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Development of Nitrendipine Controlled Release Formulations Based on SLN and NLC for Topical Delivery: In Vitro and Ex Vivo Characterization

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The aim of the investigation is to develop solid lipid nanoparticles (SLN) and nano-structured lipid carrier (NLC) as carriers for topical delivery of nitrendipine (NDP). NDP-loaded SLN and NLC were prepared by hot homogenization technique followed by sonication, and they were characterized for particle size, zeta potential, entrapment efficiency, stability, and in vitro release profiles. Also the percutaneous permeation of NDPSLN A, NDPSLN B, and NDPNLC were investigated in abdominal rat skin using modified Franz diffusion cells. The steady state flux, permeation coefficient, and lag time of NDP were estimated over 24 h and compared with that of control (NDP solution). The particle size was analyzed by photon correlation spectroscopy (PCS) using Malvern zeta sizer, which shows that the NDPSLN A, NDPSLN B, and NDPNLC were in the range of 124–300 nm during 90 days of storage at room temperature. For all the tested formulations (NDPSLN A, NDPSLN B, and NDPNLC), the entrapment efficiency was higher than 75% after 90 days of storage. The cumulative percentage of drug release at 24 h was found to be 26.21, 30.81, and 37.52 for NDPSLN A, NDPSLN B, and NDPNLC, respectively. The results obtained from in vitro release profiles also indicated the use of these lipid nanoparticles as modified release formulations for lipophilic drug over a period of 24 h. The data obtained from in vitro release from NDPSLN A, NDPSLN B, and NDPNLC were fitted to various kinetic models. High correlation was obtained in Higuchi and Weibull model. The release pattern of drug is analyzed and found to follow Weibull and Higuchi equations. The permeation profiles were obtained for all formulations: NDPSLN A, NDPSLN B, and NDPNLC. Of all the three formulations, NDPNLC provided the greatest enhancement for NDP flux (21.485 ± 2.82 μg/h/cm^2), which was fourfold over control (4.881 ± 0.96 μg/h/cm^2). The flux obtained with NDPSLN B (16.983 ± 2.91 μg/h/cm^2) and NDPNLC (21.485 ± 2.82 μg/h/cm^2) meets the required flux (16.85 μg/h/cm^2).

Keywords solid lipid nanoparticles; SLN; nanostructure lipid carriers; NLC; nitrendipine; drug release; skin permeation

INTRODUCTION

Colloidal drug carriers offer a number of potential advantages as delivery systems, such as better bioavailability for poorly water-soluble drugs. Solid lipid nanoparticles (SLNs) possess a number of features advantageous for the topical route of application. Depending on the drug, some potential problems can occur, such as drug leakage during storage and insufficient total drug load. To overcome the limitations of SLN, nano-structured lipid carriers (NLCs) have been developed (Muller, Lippacher, & Gohla, 2000a; Muller, Mader, Lippacher, & Jenning 2000b). The NLCs consist of a solid lipid matrix with a high content of liquid lipid (Radke, 2003). Recently, colloidal dispersions made from mixtures of solid and liquid lipids were described to combine controlled release characteristics with higher drug loading capacities than SLNs. It has been proposed that these NLCs are composed of oily droplets that solubilize the drug and that are embedded in a solid lipid matrix

Both carrier types are based on solid lipids; however, they can be distinguished by their inner structure. SLNs consist of pure solid lipids and NLCs contain a certain percentage of additional liquid lipid leading to imperfections in the crystal lattice. Concerning topical administration, these systems possess occlusive properties due to film formation on the skin surface. They

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reduce the transepidermal water loss and therefore enhance the penetration of drugs through the stratum corneum by increased hydration (Jenning et al., 1999). Both SLNs and NLCs possess a number of features advantageous for the topical route of application (Muller et al., 1995, 2000b). These carriers are composed of physiological and biodegradable lipids of low systemic toxicity and also low cytotoxicity (Muller, Ruhl, Runge, Schulze-Forster, & Mehnert, 1997). Most of the used lipids have an approved status or are excipients used in commercially available topical cosmetic or pharmaceutical preparations. The small size of the lipid particles ensures close contact to the stratum corneum and can increase the amount of the drug penetrating into the mucosa or skin. Because of their solid lipid matrix, controlled release from these carriers is possible. This becomes an important tool when it is necessary to supply the drug over a prolonged period of time and to increase systemic absorption.

Nitrendipine (NDP), a dihydropyridines calcium antagonist that has a very low solubility in vitro, was used as a poorly water-soluble model drug to prepare SLN and NLC as carriers for topical delivery. It is a potent peripheral vasodilator, which effectively reduces blood pressure, when given at doses of 5–20 mg per day. After single, 20-mg oral dose of NDP, peak plasma concentrations (which vary widely from 10–50 μg/L) are achieved within 1–2 h. It was reported to be well absorbed following oral administration but undergoes extensive first pass metabolism, leading to low bioavailability of 10–20%. In addition to pharmacokinetic properties, NDP has low dose, low molecular weight (360.4), extensive first pass effect, and lipophilic nature (octanol/water partition coefficient 2.88). All the above properties are enough indicators that NDP might be a good choice as a drug candidate for topical delivery.

The aim of this work was focused to develop and characterize the NDPSLN and NDPNLC systems for particle size, zeta potential, entrapment efficiency, stability, occlusive properties, and in vitro release pattern. The ex vivo permeation studies of the developed formulations were investigated in abdominal rat skin using modified Franz diffusion cell.

MATERIALS AND METHODS

Materials

NDP was a kind gift from U.S. Vitamins (Mumbai, India). Trimyristin (TM) (Dynasan 114) was generously supplied by Sasol Germany. Captex 355 EP/NF (triglycerides of caprylic and capric acid) was donated by Abitec Corporation. Soy phosphatidylcholine 99% (Epikuron 200) was donated by Degussa Texturant Systems (Deutschland, Hamburg). Tween 80 and dialysis membrane-70 were purchased from Hi-Media (Mumbai, India). Centrisart filters (molecular weight cutoff 20,000) were purchased from Sartorius (Goettingen, Germany). The other chemicals were of analytical reagent grade.

Preparation of SLN and NLC by Hot Homogenization Technique

NDP (0.2% wt/vol), Dynasan 114 (5% wt/vol), and phosphatidylcholine 95% (2% wt/vol) were dissolved in 10 mL of mixture of chloroform and methanol (1:1). Organic solvents were completely removed using a roto evaporator (Laborota 4000, Heidolph, Germany). Drug-embedded lipid layer was melted by heating at 58°C above melting point of the lipid. An aqueous phase was prepared by dissolving Tween 80 (1% wt/vol) in double-distilled water (sufficient to produce 10 mL of preparation) and heated to same temperature of oil phase. Hot aqueous phase was added to the oil phase and homogenization was carried out (at 6,000 *g* and temperature 70°C) using a Diax 900 homogenizer (Heidolph, Germany) for 3 min. Coarse hot oil in water emulsion so obtained was ultrasonicated (12T-probe) using a Sonoplus ultra homogenizer (Bandelin, Germany) for 20 min. NDPSLNs were obtained by allowing hot nanoemulsion to cool to room temperature. The composition of the investigated formulations is shown in Table 1.

NLCs were prepared in exactly the same manner as the SLN dispersions, only partially replacing 30% of the solid lipid matrix by Captex 355 EP/NF (caprylic/capric triglycerides).

Measurement of Size and Zeta Potential

Size and zeta potential of NDPSLN A, NDPSLN B, and NDPNLC were measured by photon correlation spectroscopy (PCS), with the help of Malvern zeta sizer. Samples were diluted appropriately with the aqueous phase of the formulation for the measurements, and the pH of diluted samples ranged from 6.8 to 7.4. Zeta potential measurements were done at 25°C, and the electric field strength was around 23.2 V/cm.

TABLE 1
Final Composition of the Investigated Solid Lipid Nanoparticle (SLN) and Nano-Structured Lipid Carrier (NLC) Formulations [% (wt/vol)]

Formulation	Nitrendipine	Dynasan 114	Capte 355	Epikuron 200	Tween 80
NDPSLN A	0.2	5	–	2	1
NDPSLN B	0.4	10	–	3	1
NDPNLC	0.4	7	3	3	1

Assay and Entrapment Efficiency

The prepared NDPSLN/NDPNLC (0.2 mL) was diluted to 10 mL with chloroform/methanol (1:1). Final dilution was made with mobile phase, and NDP content was determined by high-performance liquid chromatography (HPLC).

The entrapment efficiency of the system was determined by measuring the concentration of free drug in the dispersion medium/aqueous phase of undiluted NDPSLN dispersion. Ultracentrifugation was carried out using Centrisart, which consists of filter membrane (molecular weight cutoff, 20,000 Da) at the base of the sample recovery chamber. About 1 mL of undiluted sample of NDPSLN/NDPNLC dispersion was placed in the outer chamber and the sample recovery chamber placed on top of the sample. The unit was centrifuged at 8,000 *g* for 30 min. The SLN/NLC along with encapsulated drug remained in the outer chamber and aqueous phase moved intothe sample recovery chamber through filter membrane. The amount of the NDP in the aqueous phase was estimated by HPLC.

HPLC Analysis of NDP

Mobile phase was prepared by mixing acetonitrile, freshly prepared double-distilled water, and glacial acetic acid in the ratio of 60:40:0.1 vol/vol/vol (Kobayashi et al., 1993). Mobile phase was degassed with the help of bath sonicator. The chromatographic system consisted of a Shimadzu LC-10AT solvent delivery pump equipped with a 20-µL loop and rheodyne sample injector. Wakosil II 5C18RS (SGE) (25 cm × 4.6 mm ID) analytical column was used. Detector used was SPD-10A VP dual wavelength UV-Visible detector (Shimadzu, Japan), and the eluate was monitored at 235 nm. The sensitivity was set at 0.001 AUFS. Flow rate was kept at 1 mL/min. The data were recorded using Winchrome Software.

Occlusion Test

The in vitro occlusion test was adapted from de Vringer (1992). Beakers (100 mL) were filled with 50 mL of water, covered with filter paper (cellulose acetate filter, 90 mm; cutoff size, 4–7 µm), and sealed. About 200 mg of sample was spread evenly with a spatula on the filter surface (18.8 cm^2), leading to an applied amount of 10.6 mg/cm^2. A visible film formation on top of the filter paper was observed during the experiment. The samples were stored at 32°C (skin temperature) and 50–55% relative humidity (RH) for 48 h. The samples were weighed after 6, 24, and 48 h, giving water loss due to evaporation at each time (water flux through the filter paper). Beakers covered with filter paper but without applied sample served as reference values. Every experiment was performed in triplicate ($n = 3$). The occlusion factor F was calculated according to the following equation:

$$F = \frac{A - B}{A} \times 100,$$

where A is the water loss without sample (reference) and B is the water loss with sample.

An occlusion factor of zero means no occlusive effect compared to the reference and 100 is the maximum occlusion factor.

In Vitro Release Kinetics from NDPSLN and NDPNLC

In vitro release studies were performed using modified Franz diffusion cell. Dialysis membrane having pore size 2.4 nm and molecular weight cutoff between 12,000 and 14,000 was used. The membrane was soaked in double-distilled water for 12 h before mounting in a modified Franz diffusion cell. SLN/NLC dispersion (1 mL) was placed in the donor compartment, and the receptor compartment was filled with 1% SLS in phosphate buffer, pH 7.4 (12 mL). During the experiments, the solution in receptor side was maintained at 37 ± 0.5°C and stirred at 800 rpm with Teflon-coated magnetic stirring bars. At fixed time intervals, 100 µL of the sample was withdrawn from receiver compartment through side tube and analyzed by HPLC.

Data obtained from in vitro release studies were fitted to various kinetic equations (Costa & Lobo 2001; Saravanan, Bhaskar, Srinivasa Rao, & Dhanaraju, 2003) to find out the mechanism of NDP release from NDPSLN A, NDPSLN B, and NDPNLC. The kinetic models used were zero-order equation, first-order equation, Higuchi release, and Weibull equation.

Skin Membrane Preparation

The abdominal hair of Wister male rats, weighing 160 ± 25 g, was shaved using hand razors 24 h before treatment. After anesthetizing the rat with ether, the abdominal skin was surgically removed from the animal and the adhering subcutaneous fat was carefully cleaned. To remove extraneous debris and leachable enzymes, the dermal side of the skin was in contact with a saline solution for 1 h before starting the diffusion experiment. All surgical and experimental procedures were reviewed and approved by the animal and ethics review committee of Faculty of Pharmaceutical Sciences, Kakatiya University (Warangal, Andhra Pradesh, India).

Ex Vivo Permeation studies

A system employing improved Franz diffusion cells with a diffusional area of 3.56 cm^2 was used for permeation studies. The excised rat skin was set in place with the stratum corneum facing the donor compartment and the dermis facing the receptor. Two milliliters of SLN/NLC dispersion of NDP was applied on the skin surface in the donor compartment, and the receptor compartment of the cell was filled with 12 mL of phosphate buffer (pH 7.4). During the experiments, the solution in the receptor side was maintained at 37 ± 0.5°C and stirred at 800 rpm with Teflon-coated magnetic stirring bars. After application of the test formulation on the donor side,

100-μL aliquots were collected from the receptor side at designated time intervals (1, 2, 4, 8, 12, 18, and 24 h). Thereafter, an equivalent volume of receptor fluid was supplied to the receiver compartment immediately after each sample collection. The amounts of NDP in receptor fluids were analyzed by HPLC.

NDP fluxes through the skin were calculated by plotting the cumulative amount of drug penetrating the skin against time and determining the slope of the linear portion of the curve and the *x*-intercept values (lag time) by linear regression analysis. Drug fluxes (μg/cm^2/h), at steady state, were calculated by dividing the slope of the linear portion of the curve by the area of the skin surface through which diffusion took place. The target flux is calculated using the following equation (Suwanpiodokkul, Thongnopnua, & Umprayan, 2004):

$$J_{\text{target}} = \frac{CssCL_{\text{T}}BW}{A},$$

where A represents the effective diffusional area (3.56 cm^2), BW the standard human body weight of 60 kg, Css the NDP concentration at the therapeutic level (50 g/L), and CL_{T} the total clearance (20 mL/min/kg), the calculated target flux value for NDP was 16.85 μg/h/cm^2.

RESULTS AND DISCUSSIONS

Characterization of the Investigated Formulation

Three different types of lipid particles NDPSLN A, NDPSLN B, and NDPNLC were produced by hot homogenization followed by ultrasonication method. NLCs were prepared in exactly the same manner as the SLN dispersions, only partially replacing 30% of the solid lipid matrix by liquid lipid, which was discussed earlier.

Particle Size Analysis

After production, the aqueous dispersions were stored at room temperature and their particle size was measured during 90 days. The results obtained after particle size analyses of the three formulations (NDPSLN A, NDPSLN B, and NDPNLC) are summarized in Table 2. Figure 1 shows the photon correlation spectroscopy (PCS) mean particle size after 1, 60, and 90 days of storage. It could also be observed that the particle size increased with the increase of lipid concentration (NDPSLN B and NDPNLC). After 90 days of storage at room temperature, increase in size of all the formulations ranged from 47.8 to 67.6 nm. For all the formulations, the particle size was below 300 nm at room temperature 90 days after production.

Zeta Potential (ζ)

The measurement of the zeta potential allows predictions about the storage stability of colloidal dispersions (Komatsu, Kitajima, & Okada, 1995). In general, particle aggregation is less likely to occur for charged particles (high zeta potential) because of electric repulsion (Levy, Schutze, Fuhrer, & Benita, 1994). In general, lipid nanoparticles are negatively charged on the surface (Schwarz & Mehnert, 1999). The determination of ζ was performed in aqueous SLN and NLC dispersions stored at room temperature. The ζ and standard deviation (*SD*) values of NDPSLN A, NDPSLN B, and NDPNLC are summarized in Table 2. These results are in agreement with the theory, which says that increased ZP provides increased stability by electrostatic repulsion. Thus, no size increase should occur. The ζ values of all the formulations measured on day 1 and after 90 days of storage at room temperature reveal a slight decrease in the ζ value of the surface of lipid nanoparticles during storage time. In comparison to NDPSLN B formulation with the same lipid content, NDPNLC formulations show lower ζ values.

Assay and Entrapment Efficiency

Assay results showed that concentration of NDP in the total system ranged from 0.92 to 1.01 mg/mL for different formulations.

The percentage of incorporated drug in the lipid matrix (entrapment efficiency) was evaluated over a period of 90 days. Entrapment efficiencies of all the three formulations were lowered by 2.8–4.5% after 90 days of storage at room temperature. The results are shown in Figure 2. Incorporation of NDP led to high entrapment efficiency, probably because of their lipophilic character. For SLN formulations, the entrapment efficiency is comparatively lower for the sample with lower lipid concentration. Transitions of dispersed lipid from metastable forms to stable form might occur slowly on storage because of small particle size, and the presence of emulsifier may lead to drug expulsion from SLNs (Bunjes & Westesen, 1995; Mehnert & Mader, 2001; Westesen, Siekmann, & Koch, 1993). NDPNLC is responsible for higher entrapment efficiency in comparison to both SLN formulations. This result is due to the binary mixture of liquid and solid lipids, resulting in only a very weak crystallization (Jenning, Mader, & Gohla, 2000; Jenning, Thünemann, Gohla, 2000). For all the tested formulations, the entrapment efficiency was higher than 75%.

Occlusion Test

Small particles possess an adhesive effect. The increased solubility of the active compound in the adhesion increases with decreasing particle size. Intensive in vitro studies were performed to quantify the occlusivity of SLN in the form of the so-called occlusion factor. Lipid nanoparticles show adhesive properties, they tend to adhere to cells and surfaces, and because of the film formation of the nanoparticles on the skin, SLN possess occlusive properties (de Vringer, 1992; Jenning et al., 1999; Muller & Dingler, 1998; Wissing, Lippacher, & Muller, 2001). The occlusion factor is dependent on the sample volume, particle size, and crystallinity; therefore, samples of

TABLE 2
Average Particle Size, Zeta Potential, Transdermal Flux, Permeability Coefficient, and Lag Time of NDPSLN A, NDPSLN B, and NDPNLC

Formulation	Particle Size (nm)	ζ (mV)	*Jss* (μg/cm^2/h)	K_p (cm/h × 10^{-2})	*LT* (h)
NDP solution	–	–	4.881 ± 0.96	0.244 ± 0.018	0.762 ± 0.16
NDPSLN A	124.7 ± 12.6	– 32.4 ± 0.7	11.486 ± 1.84	0.5743 ± 0.61	0.566 ± 0.09
NDPSLN B	167.4 ± 15.8	– 30.7 ± 0.9	16.983 ± 2.91	0.8491 ± 0.117	0.660 ± 0.06
NDPNLC	201.9 ± 17.1	– 24.1 ± 1.4	21.485 ± 2.82	1.0742 ± 0.89	0.476 ± 0.01

ζ, zeta potential, values represent mean ± *SD* (*n* = 3); *Jss*, transdermal flux, values represent mean ± *SD* (*n* = 3), K_p, permeability coefficient, values represent mean ± *SD* (*n* = 3); LT, lag time, values represent mean ± *SD* (*n* = 3).

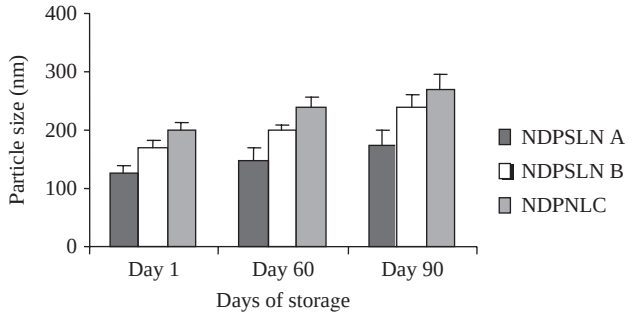

FIGURE 1. Particle size of NDPSLN A, NDPSLN B, and NDPNLC after 1, 60, and 90 days at room temperature.

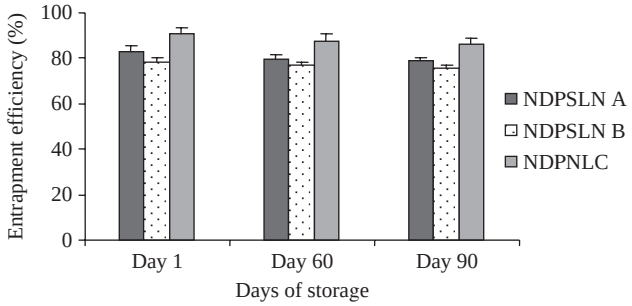

FIGURE 2. Entrapment efficiency of nitrendipine in SLN A, SLN B, and NLC formulations calculated after 1, 60 and 90 days of storage at room temperature.

200 mg were applied to the membrane of Franz cells (Wissing et al., 2001). The results of the occlusion test are shown in Figure 3. The occlusion factor depends strongly on the lipid concentration and the particle size of SLN. The results obtained from our study have shown a lower *F* for SLN containing lower lipid concentration (NDPSLN A). For the same lipid concentration (NDPSLN B and NDPNLC), a lower occlusivity can be detected for NLC than for SLN. This result is due to the solid state of the lipid matrix of SLN, which disables the evaporation of water.

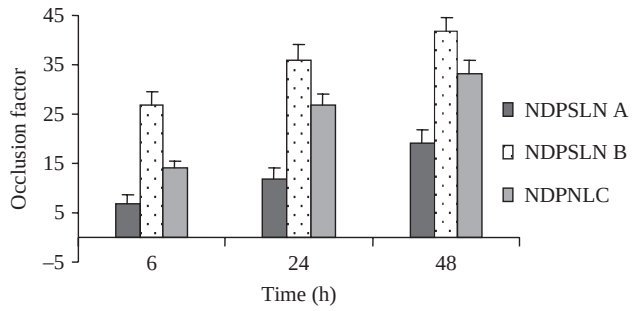

FIGURE 3. Occlusion factors of the investigated NDPSLN A, NDPSLN B, and NDPNLC formulations.

In Vitro Release Studies

The cumulative percentage release of NDP from three formulations (SLN A, SLN B, and NLC) was investigated for a period of 24 h; each sample was analyzed in triplicate. The results are shown in Figure 4. The release rate depends on the total concentration of drug in the formulation. The cumulative percentage of drug release at the end of 24 h was found to be 26.21, 30.81, and 37.52 for NDPSLN A, NDPSLN B, and NDPNLC, respectively. Because of the liquid structure of NLC, the NDPNLC shows a faster release compared to

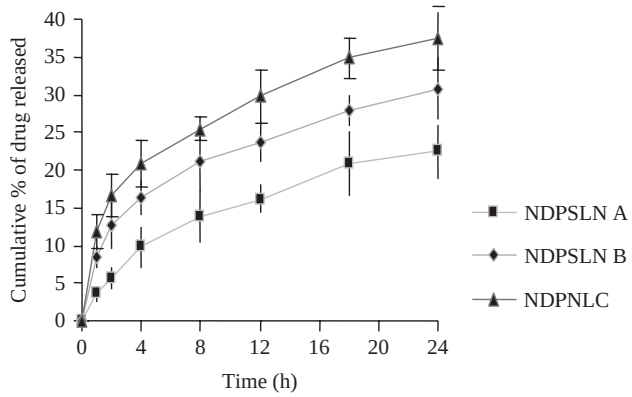

FIGURE 4. Release profiles of nitrendipine A, SLN B, and NLC formulations.

NDPSLN A and NDPSLN B. NDPSLN A and NDPSLN B could retard the release by the fact that the drug molecules are entrapped in the lipid matrix. Soluble NDP is partitioned into aqueous phase from which it is dialyzed into the dialysis medium. NDP dissolved in lipid diffuses to the surface and undergoes partitioning between lipid and aqueous phase.

Release Kinetics

The in vitro release profile was applied in various kinetic models to find out the mechanism of drug release. The best fit with the highest correlation coefficients was shown in Higuchi and Weibull equation as given in Table 3. High correlation was observed in Higuchi plot rather than first order and zero order. The drug release was proportional to square root of time indicating that the drug release from SLN and NLC is diffusion controlled. Moreover, the plots of log percent released versus log time showed a high-level linearity as given in Table 3, which in turn is another confirmation (Abubakr & Jun, 2000) that the release is diffusion controlled.

Ex Vivo Permeation Studies

The in vitro skin permeation of NDPSLN A, NDPSLN B, and NDPNLC investigated through rat skin is shown in Figure 5. NDPNLC (area of 3.56 cm^2) exhibited the greatest (924.71 ± 45.93 µg) cumulative amount of drug permeation in 24 h. When the cumulative amount of drug permeated per square centimeter was plotted against time, the permeation profiles of the drug seem to follow Higuchi's equation (Higuchi square-root model) (r^2 = 0.9844–0.9905) and first-order kinetics as it is evidenced by correlation coefficients (0.9818–0.9919).

The required flux was obtained with NDPSLN B (16.983 ± 2.91 µg/cm^2/h) and NDPNLC (21.485 ± 2.82 µg/cm^2/h). The results of drug permeation from NDPSLN A, NDPSLN B, and NDPNLC through the rat abdominal skin confirmed that NDP was released and permeated through the rat skin and hence could possibly permeate through the human skin. The flux, Jss, permeation coefficient, K_p, and lag time for NDPSLN A, NDPSLN B, and NDPNLC are tabulated in Table 2.

TABLE 3
Square Parameters of the Model Equations Applied to the Release of Nitrendipine from Solid Lipid Nanoparticle (SLN) and Nano-Structured Lipid Carrier (NLC) Formulations

Formulation	First Order (r^2)	Higuchi Model (r^2)	Weibull Equation (r^2)	Log C Versus Log t (r^2)
NDPSLN A	0.9458	0.9905	0.9893	0.9878
NDPSLN B	0.9446	0.9884	0.9981	0.9899
NDPNLC	0.9522	0.9901	0.9995	0.9943

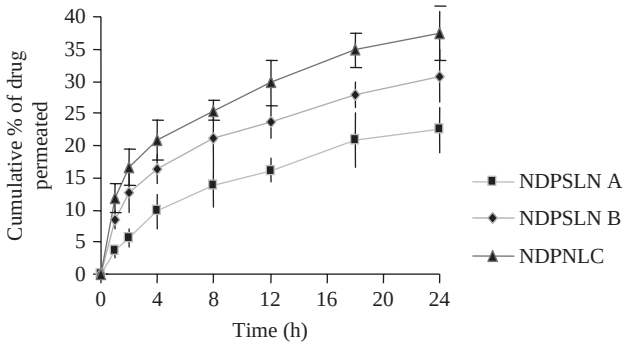

FIGURE 5. Permeation profiles of nitrendipine through rat excised skin from SLN A, SLN B, and NLC formulations.

CONCLUSION

In this study, both SLN and NLC systems can be considered as promising systems for topical administration of NDP. Stable NDPSLN and NDPNLC of size 124.7–201.9 nm were prepared by hot homogenization followed by ultrasonication method. After 90 days of storage at room temperatures, the mean particle size of NDPSLN A, NDPSLN B, and NDPNLC remains practically the same (less than 300 nm), which emphasizes the physical stability of these formulations. The entrapment efficiency and the drug release profile depend on the concentration and the lipid mixture used. NDPNLC showed higher entrapment efficiency because of their liquid parts. In agreement to these results, NDPNLC also shows a faster release profile in comparison to NDPSLN A and NDPSLN B.

The obtained results also indicated the use of these lipid nanoparticles as modified release formulations for lipophilic drugs. Future studies were focused to incorporate NDPSLN and NDPNLC in more convenient topical dosage forms such as hydrogels or creams.

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REFERENCES

Abubakr, O., & Jun, S. Z. (2000). Captopril floating and/or bioadhesive tablets: Design and release kinetics. *Drug Dev. Ind. Pharm., 26*, 965–969.

Bunjes, H., & Westesen, K. (1995). Do nanoparticles prepared from lipids solids at room temperature always possess a solid lipid matrix? *Int. J. Pharm., 115*, 129–131.

Costa, P., & Lobo, J. M. S. (2001). Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci., 13*, 123–133.

Jenning, V., Hildebrand, G. E., Gysler, A., Muller, R. H., Schafer Korting, M., & Gohla, S. (1999). Solid lipid nanoparticles (SLN) for topical application: Occlusive properties. *Proc. Int. Symp. Control. Rel. Bioact. Mater., 26*, 405–406.

Jenning, V., Thünemann, A. F., & Gohla, S. H. (2000). Characterisation of a novel solid lipid nanoparticle carrier system based on binary mixtures of liquid and solid lipids. *Int. J. Pharm., 199*, 167–177.

Jenning, V., Mader, K., & Gohla, S. H. (2000). Solid lipid nanoparticles (SLN) based on binary mixtures of liquid and solid lipids: A 1H NMR study. *Int. J. Pharm., 205*, 15–21.

Kobayashi, D., Matsuzawa, T., Sugibayashi, K., Morimoto, Y., Kobayashi, M., & Kimura, M. (1993). Feasibility of use of several cardiovascular agents in transdermal therapeutic systems with l-menthol-ethanol system on hairless rat and human skin. *Biol. Pharm. Bull., 16*, 254–258.

Komatsu, H., Kitajima, A., & Okada, S., (1995). Pharmaceutical characterization of commercially available intravenous fat emulsions: Estimation of average particle size, size distribution and surface potential using photon correlation spectroscopy. *Chem. Pharm. Bull., 43*, 1412–1415.

Levy, M. Y., Schutze, W., Fuhrer, C., & Benita, S. (1994). Characterization of diazepam submicron emulsion interface: Role of oleic acid. *J. Microencapsul., 11*, 79–92.

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

Muller, R. H., & Dingler, A. (1998). The next generation after the liposomes: Solid lipid nanoparticles (SLN, Lipopearls) as dermal carriers in cosmetics. *Eurocosmetics, 7/8*, 19–26.

Muller, R. H., Lippacher, A., & Gohla, S. (2000a). *Solid–liquid (semi-solid) lipid particles and method of producing highly concentrated lipid particle dispersions*, German Patent Application 199 45 203.

Muller, R. H., Mehnert, W., Lucks, J. S., Schwarz, C., Zur Muhlen, A., Weyhers, H., Freitas, C., & Ruhl, D. (1995). Solid lipid nanoparticles (SLN)—An alternative colloidal carrier system for controlled drug delivery. *Eur. J. Biopharm., 41*, 62–69.

Muller, R. H., Ruhl, D., Runge, S., Schulze-Forster, K., & Mehnert, W. (1997). Cytotoxicity of solid lipid nanoparticles as a function of the lipid matrix and the surfactant. *Pharm. Res., 14*, 458–462.

Muller, R. M., Mader, K., Lippacher, A., & Jenning, V. (2000b). *Festflüssige (halbfeste) Lipidpartikel und Verfahren zur Herstellung hochkonzentrierter Lipidpartikel-dispersionen*, PCT/EP00/04565.

Radke, M. (2003). *Grundlegende Untersuchungen zur Arzneistoffinkorporation—freisetzung und Struktur von SLN and NLC.* PhD thesis, Freie Universität Berlin, Germany.

Saravanan, M., Bhaskar, K., Srinivasa Rao, G., & Dhanaraju, M. D. (2003). Ibuprofen loaded ethylcellulose/polystyrene microspheres: An approach to get prolonged drug release with reduced burst effect and low ethylcellulose content. *J. Microencapsul., 20*, 289–302.

Schwarz, C., & Mehnert, W. (1999). Solid lipid nanoparticles (SLN) for the controlled drug delivery. II. Drug incorporation and physicochemical characterization, *J. Microencapsul., 16*, 205–213.

Suwanpiodokkul, N., Thongnopnua, P., & Umprayan, K. (2004). Transdermal delivery of zidovudine (AZT): The effects of vehicles, enhancers and polymer membranes on permeation across cadaver pig skin. *AAPS Pharm Sci Tech., 5*, 1–7.

de Vringer, T. (1992). *Topical preparation containing a suspension of solid lipid particles*, European Patent. No. 91200664.

Westesen, K., Siekmann, B., & Koch, M. H. J. (1993). Investigations on the physical state of the lipid nanoparticles by synchrotron radiation X-ray diffraction. *Int. J. Pharm., 93*, 189–199.

Wissing, S. A., Lippacher, A., & Muller, R. H. (2001). Investigations on the occlusive properties of solid lipid nanoparticles (SLN). *J. Cosmet. Sci., 52*, 313–323.