular administration: Colloidal drug delivery systems are considered to enhance the ocular bioavailability of drugs (drug bioavailability in the aqueous humor) (Narendar, 2017). Delivery of drugs to the tear film is routinely done with eye drops, which are well accepted and for most patients easy to use. However, attainment of an optimal drug concentration at the site of action is a major problem. Poor bioavailability of drugs from ocular dosage form is mainly due to the pre-corneal loss factors which include tear dynamics, nonproductive absorption, transient residence time in the cul-de-sac, and relative impermeability of the corneal epithelial membrane (Dudhipala, 2017). Development of an alternative to solution-type eye drop that would provide sustained delivery of a drug is a major challenge (De Campos *et al*., 2003). SLN formulations are adhesive, and could prolong the residence time of the dosage form in the eye and increase bioavailability and ingredients used in SLN formulation are generally regarded as safe (GRAS). The GRAS status of the ingredients used in the formulation of SLN makes it highly biocompatible unlike some polymeric systems, which have been shown to damage the corneal epithelium by disrupting the cell membrane, and may produce toxic products on degradation. Ocusolin™ from AlphaRx is a gentamicin loaded-SLN product is still under preclinical development. Tobramycin loaded SLNs were administered topically to the rabbits and they produced significantly higher tobramycin bioavailability in the aqueous humor when compared with the standard commercial eye drops (MelikeÜner *et al*., 2007).

Nasal administration: Nasal administration is a promising alternative noninvasive route of drug administration due to fast absorption and rapid onset of drug action, avoiding degradation of labile drugs (such as peptides and proteins) in the GI tract and insufficient transport across epithelial cell layers. In order to improve drug absorption through the nasal mucosa, approaches such as formulation development and prodrug derivatization have been employed. SLN has been proposed as alternative transmucosal delivery systems of macromolecular therapeutic agents and diagnostics by various research groups. Additionally, hydrophilic coating of SLN will permit the interaction and transport of SLN through the nasal mucosa and therefore bring great benefits and compliance as nasal drug carriers (MelikeÜner *et al*., 2007).

Application of SLNs in Pharmacodynamic studies: Solid lipid nanoparticles enhancing the oral bioavailability was reported by arious group of researchers but, their role in pharmacodynamic effect was not reported so far. In this context, we are tried to determine the pharmacodynamic effect of SLNs by using two antihypertensive drugs, namely, candesartan cilexetil (CC) and nisoldipine. Pharmacodynamic study of CC-SLNs in fructose induced hypertensive rats showed a decrease in systolic blood pressure for 48 h, while suspension showed a decrease in systolic blood pressure for only 2 h (Narendar and Kishan, 2016).The administration of CC-SLN resulted in sustained and continued drug release for 24 h and beyond. Thus, the designed SLNs were able to control the hypertension throughout 48h period. Clearly, the prepared SLN formulation was capable of surmounting the shortcomings of oral administration of CC, such as low bioavailability and high first-pass metabolism. Further, it becomes a clinical advantage in controlling the hypertension slowly, steadily and for extended period by designing the drugs in SLN formulation.

Similarly, of nisoldipine-loaded solid lipid nanoparticles (ND-SLNs) for improved pharmacodynamic effect by using a two factor, three-level central composite design was developed (Narendar and Kishan, 2015). According to this study, a significant reduction in the systolic blood pressure (BP) was observed, which sustained for a period of 36h with optimized ND-SLNs when compared with a controlled suspension. Similarly, the pharmacodynamic effect of isradipine also improved by SLN approach (Thirupathi *et al*., 2017). The anti-hyperlipidemic activity of rosuvastatin calcium loaded solid lipid nanoparticles (RC-SLN) were evaluated by lipid lowering

studies using a Triton-induced hyperlipidemia model, when compared with a control suspension. From the results, pharmacodynamic effect of RC-SLN showed a significant decrease in the total cholesterol, LDL, VLDL, TG and increased in HDL level was observed for a period of 36h, where as RC suspension showed the effects for a period of 24h (Narendar and Kishan, 2017).

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