REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Solid lipid nanoparticles: a prospective approach for topical drug delivery

Passant M. Al-Maghrabi[a], *Shadeed Gad*[a], *El-Sayed Khafagy*[a,b], *Mamdouh M. Ghorab*[a]

[a] *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt,*[b] *Department of of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-kharj, 11942, Saudi Arabia*

Received on: 13. 02. 2020

Revised on: 25. 04. 2020

Accepted on: 28. 04. 2020

Correspondence Author:

Tel: +201022649998

E-mail address:

passantalmaghrabi@pharm.suez.edu.eg

Abstract

Solid lipid nanoparticles (SLNs) are categorized as a novel generation of nanocarriers attracting huge attention as innovative colloidal carrier systems used for drug delivery as they integrate the advantages and avoid the disadvantages of other colloidal carries such as liposomes and polymeric nanoparticles. SLNs are biocompatible and biodegradable as they are made from physiological lipids, which decrease the danger of toxicity. Moreover, SLNs have been used as a possible attractive drug-carrier for topical drug delivery. These review discuses on many aspects of SLNs such as advantages disadvantages, method of preparation, SLNs and topical delivery and their therapeutic applications.

Key words: Solid lipid nanoparticles, Colloidal carriers, Topical delivery, nanotechnology.

1. Solid lipid nanoparticles (SLNs)

SLNs are considered as a novel generation of nano-carriers attracting huge attention as innovative colloidal carrier systems used for topical applications (Fang, Fang, Liu, & Su, 2008). This carrier system combines the advantages of liposomes in addition to polymeric nanoparticles and avoids their limitations (Aljaeid & Hosny, 2016; Madan, Khude, & Dua, 2014; Pouton, 2006). SLNs are consisting of biodegradable and biocompatible lipid materials and can be used for controlled drug delivery (Liu et al., 2007; Mehnert & Mader, 2001).

The major advantage of SLNs is that the lipid matrix is fabricated from physiological lipids, which reduce the possibility and danger of toxicity. Lipids and surfactants used in SLN have an authorized status, e.g. GRAS status (Generally Recognized as Safe) due to their low toxicity, and as they are already used as excipients in cosmetics or pharmaceuticals (S. Jain et al., 2010). SLNs tend towards drug penetration into the skins due to small sized particles;(Jenning, Schafer-Korting, & Gohla, 2000; Wissing & Muller, 2003) they also have the

advantage of maintaining slow controlled drug release manner to avoid systemic absorption (zur Muhlen, Schwarz, & Mehnert, 1998).Moreover, SLNs can act as ultraviolet sunscreen minimizing skin irritation (S. Jain et al., 2010; Liu et al., 2007; Sivaramakrishnan et al., 2004).

SLNs have attracted major attention as innovative colloidal drug carriers for the administration of drugs by various routes, such as oral, parenteral, topical, ophthalmic and rectal. Table I presents advantages and disadvantages of SLNs.

1.1 Solid lipid nanoparticles excipients

The general excipients used in any SLNs preparations are solid lipids, emulsifiers, co-emulsifiers and water. The term lipids may include fatty acids, waxes (e.g. cetyl palmitate) and steroids. All classes of emulsifiers (with respect to charge and molecular weight) have been used to stabilize the lipid dispersion. In addition, it has been found that the combination of emulsifiers might prevent particle agglomeration.

1.2 Influence of various excipients used on product quality

1.2.1 Influence of the lipid:

Chemically most lipids are mixtures of various compounds so their composition can vary from different suppliers and also from batch to batch but these small differences affect SLNs to a great extent (e.g. by varying the zeta potential, retarding crystallization processes), Increasing the lipid content over 10% result in larger particles and broader particle size distribution in most cases.

1.2.2 Influence of emulsifier:

Choice of emulsifier has a great impact on 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. The addition of some co-emulsifying agent like Sodium Glycocholate further decreases the particle size.

1.3 Methods of Solid Lipid Nanoparticles preparation

Strategy for SLNs preparation includes high shear homogenization, microemulsion based SLN preparation, ultrasonication, supercritical fluid technique innovation, spray drying, solvent emulsification/evaporation method, solvent infusion and solvent emulsification-diffusion method (Omray, 2014).

1.3.1 High shear homogenization and ultrasound:

One of the methods for SLNs production is ultrasonication or high-shear homogenization. High shear homogenization utilizes a rotor-stator homogenizer. Rotor-stator homogenizers were developed to intensify shear forces while maintaining power consumption within a reasonable level. The devices have gained substantial use in the pharmaceutical and food industries for emulsion generation. The rotor-stator design comprises a rotor containing multiple blades and a stator with multiple slits oriented vertically or diagonally around the homogenizer shaft. The rotor is housed concentrically within the stator. As the rotor rotates, liquid is centrifugally forced out through the stator slits. A vacuum results and induces bulk liquid to be drawn upward into the rotor region. A high level of mechanical energy is applied in a small space with minimal vortex formation (Gardouh, Ghorab, & Gad, 2012; Hou, Xie, Huang, & Zhu, 2003). Figure I, taken from

Maa and Hsu, illustrates the basic rotor-stator homogenizer architecture.(Maa & Hsu, 1996) This technique uses the simple apparatuses that can be found in every laboratory (Manjunath, Reddy, & Venkateswarlu, 2005; Patwekar et al., 2014).

1.3.2 High pressure homogenization:

High pressure homogenization (HPH) is a dependable and powerful technique used for SLNs production conducted by high pressure (100-200 bars) through a narrow gap (few microns). The fluid accelerates a very short distance to a very high velocity (over 1000 Km/h). Commercially available homogenizers of different sizes are used for this process. Extremely high shear stress and cavitation forces disrupt the particles down to the submicron range. In general 5-10% lipid content is used but up to 40% lipid content has also been examined (Mehnert & Mader, 2001).

Hot homogenization and cold homogenization are two general approaches of HPH; work at the exact same conception of mixing the drug in bulk of lipid melt. These methodologies of the homogenization step, the hot and the cold homogenization techniques, can be used for SLN production. In both cases, a preliminary step includes the incorporation of drug into the bulk lipid by

dispersing or dissolving the drug in the lipid melt (Gohla & Dingler, 2001; Müller et al., 1995). Figure II shows comparison between hot and cold homogenization technique.

1.3.3 Microemulsions based SLN:

Microemulsions, or swollen micelles, represent an interesting approach for SLNs production.

This process is based on microemulsions dilution. As micro-emulsions are two-phase systems consists of an inner and outer phase. They are clear, thermodynamically stable system consists of a lipophilic phase, water, surfactant and co-surfactant (Sinha, Srivastava, Goel, & Jindal, 2010).

Given appropriate conditions, the lipid/surfactant constituents of microemulsions self-assemble into spherical particles typically ranging 5-100 nm. These particles are polydisperse in nature, but polydispersity decreases with decreasing particle size. The microemulsion technique was developed by Gasco (Cavalli, 1998; Gasco, 1993; Kotmakci, Akbaba, Erel, Ertan, & Kantarci, 2017). They are prepared by stirring an optically transparent mixture at 65~70ºC which is usually consist of a low melting fatty acid (e.g. stearic acid), an emulsifier (e.g. polysorbate 20, polysorbate 60, soy phosphatidylcholine), co-emulsifiers (e.g. butanol) and water. The hot microemulsion is dispersed in cold water (2–3 ºC) under stirring.

Cavalli et al. reported stearic acid average particle sizes of 70 ± 2 nm and 200 ± 5 nm when stabilized by ionic and nonionic surfactants, respectively (Cavalli, 1998).

Shao et al., prepared nanostructure lipid carrier by microemulsion using soya, lecithin, glyceryl monostearate acted as the solid lipid, oleic acid as the liquid lipid, and Tween-80 presenting the surfactant to entrap paclitaxel. The particle size acquired was 79 nm, and the encapsulation efficiency was 87.1 _ 2.1% (Shao et al., 2015).

1.3.4 Solvent emulsification-evaporation technique:

An additional technique to produce SLN is the solvent emulsification–evaporation method (Siekmann & Westesen, 1996; Sjöström & Bergenstahl, 1992). In this process, the lipophilic material and hydrophobic drug were dissolved in a water immiscible organic solvent (e.g. toluene, cyclohexane, chloroform).

Once evaporation of the solvent occurs under reduced pressure, nanoparticle dispersion is formed by precipitation of the lipid in the aqueous medium. Depending on the solid lipid and emulsifier used, particles with average diameters of 30–100 nm can be obtained (Jagdevappa et al., 2013; Kamboj, Bala, & Nair, 2010).

Nanoparticles obtained by this process are small, monodisperse with high entrapment efficiency. The process can be scaled-up and automated for a large amount of nanoparticles production (Jaiswal, Gupta, & Kreuter, 2004).

The advantage of this process over the cold homogenization process is thermal stress avoidance. An indisputable disadvantage is the use of organic solvents (Gharge et al., 2017; Naseri, Valizadeh, & Zakeri-Milani, 2015). Muller et al., chose the emulsion evaporation method to entrap ketoprofen producing particle sizes of 50–150 nm range (Muller, Petersen, Hommoss, & Pardeike, 2007).

1.3.5 Solvent Emulsification-Diffusion Method:

In solvent emulsification-diffusion technique, the solvent used (e.g. benzyl alcohol, butyl lactate, methyl acetate) must be partially miscible with water and this method can be done either in oil or in aqueous phase. At first, both the solvent and water are mutually saturated so as to guarantee the initial thermodynamic equilibrium of both liquids. When heating is necessary to solubilize the lipid, the saturation step is executed at that temperature. Then the lipid and drug were dissolved in water saturated solvent and the organic phase (internal phase) is emulsified with solvent saturated aqueous solution containing stabilizer (dispersed phase) by means of mechanical stirrer (Nair, Deshkar, Boraste, & Sharma, 2016). Yuan et al., developed SLNs in a nonreactor system using the solvent diffusion method to enhance SLN drug entrapment efficiency (Yuan et al., 2008).

1.3.6 Double emulsion technique:

For the hydrophilic drug loaded SLN preparation, a novel technique based on solvent emulsification – evaporation has been used. Here the drug is encapsulated with a stabilizer to avoid drug partitioning to external water phase during solvent

evaporation in the external water phase of w/o/w double emulsion (Yadav et al., 2014). Warm w/o/w double microemulsions can be prepared in two steps. First, w/o microemulsion is prepared by addition of aqueous solution having drug to a mixture of melted lipid, surfactant and co-surfactant at a temperature just above the melting point of lipid to achieve a clear system. In the second step, w/o microemulsion formed is added to a mixture of water, surfactant and co-surfactant to acquire a clear w/o/w system. SLNs can be obtained by dispersing the warm micro double emulsions in cold afterwards washed with dispersion medium via ultra-filtration system (Ekambaram, Sathali, & Priyanka, 2012; Lv et al., 2009). Toxicological problems can arise from solvent residues from the product obtained by this method (Q. Li et al., 2017). Z. Li et al., prepared SLNs loaded with bovine serum albumin using double emulsion method (Z. Li et al., 2010).

1.3.7 Precipitation method:

SLNs can as well be prepared by a precipitation method which is characterized by the necessity 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 creating nanoparticles (Chavan, Gangode, Jadhav, Patil, & Kshirsagar, 2017; Ekambaram et al., 2012; Yadav et al., 2014). Xing et al., (Xing et al., 2016) applied this process for paclitaxel entrapment and achieve 321 ±0.76 nm.

1.3.8 Supercritical Fluid Technology:

Supercritical fluid technology is an innovative technique applied for SLNs production (Cavalli, Marengo, Rodriguez, & Gasco, 1996). A fluid is described as supercritical when its pressure and temperature are beyond their corresponding critical value. The capability of the fluid to liquefy samples increases. This technology involves several processes for nanoparticle production for example rapid expansion of supercritical solution, particles from gas saturated solution, aerosol solvent extraction solvent, supercritical fluid extraction of emulsions. Particles obtained as a dry powder depend upon mild temperature and pressure conditions. Carbon dioxide solution is the good choice selected as a solvent for this system (Y. J. Chen et al., 2006). The advantages of this system include avoidance of the solvents use.

Thote and Gupta produced nanoparticles of the hydrophilic.drug dexamethasone phosphate by the use of supercritical carbon dioxide (Thote & Gupta, 2005)

1.3.9 Solvent Injection Technique:

In this method the drug and lipid are dissolved in a water-miscible organic solvent (e.g. acetone) then this solution is injected through a syringe needle in water under stirring; lipid precipitates as nanoparticles while contacting water, encapsulating the drug. lipid type, solvent used, surfactants as well as the outer phase viscosity can affect particulate size (Chavan et al., 2017).

1.3.10 Film-ultrasound dispersion:

The lipid and the drug were put into appropriate organic solutions, after decompression, rotation and evaporation of the organic solutions, a lipid film is formed, afterwards the aqueous solution that includes the emulsions was added. At last, uniform SLN particle size is formed using ultrasound with the probe (Chavan et al., 2017; Ekambaram et al., 2012; Gharge et al., 2017).

1.3.11 Spray drying method:

This recommends using lipid with high melting point ≥70ºC. The lipid melting can be reduced by usage of ethanol–water mixtures as an alternative to pure water as cooling leads to small and heterogeneous crystals formation, at the low inlet temperatures (Ekambaram et al., 2012; Freitas & Mullera, 1998; Mehnert & Mader, 2001; Mukherjee, Ray, & Thakur, 2009b). This method causes particle aggregation due to high temperature, shear forces and partial melting of the particle (Yadav et al., 2014). It is an alternative and cheaper technique to the lyophilization process.

1.4 Solid lipid nanoparticles and topical delivery of drugs

Solid lipid nanoparticles are widely studied for their therapeutic efficacy through skin delivery route. Compared to lipid-based vesicular carriers, SLNs provide flexibility in modulating the drug release, higher drug loading of lipophilic drugs, and enhance drug stability by protecting the drugs from chemical degradation, oxidation, light degradation, and moisture. Due to small particle size and consequently higher surface area, these nanoparticles achieve close contact with superficial junction of corneocyte bundles and channels of

stratum corneum, this is particularly important to improve drug localization and depot release formation, which can be used for controlled delivery of the drug over a period of time (Muller, Mader, & Gohla, 2000).

SLNs also possess a distinct occlusive property, which may enhance the penetration of drugs through stratum corneum by decreasing transepidermal water loss. In addition, due to higher water content of SLNs, lipid nanoparticle dispersions are now incorporated into commonly used dermal carriers to obtain semisolid formulations (Shin, Kim, & Oh, 2000; Vaghasiya, Kumar, & Sawant, 2013). Furthermore, it has been reported that SLNs enhance the penetration and transport of active substances, particularly lipophilic drugs, and therefore intensify the concentration of these agents in the skin (Bhalekar, Pokharkar, Madgulkar, Patil, & Patil, 2009; Mehnert & Mader, 2001; Muller et al., 2000; Schafer-Korting, Mehnert, & Korting, 2007; Trombino, Mellace, & Cassano, 2016).

Major researches have been reported on using SLNs for topical delivery of various drugs for different purposes. For instance:

- Drugs for skin diseases such as adapalene (A. K. Jain et al., 2014), psoralen (Fang et al., 2008) and

Curcuminoids (Chirio et al., 2011; Nayak, Tiyaboonchai, Patankar, Madhusudhan, & Souto, 2010; Tiyaboonchai, Tungpradit, & Plianbangchang, 2007).

-Antioxidants such as hydroquinone (Ghanbarzadeh et al., 2015), Idebenone (Montenegro, Sinico, Castangia, Carbone, & Puglisi, 2012), and Isotretinoin (Liu et al., 2007; Raza, Singh, Singal, Wadhwa, & Katare, 2013).

-Drugs for treatment of chronic wounds (Gainza et al., 2015; Gainza et al., 2014).

-Nonsteroidal anti-inflammatory drugs (NSAIDS) such as Dexflurbiprofen , Meloxicam (R. M. Khalil, Abd-Elbary, Kassem, Ghorab, & Basha, 2014; Khurana, Bedi, & Jain, 2013) and ketoprofen (Kheradmandnia, Vasheghani-Farahani, Nosrati, & Atyabi, 2010).

-Glucocorticoids such as Fluocinolone acetonide (Pradhan, Singh, & Singh, 2015) and betamethasone dipropionate (Sonawane, Harde, Katariya, Agrawal, & Jain, 2014).

-In addition, antifungal agents such as griseofulvin (Tan, Lee, Er, Lim, & Wong, 2016), Amphotericin B (Butani, Yewale, & Misra, 2016), Terbinafine hydrochloride (Vaghasiya et al., 2013), Nystatin (R. Khalil, Kassem, Elbary, El Ridi, & AbouSamra, 2013) and Miconazole nitrate (Bhalekar et al., 2009).

1.5 Topical treatment of fungal infection

Fungal infections are superficial infections which occur in the skin, nails, and mucous membranes. Candidiasis is one of the most widespread types of superficial fungal infections and can invade into deep tissue in cases of weakness in the immune system. It usually affects wet, warm, and furrowed areas such as the underarms and intergluteal areas.

The topical delivery and efficacy of various antifungal drugs formulated in SLNs form for treatment of mycosis had been investigated. In recent studies, several antifungal agents have been incorporated in SLNs formulae e.g; Clotrimazole (Cassano et al., 2016; Souto, Wissing, Barbosa, & Muller, 2004), Econazole nitrate (Sanna, Gavini, Cossu, Rassu, & Giunchedi, 2007), Amphotericin B(Bianco, Gallarate, Trotta, & Battaglia, 2010; Butani et al., 2016), Itraconazole (Mukherjee, Ray, & Thakur, 2009a), Fluconazole (Moazeni et al., 2016), Nystatin (R. Khalil et al., 2013), Terbinafine

(Y. C. Chen et al., 2012), and Miconazole nitrate (Bhalekar et al., 2009; S. Jain et al., 2010).

The topical delivery of these drugs was found to be higher than the conventional methods of delivery. This is attributed to the ability of SLNs to overcome the barrier properties of the stratum corneum, the outermost layer of the skin and the main barrier for drug penetration, hence improving their antifungal activity (Mulani & Bhise, 2017; Qushawy, Nasr, Abd-Alhaseeb, & Swidan, 2018).

Disclosure

The author reports no conflicts of interest in this work.

References

Aljaeid, B. M., & Hosny, K. M. (2016). Miconazole-loaded solid lipid nanoparticles: formulation and evaluation of a novel formula with high bioavailability and antifungal activity. Int J Nanomedicine, 11, 441-447

Bhalekar, M. R., Pokharkar, V., Madgulkar, A., Patil, N., & Patil, N. (2009). Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS PharmSciTech, 10(1), 289-296.

Bianco, M. A., Gallarate, M., Trotta, M., & Battaglia, L. (2010). Amphotericin B loaded SLN prepared with the coacervation technique. J Drug Deliv Sci Technol., 20(3), 187-191.

Butani, D., Yewale, C., & Misra, A. (2016). Topical Amphotericin B solid lipid nanoparticles: Design and development. Colloids Surf B Biointerfaces, 139, 17-24.

Cassano, R., Ferrarelli, T., Mauro, M. V., Cavalcanti, P., Picci, N., & Trombino, S. (2016). Preparation, characterization and in vitro activities evaluation of solid lipid nanoparticles based on PEG-40 stearate for antifungal drugs vaginal delivery. Drug Deliv, 23(3), 1047-1056.

Cavalli, R. (1998). The effect of the components of microemulsions on both size and crystalline structure of solid lipid nanoparticles (SLN) containing a number of model molecules. Pharmazie, 53(6), 392-396.

Cavalli, R., Marengo, E., Rodriguez, L., & Gasco, M. R. (1996). Effects of some experimental factors on the production process of solid lipid nanoparticles. Eur J Pharm Biopharm, 42(2), 110-115.

Chavan, D., Gangode, B., Jadhav, A., Patil, M., & Kshirsagar, S. (2017). Solid lipid nanoparticles: a modern formulation approach in Drug delivery system. IJOD, 5(2).

Chen, Y. C., Liu, D. Z., Liu, J. J., Chang, T. W., Ho, H. O., & Sheu, M. T. (2012). Development of terbinafine solid lipid nanoparticles as a topical delivery system. Int J Nanomedicine, 7, 4409-4418.

Chen, Y. J., Jin, R. X., Zhou, Y. Q., Zeng, J., Zhang, H., & Feng, Q. R. (2006). Preparation of solid lipid nanoparticles loaded with Xionggui powder-supercritical carbon dioxide fluid extraction and their evaluation in vitro release. Zhongguo Zhong Yao Za Zhi, 31(5), 376-379.

Chirio, D., Gallarate, M., Peira, E., Battaglia, L., Serpe, L., & Trotta, M. (2011). Formulation of curcumin-loaded solid lipid nanoparticles produced by fatty acids coacervation technique. J Microencapsul, 28(6), 537-548.

Ekambaram, P., Sathali, A. H., & Priyanka, K. (2012). Solid lipid nanoparticles: a review. Sci Revs Chem Commun., 2(1), 80-102.

Fang, J. Y., Fang, C. L., Liu, C. H., & Su, Y. H. (2008). Lipid nanoparticles as vehicles for topical psoralen delivery: solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC). Eur J Pharm Biopharm, 70(2), 633-640.

Freitas, C., & Mullera, R. H. (1998). Spray-drying of solid lipid nanoparticles (SLN TM). Eur J Pharm Biopharm, 46(2), 145-151.

Gainza, G., Chu, W. S., Guy, R. H., Pedraz, J. L., Hernandez, R. M., Delgado-Charro, B., & Igartua, M. (2015). Development and in vitro evaluation of lipid nanoparticle-based dressings for topical treatment of chronic wounds. Int J Pharm, 490(1-2), 404-411.

Gainza, G., Pastor, M., Aguirre, J. J., Villullas, S., Pedraz, J. L., Hernandez, R. M., & Igartua, M. (2014). A novel strategy for the treatment of chronic wounds based on the topical administration of rhEGF-loaded lipid nanoparticles: In vitro bioactivity and in vivo effectiveness in healing-impaired db/db mice. J Control Release, 185, 51-61.

Gardouh, A. R., Ghorab, M. M., & Gad, S. (2012). Effect of viscosity, method of preparation and homogenization speed on physical characteristics of solid lipid nanoparticles. Asian Res. Publ. Netw.-J. Eng. Appl. Sci., 2(2225-7217), 996-1006.

Gasco, M. R. (1993). USA patent US5250236A Patent No. USA patent U. States.

Ghanbarzadeh, S., Hariri, R., Kouhsoltani, M., Shokri, J., Javadzadeh, Y., & Hamishehkar, H. (2015). Enhanced stability and dermal delivery of hydroquinone using solid lipid nanoparticles. Colloids Surf B Biointerfaces, 136, 1004-1010.

Gharge, V. G., Ghadge, D. M., Gore, M. M., Patil, A. A., Pawar, P. K., & Yadav, A. V. (2017). Different techniques for preparation of nanostructured lipid carrier with characterisation and various application of it: a review. IJUPBS, 6(1), 58-76.

Gohla, S. H., & Dingler, A. (2001). Scaling up feasibility of the production of solid lipid nanoparticles (SLN). Pharmazie, 56(1), 61-63.

Hou, D., Xie, C., Huang, K., & Zhu, C. (2003). The production and characteristics of solid lipid nanoparticles (SLNs). Biomaterials, 24(10), 1781-1785.

Jagdevappa, P., Prashant, G., Ravindra, K., Sachin, J., Satish, M., & Meghanath, S. (2013). Applications of solid lipid nanoparticle in novel drug delivery system. Br Biomed Bull, 1(2), 103-118.

Jain, A. K., Jain, A., Garg, N. K., Agarwal, A., Jain, A., Jain, S. A., . . . Agrawal, G. P. (2014). Adapalene loaded solid lipid nanoparticles gel: an effective approach for acne treatment. Colloids Surf B Biointerfaces, 121, 222-229.

Jain, S., Jain, S., Khare, P., Gulbake, A., Bansal, D., & Jain, S. K. (2010). Design and development of solid lipid nanoparticles for topical delivery of an anti-fungal agent. Drug Deliv, 17(6), 443-451.

Jaiswal, J., Gupta, S. K., & Kreuter, J. (2004). Preparation of biodegradable cyclosporine nanoparticles by high-pressure emulsification-solvent evaporation process. J Control Release, 96(1), 169-178.

Jenning, V., Schafer-Korting, M., & Gohla, S. (2000). Vitamin A-loaded solid lipid nanoparticles for topical use: drug release properties. J Control Release, 66(2-3), 115-126.

Kamboj, S., Bala, S., & Nair, A. (2010). Solid lipid nanoparticles: an effective lipid based technology for poorly water soluble drugs. Int J Pharm Sci Rev Res., 5(2), 78-90.

Khalil, R., Kassem, M., Elbary, A. A., El Ridi, M., & AbouSamra, M. (2013). Preparation and characterization of Nystatin-loaded solid lipid nanoparticles for topical delivery. Int J Pharm Sci Res, 4(6), 2292-2300.

Khalil, R. M., Abd-Elbary, A., Kassem, M. A., Ghorab, M. M., & Basha, M. (2014). Nanostructured lipid carriers (NLCs) versus solid lipid nanoparticles (SLNs) for topical delivery of meloxicam. Pharm Dev Technol, 19(3), 304-314.

Kheradmandnia, S., Vasheghani-Farahani, E., Nosrati, M., & Atyabi, F. (2010). Preparation and characterization of ketoprofen-loaded solid lipid nanoparticles made from beeswax and carnauba wax. Nanomedicine, 6(6), 753-759.

Khurana, S., Bedi, P. M., & Jain, N. K. (2013). Preparation and evaluation of solid lipid nanoparticles based nanogel for dermal delivery of meloxicam. Chem Phys Lipids, 175-176, 65-72.

Kotmakci, M., Akbaba, H., Erel, G., Ertan, G., & Kantarci, G. (2017). Improved method for solid lipid nanoparticle preparation based on hot microemulsions: preparation, characterization, cytotoxicity, and hemocompatibility evaluation. AAPS PharmSciTech, 18(4), 1355-1365.

Li, Q., Cai, T., Huang, Y., Xia, X., Cole, S. P. C., & Cai, Y. (2017). A Review of the Structure, Preparation, and Application of NLCs, PNPs, and PLNs. Nanomaterials., 7(6), 1-55.

Li, Z., Li, X., Zheng, L., Lin, X., Geng, F., & Yu, L. (2010). Bovine serum albumin loaded solid lipid nanoparticles prepared by double emulsion method. Chem Res Chinese Universities, 26(1), 136-141.

Liu, J., Hu, W., Chen, H., Ni, Q., Xu, H., & Yang, X. (2007). Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. Int J Pharm, 328(2), 191-195.

Lv, Q., Yu, A., Xi, Y., Li, H., Song, Z., Cui, J., . . . Zhai, G. (2009). Development and evaluation of penciclovir-loaded solid lipid nanoparticles for topical delivery. Int J Pharm, 372(1-2), 191-198.

Maa, Y. F., & Hsu, C. (1996). Liquid-liquid emulsification by rotor/stator homogenization. J Control Release, 38(2), 219-228.

Madan, J. R., Khude, P. A., & Dua, K. (2014). Development and evaluation of solid lipid nanoparticles of mometasone furoate for topical delivery. Int J Pharm Investig, 4(2), 60-64.

Manjunath, K., Reddy, J. S., & Venkateswarlu, V. (2005). Solid lipid nanoparticles as drug delivery systems. Methods Find Exp Clin Pharmacol, 27(2), 127-144.

Mehnert, W., & Mader, K. (2001). Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev, 47(2-3), 165-196.

Moazeni, M., Kelidari, H. R., Saeedi, M., Morteza-Semnani, K., Nabili, M., Gohar, A. A., . . . Nokhodchi, A. (2016). Time to overcome fluconazole resistant Candida isolates: Solid lipid nanoparticles as a novel antifungal drug delivery system. Colloids Surf B Biointerfaces, 142, 400-407.

Montenegro, L., Sinico, C., Castangia, I., Carbone, C., & Puglisi, G. (2012). Idebenone-loaded solid lipid nanoparticles for drug delivery to the skin: in vitro evaluation. Int J Pharm, 434(1-2), 169-174.

Mukherjee, S., Ray, S., & Thakur, R. S. (2009a). Design and evaluation of itraconazole loaded solid lipid nanoparticulate system for improving the antifungal therapy. Pak J Pharm Sci, 22(2), 131-138.

Mukherjee, S., Ray, S., & Thakur, R. S. (2009b). Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian J Pharm Sci, 71(4), 349-358.

Mulani, H., & Bhise, K. (2017). QbD Approach in the formulation and evaluation of Miconazole Nitrate loaded ethosomal cream-o-gel. Int Res J Pharm Sci., 8, 1-37.

Muller, R. H., Mader, K., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug

delivery - a review of the state of the art. Eur J Pharm Biopharm, 50(1), 161-177.

Müller, R. H., Mehnert, W., Lucks, J. S., Schwarz, C., Zur Mühlen, A., Weyhers, H., . . . Rühl, D. (1995). Solid lipid nanoparticles (SLN)—An alternative colloidal carrier system for controlled drug delivery. Eur J Pharm Biopharm, 41(1), 62-69.

Muller, R. H., Petersen, R. D., Hommoss, A., & Pardeike, J. (2007). Nanostructured lipid carriers (NLC) in cosmetic dermal products. Adv Drug Deliv Rev, 59(6), 522-530.

Nair, A. T., Deshkar, S. S., Boraste, S. S., & Sharma, R. M. (2016). Solid lipid nanoparticles a potential approach for Delivery of lipophilic drugs: a review WJPPS, 5(4), 2238-2253.

Naseri, N., Valizadeh, H., & Zakeri-Milani, P. (2015). Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application. Adv Pharm Bull, 5(3), 305-313.

Nayak, A. P., Tiyaboonchai, W., Patankar, S., Madhusudhan, B., & Souto, E. B. (2010). Curcuminoids-loaded lipid nanoparticles: novel approach towards malaria treatment. Colloids Surf B Biointerfaces, 81(1), 263-673.

Omray, L. (2014). Formulation and characterization of solid lipid nanoparticles for transdermal delivery of testosterone. Int J Pharm Sci Res, 5(7), 323-328.

Patwekar, S., Gattani, S., Giri, R., Bade, A., Sangewar, B., & Raut, V. (2014). Review on nanoparticles used in cosmetics and Dermal products. WJPPS, 3(8), 1407-1421.

Pouton, C. W. (2006). Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci, 29(3-4), 278-287.

Pradhan, M., Singh, D., & Singh, M. R. (2015). Development characterization and skin permeating potential of lipid based novel delivery system for topical treatment of psoriasis. Chem Phys Lipids, 186, 9-16.

Qushawy, M., Nasr, A., Abd-Alhaseeb, M., & Swidan, S. (2018). Design, Optimization and Characterization of a Transfersomal Gel Using Miconazole Nitrate for the Treatment of Candida Skin Infections. Pharmaceutics, 10(1), 1-22.

Raza, K., Singh, B., Singal, P., Wadhwa, S., & Katare, O. P. (2013). Systematically optimized biocompatible isotretinoin-loaded solid lipid nanoparticles (SLNs) for topical treatment of acne. Colloids Surf B Biointerfaces, 105, 67-74.

Sanna, V., Gavini, E., Cossu, M., Rassu, G., & Giunchedi, P. (2007). Solid lipid nanoparticles (SLN) as carriers for the topical delivery of econazole nitrate: in-vitro characterization, ex-vivo and in-vivo studies. J Pharm Pharmacol, 59(8), 1057-1064.

Schafer-Korting, M., Mehnert, W., & Korting, H. C. (2007). Lipid nanoparticles for improved topical application of drugs for skin diseases. Adv Drug Deliv Rev, 59(6), 427-443.

Shao, Z., Shao, J., Tan, B., Guan, S., Liu, Z., Zhao, Z., . . . Zhao, J. (2015). Targeted lung cancer therapy: preparation and optimization of transferrin-decorated nanostructured lipid carriers as novel nanomedicine for co-delivery of anticancer drugs and DNA. Int J Nanomedicine, 10, 1223-1233.

Shin, S. C., Kim, J. Y., & Oh, I. J. (2000). Mucoadhesive and physicochemical characterization of Carbopol-Poloxamer gels containing triamcinolone acetonide. Drug Dev Ind Pharm, 26(3), 307-312.

Siekmann, B., & Westesen, K. (1996). Investigation on solid lipid nanoparticles prepared by precipitation in o/w emulsion. Eur J Pharm Biopharm, 43(1), 104-109.

Sinha, V. R., Srivastava, S., Goel, H., & Jindal, V. (2010). Solid Lipid Nanoparticles (SLN'S) -Trends and Implications in Drug Targeting. Int J Adv Pharm Sci., 1(3), 65-89.

Sivaramakrishnan, R., Nakamura, C., Mehnert, W., Korting, H. C., Kramer, K. D., & Schafer-Korting, M. (2004). Glucocorticoid entrapment into lipid carriers--characterisation by parelectric spectroscopy and influence on dermal uptake. J Control Release, 97(3), 493-502.

Sjöström, B., & Bergenstahl, B. (1992). Preparation of submicron drug particles in lecithin-stabilized o/w emulsions I. Model studies of the precipitation of cholestreryl acetate. Int J Pharm., 88(1-3), 53-62.

Sonawane, R., Harde, H., Katariya, M., Agrawal, S., & Jain, S. (2014). Solid lipid nanoparticles-

loaded topical gel containing combination drugs: an approach to offset psoriasis. Expert Opin Drug Deliv, 11(12), 1833-1847.

Souto, E. B., Wissing, S. A., Barbosa, C. M., & Muller, R. H. (2004). Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm, 278(1), 71-77.

Tan, Y. J., Lee, C. S., Er, H. M., Lim, W. H., & Wong, S. F. (2016). In-vitro evaluation of griseofulvin loaded lipid nanoparticles for topical delivery. J Drug Deliv Sci Technol., 31, 1-10.

Thote, A. J., & Gupta, R. B. (2005). Formation of nanoparticles of a hydrophilic drug using supercritical carbon dioxide and microencapsulation for sustained release. Nanomedicine, 1(1), 85-90.

Tiyaboonchai, W., Tungpradit, W., & Plianbangchang, P. (2007). Formulation and characterization of curcuminoids loaded solid lipid nanoparticles. Int J Pharm, 337(1-2), 299-306.

Trombino, S., Mellace, S., & Cassano, R. (2016). Solid lipid nanoparticles for antifungal drugs delivery for topical applications. Ther Deliv, 7(9), 639-647.

Vaghasiya, H., Kumar, A., & Sawant, K. (2013). Development of solid lipid nanoparticles based controlled release system for topical delivery of terbinafine hydrochloride. Eur J Pharm Sci, 49(2), 311-322.

Wissing, S. A., & Muller, R. H. (2003). The influence of solid lipid nanoparticles on skin hydration and viscoelasticity--in vivo study. Eur J Pharm Biopharm, 56(1), 67-72.

Xing, L., Shi, Q., Zheng, K., Shen, M., Ma, J., Li, F., . . . Du, L. (2016). Ultrasound-Mediated Microbubble Destruction (UMMD) Facilitates the Delivery of CA19-9 Targeted and Paclitaxel Loaded mPEG-PLGA-PLL Nanoparticles in Pancreatic Cancer. Theranostics, 6(10), 1573-1587.

Yadav, P., Soni, G., Mahor, R., Alok, S., Singh, P., & Verma, A. (2014). Solid lipid nanoparticles: an effective and promising drug delivery system- a review. Int J Pharm Sci Res, 5(3), 1152-1162.

Yuan, H., Huang, L. F., Du, Y. Z., Ying, X. Y., You, J., Hu, F. Q., & Zeng, S. (2008). Solid lipid nanoparticles prepared by solvent diffusion method in a nanoreactor system. Colloids Surf B Biointerfaces, 61(2), 132-137.

zur Muhlen, A., Schwarz, C., & Mehnert, W. (1998). Solid lipid nanoparticles (SLN) for controlled drug delivery--drug release and release mechanism. Eur J Pharm Biopharm, 45(2), 149-155.