

DEVELOPMENT OF MICONAZOLE NITRATE CONTROLLED RELEASE FORMULATIONS BASED ON SLN AND NLC FOR TOPICAL DELIVERY

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ABSTRACT

Objective: The aim of the investigation is to develop solid lipid nanoparticles (SLN) and nanostructured lipid carrier (NLC) as carriers for topical delivery of Miconazole nitrate (MN).

Methods: MN loaded SLN and NLC were prepared by hot homogenization technique and they were characterized for particle size, zeta potential, entrapment efficiency and in vitro release profiles. Also the percutaneous permeation of MN/SLN and MN/NLC were investigated in abdominal rat skin using modified Franz diffusion cells. The particle size parameters and the surface electrical charge (ZP) have been evaluated immediately after production of the systems, and during one month of storage at three different temperatures 4°C, 25°C and 40°C.

Results: The particles remained in their colloidal state during 1 months of storage at 4 °C, 20 °C and 40°C. For all tested formulations the entrapment efficiency was higher than 90%. Differential scanning calorimetry (DSC) studies were performed to characterize the physicochemical properties of the SLN and NLC. High amount of MN release was facilitated through abdominal skin of rats from MN-SLN than MN-NLC.

Conclusion: Research work could be concluded as successful development of MN-loaded NLC to increase the encapsulation efficiency of colloidal lipid carriers with advantage of improved performance in terms of stability and provides a sustaining MN topical effect as well as faster relief from fungal infection.

Keywords: Miconazole nitrate; Nanostructured lipid carriers (NLC); Topical gels; Topical delivery.

INTRODUCTION

Colloidal drug carriers offer a number of potential advantages as delivery systems, such as better bioavailability for poorly water-soluble drugs. Biodegradable nanoparticles, such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are stable colloidal systems with notable advantages as drug delivery systems, i.e. physicochemical stability, versatility, biocompatibility, biodegradability and controlled drug release [1]. SLN and NLC are colloidal carrier systems providing controlled release profiles for many substances [2].

Solid lipid nanoparticles (SLN) 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, nanostructured lipid carriers (NLCs) have been developed [3,4]. The NLCs consist of a solid lipid matrix with a high content of liquid lipid [5]. Recently, colloidal dispersions made from mixtures of solid and liquid lipids were described to combine controlled release characteristics with higher drug loading capacities than SLN. It has been proposed that these NLC are composed of oily droplets that solubilize the drug and that are embedded in a solid lipid matrix.

Miconazole nitrate (MN) is a broad-spectrum antifungal agent of the imidazole group [6]. It acts by means of a combination of two mechanisms: ergosterol biosynthesis inhibition, which causes lysis of fungal cell membranes because of the changes in both membrane integrity and fluidity and direct membrane damage of the fungal cells. The drug is primarily used as a topical treatment for cutaneous mycoses [7]; poor dissolution and lack of absorption make it a poor candidate for oral administration. However, MN can be used as a systemic antifungal agent when amphotericin B or ketoconazole is either ineffective or contraindicated. MN's poor skin-penetration capability presents a problem in the treatment of cutaneous diseases by topical application. The stratum corneum is the target organ of

anti-mycotic treatment, and the improvement of local bioavailability leads to enhanced efficacy of the applied formulation. For effective treatment, the drug must be delivered in sufficient concentration to the site of infection. Various approaches have been used to enhance the access of such poorly skin-partitioned drug molecules. For example, the use of complexation with cyclodextrins has been reported to improve oral and topical delivery of MN [8, 9]. Several reports have described the potential use of liposomes to topically deliver drugs into the deep layers of the skin.

The aim of this work was focused to develop and characterize the MN/SLN and MN/NLC systems for particle size, zeta potential, entrapment efficiency, SEM and in vitro release pattern. The influences of the SLN and NLC on ex-vivo drug skin permeation were investigated in abdominal rat skin using modified Franz diffusion cell.

MATERIALS AND METHODS

Materials

Miconazole nitrate was gifted by Glenmark Pharma, Ltd., Mumbai, India. Dynasan 116 (glyceryl tripalmitate) and Miglyol 812 were obtained from Guangdong, China. Poloxamer 188, Methyl Paraben and Propylene glycol were purchased from SD Fine Chemicals, Mumbai, India. Carbopol 934P was obtained as a gift sample from Colorcon Asia Pvt. Ltd., Mumbai, India. All the other chemicals were of the analytical grade. Water was used in double-distilled quality.

Screening of components

One of the most important factors that determine the loading capacity of the drug in the lipid is the solubility of drug in melted lipid. 10 mg of MN was dispersed in a mixture of melted lipid (1g) and 1 ml of hot distilled water and shaken for 30 min in a hot water bath. Aqueous phase was separated after cooling by ultracentrifugation and analyzed for drug content by spectrophotometric method at 272 nm [10].

Solubility of drug in the lipid phase is one of the most important factors that determine the loading capacity of the drug in the lipid carrier. The solubility of MN was determined in different liquid lipids and surfactants. An excess of drug was added individually to liquid lipids and surfactants (5 ml each) in screw capped tubes. After 24 h, each sample was centrifuged and 0.5 ml of the clear supernatant layer was diluted suitably with methanol, and analyzed by spectrophotometric method at 272 nm.

Preparation of lipid nanoparticles

The method chosen for preparation of SLN and NLC was the hot high pressure homogenization technique described by slightly modified by Muller [11]. Table 1 reports the composition of the prepared SLN

and NLC dispersions. The lipid was heated up to 90 °C and MN was added to the melted Dynasan 116. In order to prepare NLC, the lipid phase has been melted at 5-10°C above the melting point of the solid lipid. At the same time, an aqueous surfactant solution has been prepared and heated at the same temperature. The hot lipid phase was then dispersed in the hot surfactant solution using an Ultra-Turrax T25 Stirrer (IKA-Werke, Staufen, Germany) at 8000 rpm for 4 min. The obtained pre-emulsion was homogenized at a temperature 5°C to 10°C higher than the melting point of the bulk lipid, using an homogenizer (APV Micron Lab 40 Italy) and applying a pressure of 500 bar and 5 homogenization cycles. The obtained dispersion was cooled in an ice bath in order to solidify the lipid matrix and to form SLN and NLC.

Table1: Composition of SLN and NLC formulations with different % of lipids and surfactant (% ,m/m)

Formulation code	Composition					Parameters (Immediately after production)			
	Miconazole nitrate	Dynasan 116	Miglyol 812	Poloxamer 188	Water ad	Particle size (nm)	Polydispersity Index (PI)	ZP (mV)	% Drug Entrapment
SLN	-	19.0	-	5.0	100	243.8±325	0.392±0.012	-26.3±0.2	-
MNSLN-1	1.0	19.0	-	5.0	100	215.1±2.18	0.325±0.002	-15.1±0.4	94.62±5.08
MNSLN-2	1.0	19.0	-	2.5	100	228.2±2.08	0.342±0.002	-13.7±0.2	91.82±4.53
MNSLN-3	1.0	18.0	-	5.0	100	235.6±2.53	0.351±0.003	-14.2±0.3	84.77±1.38
MNSLN-4	1.0	18.0	-	2.5	100	237.1±2.51	0.353±0.001	-15.5±0.8	87.03±7.15
NLC	-	13.5	5.5	5.0	100	238.4±7.51	0.356±0.003	-19.6±0.9	-
MNNLC-1	1.0	13.5	5.5	5.0	100	206.3±1.48	0.311±0.002	-13.2±0.4	97.08±2.12
MNNLC-2	1.0	13.5	5.5	5.0	100	218.2±2.08	0.334±0.001	-13.4±0.2	92.13±4.31
MNNLC-3	1.0	12.5	6.5	2.5	100	233.9±2.52	0.352±0.001	-13.9±0.1	88.32±1.66
MNNLC-4	1.0	12.5	6.5	5.0	100	229.7±2.51	0.344±0.002	-13.5±0.8	86.31±2.81

Measurement of Size and Zeta Potential

Particle size and size distribution measurements of the SLN and NLC suspended in the original dispersions were performed using photon correlation spectroscopy (PCS). The average particle size (z-average size) and polydispersity index (PI) were measured by photon correlation spectroscopy (PCS, Malvern Mastersizer Hydro 2000G U.K.) at 25 °C under a fixed angle of 90° in disposable polystyrene cuvettes. The count rate was kept at around 200 kcps with varying duration greater than 50s. The dispersant used was water and its RI (1.33), viscosity (0.8872 cP) and Dielectric constant (78.5) were kept constant for all determinations. Zeta potential was measured in folded capillary cells using the Nano ZS90 zetasizer. 1 ml sample was taken from each formulated nanosuspension and dispersed with 10ml of double distilled water. The samples were ultrasonicated for 5 min prior to size determination to measure the primary particle size. Then the sample was taken in disposable sizing cuvette and placed in the instrument for size and zeta potential measurements.

Dug entrapment efficiency

The amount of encapsulated MN was calculated by subtracting the free amount of the drug from MN-SLN and MN-NLC dispersion by ultracentrifugation at 55,000 rpm for 1 hr. The solution was filtered and diluted with methanol and MN content was determined spectrophotometrically. Entrapment efficiency (EE %) was calculated from the following equation $EE = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug loaded expected}} \times 100$

DSC Analysis

DSC analyses were performed on Physical mixtures of Dynasan 116 and Miconazole nitrate, and physical mixtures of Dynasan 116, Miglyol 812 and miconazole nitrate by a Mettler Toledo DSC 8220 instrument (Perkin-Elmer DSC-7). 6-8 mg of samples has been accurately weighted in 40 µl aluminium pans. DSC scans have been recorded at a heating rate of 10 °C /min and was run over the range 25-300 °C, using an empty pan as reference.

In Vitro Drug Release

The in vitro drug release profile of SLN and NLC dispersion were studied using a dialysis bag. Formulations were taken into a dialysis

bag (molecular weight cut-off, 12 KDa, Himedia, India) and placed in a beaker containing 20 ml of mixture of methanol: PBS (pH 6.4) (30:70). Then, the beaker was placed over a magnetic stirrer and the temperature of the assembly was maintained at 37 ± 1°C throughout the study. Samples (1 ml) were withdrawn at definite time intervals and replaced with equal amounts of fresh buffer.

The samples were analyzed for drug concentration by UV-VIS spectrophotometer at 272 nm. Data obtained from in vitro release studies were fitted to various kinetic equations [12, 13] to find out the mechanism of MN release from MNSLN 1 and MNNLC 1. The kinetic models used were zero-order equation, first-order equation and Higuchi release.

Ex Vitro skin permeation Studies

Ex vitro permeation of MN from SLN and NLC dispersion were performed using excised full thickness hairless abdominal skin of rats (Male albino rats, Sprague Dawley; 100–150 g).

The skin samples were mounted on modified Franz diffusion cells (Crown Glass Co., NJ) with a surface of 3.14 cm². 1.75 millilitres of SLN/NLC dispersion of MN was applied on the skin surface in the donor compartment and a receptor volume of 10 ml such that the dermal side of the skin was exposed to the receptor fluid [methanol: PBS (pH 6.4), i.e. 30:70] ratio and the stratum corneum remained in contact with the content of donor compartment. Formulations were placed in the donor compartment enabling one to cover the entire skin surface evenly.

The temperature was maintained at 37 ± 1°C. Serial sampling (0.5 ml) was performed at specified time intervals (1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24 h) by removing the contents of the receptor compartment and replacing it with the fresh medium.

The samples were analyzed using Jasco UV-VIS spectrophotometer at 272 nm and mean cumulative amount diffused Q (mg/cm²) at each sampling time points was calculated. At the end of 24 h, the skin was cut, homogenized, and extracted, first with methanol and then filtered; then ethanolic extract was evaporated and the residue was again extracted with DMF, filtered, diluted with 0.1 N HCl and analyzed spectrophotometrically at 272 nm [14].

RESULTS AND DISCUSSION

Screening of components

Determination of the partitioning behavior of the drug is an important criterion, as it affects the entrapment efficiency as well as the release of the drug from the formulation. For the current study, SLN and NLC were successfully prepared and the composition of the formulations prepared is shown in Table 1. Calibration curve ($y=0.0215x+0.0134$, $R^2=0.9993$) of MN was used to calculate the concentration of MN in the aqueous phase. Partition coefficients (ratio of the amount of MN in lipid to the amount of miconazole nitrate in aqueous phase) obtained by analyzing drug content in aqueous phase were 39.10 ± 3.34 , 56.67 ± 6.13 , and 78.81 ± 2.56 for Stearic acid, Compritol 888 ATO and Dynasan116. Dynasan116 has been selected as the solid lipid for both SLN and NLC because MN exhibited higher partition coefficient and after usual inspection of drug crystals in different melted lipids, based on the light they scatter using a black and white background light box. Among the selected liquid lipid oils that were screened, maximum solubility of MN was found in Miglyol 812 (79.52 ± 4.9 mg/g) followed by Miglyol 808 (61.33 ± 8.3 mg/g). The selection of Miglyol 812 as liquid lipid for NLC preparation was based on solubility studies.

Preparation of lipid nanoparticles

Table 1 shows the composition of the developed SLN and NLC formulations. In the present investigation, 10 different SLN and NLC formulations were produced by hot high pressure homogenization. Various parameters were optimized by varying one parameter while keeping others constant. For the production of NLC formulations the optimized ratio between Dynasan 116 and Miglyol 812 has been determined after screening different proportions of both lipids by DSC studies to evaluate the absence of free oil in the melted mixtures. No free oil has been detected after running the mixtures of solid and liquid lipids until -50°C [15]. Mixtures of Dynasan116 and Miglyol 812 at different ratios have been melted at 85°C and further analysed by DSC (Fig.1). The SLN and NLC dispersion was white in color and odorless and did not show sedimentation even after centrifugation at 2,000 rpm for 30 min.

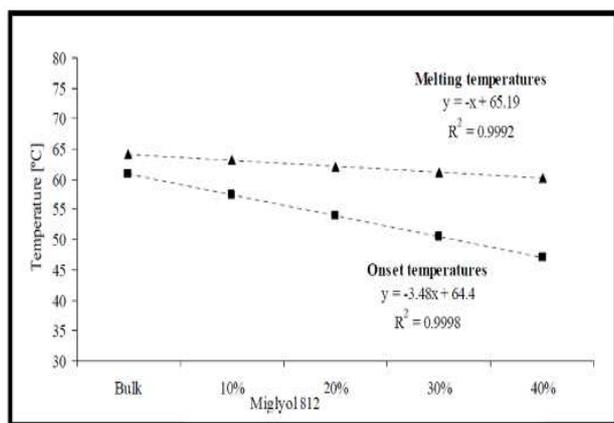


Fig. 1: Melting temperature (= peak maximum) and onset temperature values of bulk lipid (Dynasan 116) with increasing amounts of liquid lipid (Miglyol 812) from 10% to 40% (m/m).

Dug entrapment efficiency

Yields of production obtained were always relatively high and was in the range 80–98%. Lipids show positive influence on entrapment efficiency, this result can probably be attributed to the high affinity of the lipophilic drug for the lipidic material. MNSLN-1, MNSLN-2, MNLC-1 and MNLC-2 dispersion shows of about 90% while MNSLN-3, MNSLN-4, MNLC-3 and MNLC-4 dispersion show less % entrapment efficiency. The entrapment efficiency of the different formulations is presented in Table 1. After hot high pressure homogenization the lipid recrystallizes in higher energy

modifications, i.e. α and β -forms [16]. During storage, these polymorphic forms can transform to a more ordered modification (β), which is characterized by a lower energy modification and a higher degree of crystallinity. These parameters are strongly correlated with drug incorporation [17]. Drug expulsion in SLN and NLC can occur when the lipid matrix transforms from high energy modifications, characterized by the presence of many imperfections, to the β -modification forming a perfect crystal with no room for guest molecules. A high amount of drug could be incorporated in nanoparticle dispersion. Such high incorporation was possible because of lipid solubility of MN.

Particle size and Zeta potential of the SLN and NLC

It is known that the particle size distribution is one of the most important characteristics for the evaluation of the stability of colloidal systems and also influences the penetration mechanism of drugs into the skin [18]. Therefore, the particle size parameters and the surface electrical charge (ZP) have been evaluated immediately after production of the systems (Table 1), and during one month of storage at three different temperatures 4°C , 25°C and 40°C . Under optimized production conditions (500 bar and 5 homogenization cycles) very small lipid nanoparticles with a negatively charged surface could be obtained. The macroscopic appearance of the systems resembled a milky dispersion immediately after production and also after the cooling step. The preparation of aqueous SLN and NLC dispersions with a mean particle size lower than 300 nm and size distribution ($PI < 0.350$) has been obtained in previous studies using only 5% of surfactant (Poloxamer 188) stabilizing 20% of lipid mass. The incorporation of MN decreased the electrical charge at the surface of both SLN and NLC and, when comparing both systems, NLC also revealed lower ZP values than the respective SLN system. These results could be taken as an indication that MN is entrapped in the lipid matrix of SLN and NLC. The pH values of all aqueous dispersions measured immediately after production ranged between 5.5 and 6.0, showing no significant differences between the formulations.

The developed formulations have been stored at three different temperatures to challenge the systems under stress conditions. The assessment of physical stability at 4°C , 25°C and 40°C of storage has been performed one month after production of the aqueous dispersions. In all storage temperatures, the systems remained in their colloidal particle size range ($< 1 \mu\text{m}$). The mean size was maintained lower than 300 nm, with a PI in the same magnitude as the values obtained immediately after production ($PI < 0.350$). After one month of storage, all lipid nanoparticles showed a negative charge at their surface. Also the pH values did not vary notably between the variables investigated. Particle size and polydispersity index of formulation are shown in Fig 2. The differences between the evaluated parameters were not significant, neither under different storage temperatures nor with the presence of drug molecules, meaning that the systems are physicochemically stable under stress conditions for. No gel formation has been observed after one month of shelf life at three different temperatures. Poloxamer 188 could stabilize the developed formulations even under stress conditions. Zeta potential of SLN and NLC based formulation are shown in Fig 3

DSC Analysis

DSC analysis of the physical mixtures of 1% (m/m) drug and bulk Dynasan 116 (1+99) revealed only the melting events of the lipid at 63.65°C (enthalpy of 180.27 J/g) showing that the drug is obviously dissolved in the lipid (Fig. 4, upper). This means that miconazole nitrate is molecularly dispersed in the lipid phase. After tempering the mixture, the melting point slightly decreased to 58.40°C , revealing an enthalpy of 174.02 J/g (Fig. 4, lower). Table VI shows the registered DSC parameters. The observed results do not support a crystalline character of miconazole nitrate, on the contrary, reveal that the drug is dissolved in the melted lipid. Based on the production process, the physical mixtures were heated from 25°C to 85°C to give Miconazole nitrate the possibility to dissolve to its maximum solubility, then the mixtures were cooled in order to recrystallize (Fig. 4, upper). This procedure imitates the production process of the lipid nanoparticles. Then the mixtures were heated a second time.

The second heating curve corresponds now to the heating of the produced aqueous SLN or NLC dispersions, meaning that a fraction of the lipid matrix of the prepared nanoparticles might also be in an amorphous state. After running a second heating of the physical mixture, the presence of the polymorphic α form was detected at approximately 43°C. Concerning the cooling curves only minor

differences were detected between both curves. Once the NLC system is also composed of an oil fraction, the physical mixtures of solid lipid, liquid lipid and drug have been analyzed by DSC as well (Fig. 5). Distortion of the crystal lattice of Dynasan 116 increased with the presence of Miglyol 812 in the mixture leading to a reduction of the onset temperature and melting peak (Fig. 5, Table 2).

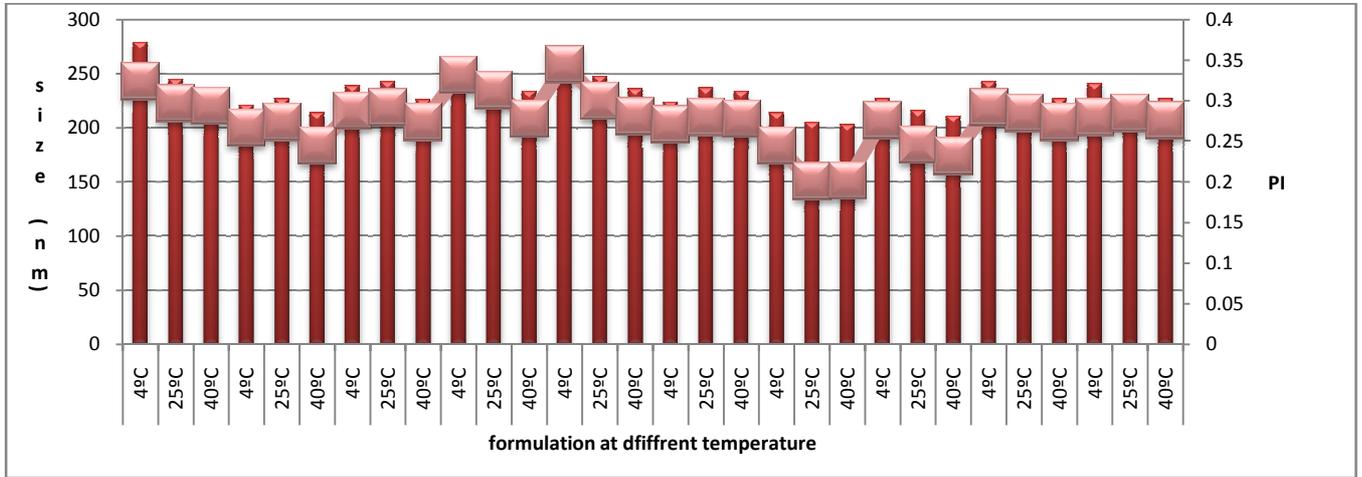


Fig.2: Particle size parameters and Polydispersity Index (PI) of SLN and NLC formulations stored at different temperatures and obtained one month after production.

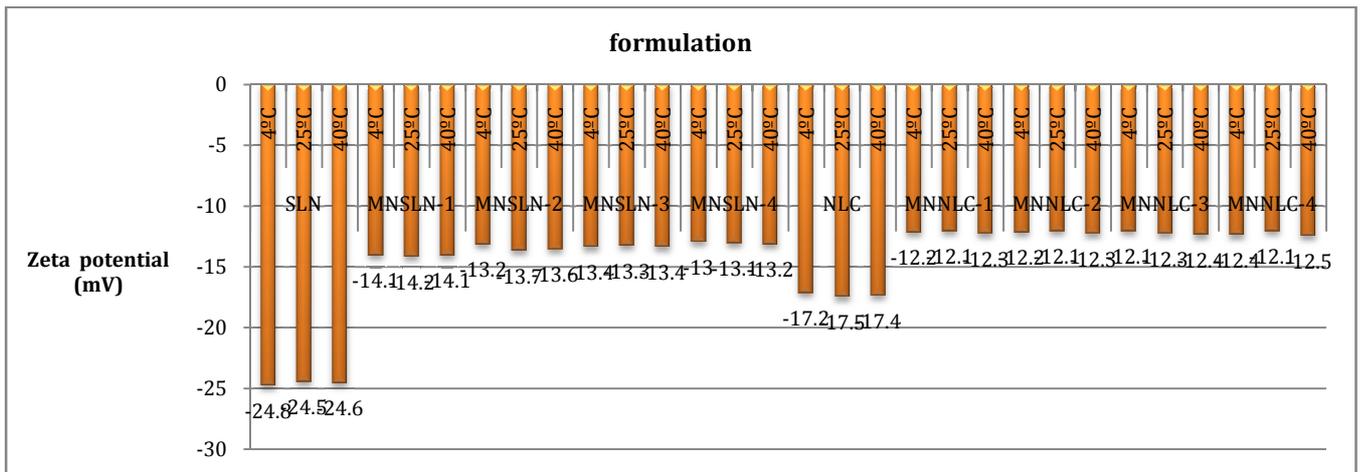


Fig.3: Zeta potential of SLN and NLC formulations stored at different temperatures and obtained one month after production.

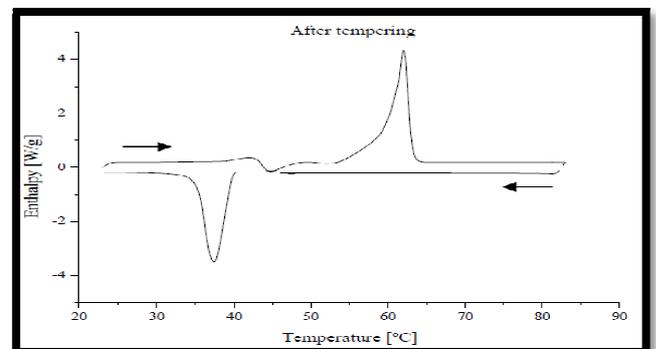
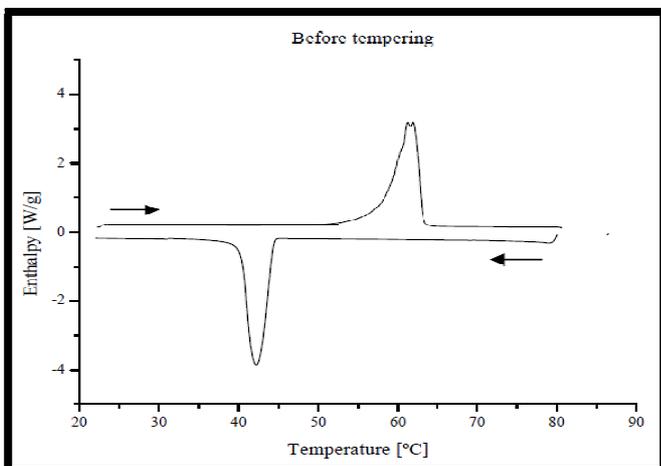


Fig. 4 : DSC patterns of physical mixtures of Dynasan 116 and Miconazole nitrate (99+1) recorded before (upper) and after (lower) tempering the mixture under heat exposure (90°C) for 1 hr.

Before tempering the mixture of Dynasan 116, Miglyol 812 and miconazole nitrate, the presence of the stable polymorph β of the lipid was hardly detected, while after tempering the presence of β form was recorded at approximately 63°C. Before tempering, the heating curve revealed a less pronounced shoulder, which corresponds to the β' modification of tripalmitin. After tempering no more shoulder was visible being substituted by a well defined small peak at approximately 61.5°C. The main peak in both curves corresponds to the stable β modification. The influence of Miglyol 812 was also observed during the cooling process in both curves. Concerning the cooling curves, the peak recorded between 40°C and 25°C both before and after tempering shows the presence of Miglyol 812. The difference of shape between them is due to the presence of well defined polymorphic modifications.

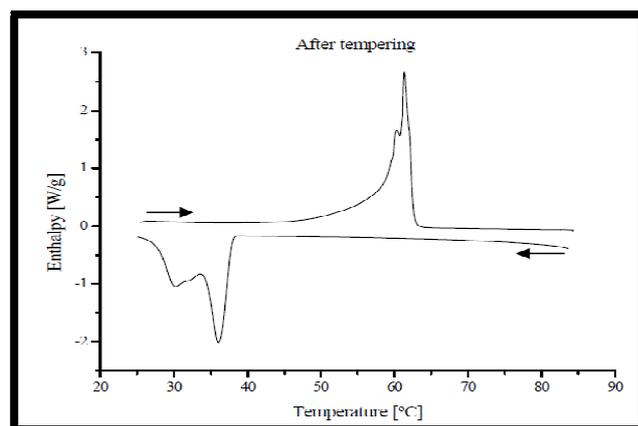
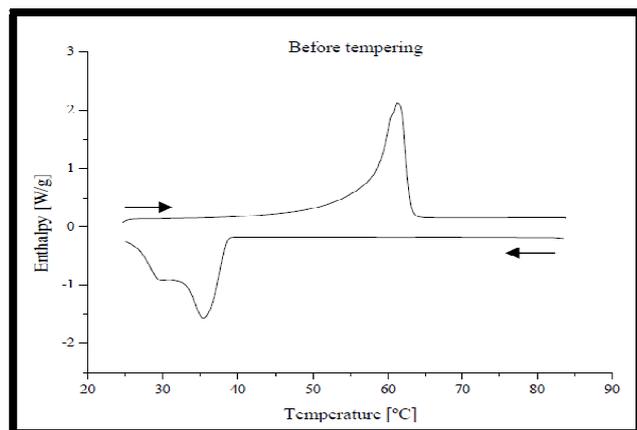


Fig. 5: DSC patterns of physical mixtures of Dynasan 116, Miglyol 812 and miconazole nitrate (69.3+29.7+1) recorded before (upper) and after (lower) tempering the mixture under heat exposure (90°C) for 1 hr.

The calculated melting enthalpy of the lipid fraction in the mixtures shows little difference in comparison to the melting enthalpy of the bulk Dynasan 116. Based on this observation, it can be stated that all mixtures might be preferentially in the β' modification with an onset temperature higher than 40°C. This is the main pre-requisite for preparation of lipid nanoparticles for topical drug delivery. Taking into account that the lipid particle matrix should be in the solid state at skin temperature (32°C); the selected mixtures seem to be appropriated for the preparation of miconazole nitrate-loaded SLN and NLC. The endotherms recorded in Fig. 5 show the crystals of Miglyol 812 (small shoulder) of the main peak of the cooling scan

Table 2: DSC parameters of physical mixtures of Dynasan 116 and Miconazole nitrate (99+1) and physical mixtures of Dynasan 116, Miglyol 812 and Miconazole nitrate (69.3+29.7+1) recorded before and after tempering the mixture under heat exposure (90°C) for 1 hr.

Physical mixtures	Heat exposure (90°C)	Melting point (°C)	Onset (°C)	Integral (mJ)	Enthalpy (J/g)
Dynasan 116 and Miconazole nitrate	Before tempering	63.65	61.35	1380.28	180.27
	After tempering	58.40	57.01	1365.72	174.02
Dynasan 116, Miglyol 812 and Miconazole nitrate	Before tempering	60.17	57.48	11795.59	120.72
	After tempering	60.49	59.54	754.23	106.27

Table 3: Kinetic release rate constants, correlation coefficient and diffusion exponent of various models (n=3)

Formulation	Zero order		First order		Higuchi model		Hixon-crowell		Korsemeyer peppas		
	K ₀	R ²	K ₁	R ²	K _h	R ²	K _H	R ²	K	N	R ²
MN-SLN	20.228	0.948	0.747	0.894	54.035	0.845	0.645	0.953	0.080	1.856	0.995
MN-NLC	17.876	0.915	0.784	0.868	70.587	0.892	0.630	0.975	0.057	1.953	0.986

In Vitro Drug Release

To evaluate the drug release pattern, MNSLN-1 and MNLC-1 dispersion has been selected and the dialysis bag method was used where a mixture of methanol: PBS (pH6.4) (30:70) was used as the diffusion medium. In order to evaluate the controlled release potential of the investigated formulations, the diffusion of Miconazole nitrate from the lipid particles was investigated over 24 h. Each sample was analyzed in triplicate.

The results are shown in Fig. 6. Different release patterns were observed from the MNLC and MNSLN. An initial rapid release was observed in the case of MNLC, whereas MNSLN depicted a slow initial release with a lag time of 0.5 h and 1 h, respectively. MN-loaded NLC formulations depicted better controlled drug release

profile for a prolonged period, suggesting their applicability in topical drug delivery.

The release data were fitted to various kinetic models in order to calculate the release constant and regression coefficients (R²). Among the models tested, the drug release profiles for the MNSLN and MNLC were best fitted with Hixon crowell cube root model based on the regression coefficients (R² of 0.95 and 0.97 respectively) as given in Table 3.

The diffusion exponent (n) values for both batches were within 0.4 which indicated that drug release mechanism followed pure Fickian diffusion. MN-loaded SLN-bearing hydrogel formulations depicted better controlled drug release profile for a prolonged period, suggesting their applicability in topical drug delivery [19].

Ex Vitro skin permeation Studies

The ex vivo permeation of MN from MNSLN and MNLC was evaluated using Franz diffusion cell. The mean cumulative amount diffused Q (mg/cm^2) at each sampling time point was calculated; high amount of Miconazole nitrate release was facilitated through abdominal skin of rats from MNSLN ($0.687 \text{ mg}/\text{cm}^2$) of Miconazole nitrate than MNNLC ($0.260 \text{ mg}/\text{cm}^2$) are shown in Fig. 7. MN-NLC produced significantly higher deposition of Miconazole nitrate in skin ($67 \pm 0.13\%$) than MNSLN ($55 \pm 0.09\%$) (Table 4). Nanoparticulate gel shows higher localization of MN in skin as compared to conventional gel.

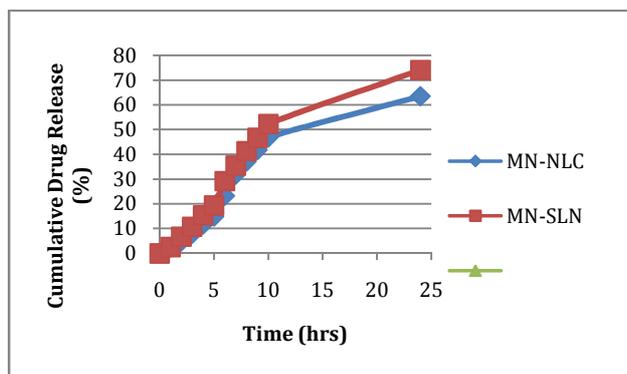


Fig 6: In vitro release studies of MN-SLN and MN-NLC. Data are means \pm s.d., $n = 3$.

Thus, drug-localizing effect in the skin seems possible with novel colloidal particulate drug carriers such as NLC. This colloidal carrier, being submicron in size, enhances the drug penetration into the skin, and, because of its lipoidal nature, the penetrated drug concentrates in the skin and remains localized for a longer period of time, thus enabling drug targeting to the skin [20]. The release of active substances from the lipid matrix is influenced by the crystal structure of the lipid molecules. Drug penetration into certain layers of the skin can be achieved using NLC as a consequence of the creation of a supersaturated system [21].

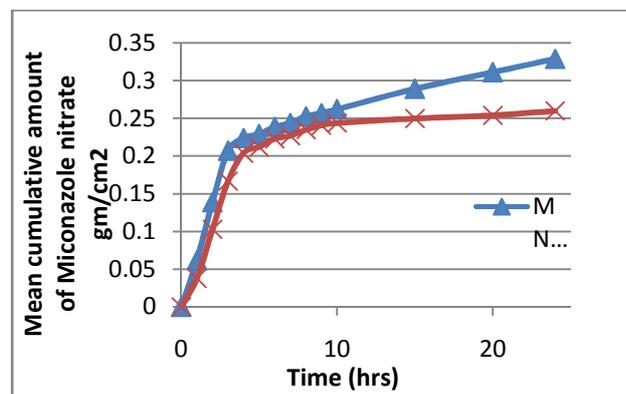


Fig 7: Ex Vitro release of miconazole nitrate from MNSLN Gel, MNNLC Gel and Marketed gel.

Table 4: Mean Amount of Miconazole Nitrate Deposited into abdominal skin of rats.

Test formulation	Amount of MN Deposited skin (%) mean (\pm SD)	Receptor compartment (%) mean (\pm SD)	Remained on the skin (%) mean (\pm SD)
MNSLN Gel	55 ± 0.09	18 ± 0.31	27 ± 0.24
MNNLC Gel	67 ± 0.13	12 ± 0.26	21 ± 0.11

CONCLUSION

In this study, both SLN and NLC systems can be considered as promising systems for topical administration of Miconazole nitrate. Stable MNSLN and MNNLC were prepared by hot high pressure homogenization method. At different temperatures the mean diameters of SLN and NLC remain practically the same, which emphasizes the physical stability of these lipid particles. The entrapment efficiency and the drug release profile depend on the concentration and the lipid mixture employed. NLC show higher entrapment efficiency due to their liquid parts. In agreement to this results NLC also show a faster release profile in comparison to SLN with the same lipid concentration. The obtained results reflect the potential of SLN and NLC as a carrier for topical administration of MN which is demonstrating greater drug deposition into skin. The obtained results also indicated the use of these lipid nanoparticles as modified release formulations for lipophilic drugs. In conclusion, the developed systems are promising alternative drug carriers for topical pharmaceuticals. Future studies were focused to incorporate MNSLN and MNNLC in more convenient topical dosage forms such as hydrogels or creams.

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