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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF NANO-STRUCTURED LIPID CARRIERS ENCAPSULATED TOLNAFTATE EMULGEL

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ABSTRACT

This research work aimed to "Formulation of tolnaftate (TNF) loaded NLCs emulgel using hot homogenization method followed by ultrasonication method for topical application. The various parameters such as concentration of solid lipid (GMS), liquid lipid (Gelucire 44/14), and the concentration of gelling agent (Carbopol 940) were studied for particle size, zeta potential, %EE, and Viscosity of emulgel. The optimized formulation (F6) was found to be spherical in shape with a mean particle size of 104.8±44.30nm and zeta potential -33.0mV. The maximum % entrapment of tolnaftate in the optimized formulation was found to be 98.23±0.963. The in vitro drug release study demonstrated that the release of the drug from TNF-NLCs emulgel was shown in comparison to marketed formulation (KT5DERM) and pure TNF. Overall, the developed TNF-NLCs emulgel was considered as a potential anti-fungal nano-drug, providing a new direction to the fungal infection treatment.

Key-words: Nanostructured lipid carriers, nanogel, nanotechnology, recent patents, drug delivery, emulgel.

INTRODUCTION

Fungal infections on the surface of the skin are one of the most prevalent skin disorders, affecting millions of people worldwide. Dermatophytes, yeasts, and non-dermatophyte molds cause these infections, which may affect both healthy and immune-compromised people. Trichophyton, Epidermophyton, and Microsporum are dermatophytes. The majority of superficial fungal infections are caused by yeasts such as Candida albicans. Candida-related infections are rising, accounting for about 10-15% of all infections. Cases with bacterial infections[1,2].

Topical drug delivery has long been a popular treatment choice for local fungal infections, owing to its localized effect and lack of side effects associated with oral therapy[3,4]. The topical method, on the other hand, is one of the most difficult since it involves many pharmaceutical and biological products. The probability and degree to which a drug will be administered, as well as the transportation of drugs through the environment, are determined by a variety of factors. The topical path is also an obstacle. The number of drugs is hydrophobic in nature and belongs to one of two classes. Class II or IV of the BCS (biopharmaceutical classification system). BCS class IV drugs, on the other hand, are riskier when contemplating.

Gels are a comparatively newer type of drug delivery system that consists of a complex network of solid particles that can contain either inorganic substances such as aluminium salts or organic polymers of natural or synthetic origin[6]. They have a greater aqueous component. When compared to an ointment or cream base, it helps in drug dissolution and promotes fast drug release into the vehicle, which is a liquid[7,8]. The drug formulations are referred to as emulgels when gels and emulsions are used together[7-9]. Emulgels for the dermatological application have a certain distinct advantage over other competitors, such as being translucent, thixotropic, non-staining, conveniently spreadable, easy to remove, pleasing appearance, and greaseless[8-11].

Tolnaftate (TNF) is a BCS class IV compound that is a synthetic thiocarbamate used as an antifungal agent. TNF was shown to be active when applied topically but ineffective when delivered orally or intra-peritoneally, according to a growing body of evidence. Tolnaftate comes in several topical dosage formulations, including cream, gel, mist as well as liquid aerosol[12, 13].

Several studies on TNF formulation production have also been published, with a focus on novel formulations like solid-lipid nanoparticles, liposomes, and nanostructured lipid carriers[14-16.] However, no prior literature has been published on the formulation of topical delivery with enhanced skin permeation using an easy and industrially feasible method.

Using Carbopol 940 as a gelling agent and one form of a penetration enhancer, namely Gelucire 44/14, an attempt was made to produce an emulgel formulation of TNF to improve its solubility and more permeability for topical application. The optimized formulation was then tested to see whether it met the following criteria: physicochemical properties, in vitro drug release, drug loading capacity, etc., were all investigated.

MATERIAL AND METHODS

Tolnaftate was received as a gift sample from Belco Pharma (Bahadurgarh, Haryana). Stearic acid, Carbopol 940, Triethanolamine and Span 20 were obtained from Central Drug House (P) Ltd (New Delhi, India), GMS was obtained from Himedia Laboratories Private. Limited (Mumbai, India), Gelucire

44/14 received as a gift sample from Lauroyl Macrogol-32 Glyceride Rattefosse (France), Tween 80 from Qualikems Fine chemicals Pvt. Ltd. (New Delhi).

Screening of components

As a result, no standard method for selecting lipids has been established; however, the process and results are similar to the findings of a previous study[17,18].

Screening of lipids

The lipids were choosing on the basis of partition coefficient, encapsulation efficiency and loading capacity of drug [18]. The lipids were screen for NLCs that are Stearic acid, GMS, Glyceryl behenate and Gelucire 44/14. The tolnaftate (10mg) was dissolved in minimum quantity of methanol and dispersed in melted (above 5°C) of melting point of lipids each selected lipids (1gm) and 5ml of hot (same temperature of lipid) was added and shake for 30 minute using water bath shaker (HICON®ISO 9001: 2000). The aqueous phase was cold and separated by ultracentrifuge (R-8C Laboratory Centrifuge) the supernatant was filtered through .022µm nylon syringe filter and analysed for drug content.

Screening of Emulsifiers

In the study, for emulsifiers (Tween 80, Tween 20, Pluronic F68 and Pluronic F27) were selected. The selection of emulsifier was carried out by preparing nano-emulsion at a fixed concentration of emulsifiers that is 1% w/v in aqueous solution. All the prepared nano-emulsions using these emulsifiers were evaluated for particle size.

FORMULATION METHODOLOGY

Preparation of NLC's of Tolnaftate

The pre-calculated quantity of drug is added in lipid phase and heated at 5°C above of the melting point of lipids. The aqueous solution of surfactant was heated at the same temperature of lipid phase, separately and maintained at 70°C. Therefore, lipid phase was poured into the aqueous phase drop-by-drop with continues stirring using homogenizer (IKA®T18 Digital Ultra Turrax) for set of 4 (2 min stirring and 3 min rest) at 12000-15000 rpm. The obtained NLC's dispersion was sonicated for 5 min by using ultra-sonicator (Orchid Scientifics Ultrasonic Homogeniser) at 70% power. The temperature of the NLC's was maintain all over the preparation method. After sonication, the dispersion was cooled down at room temperature. (Table 1)

Optimization and Characterization of NLC's of Tolnaftate

Percentage entrapment efficiency

The tolnaftate NLC's dispersion was shake gently. The tolnaftate NLC's dispersion was centrifuge foe 30 min. at 10,000rpm. After that take 1ml of supernatant, and filtered it by using nylon siring filter. Take 1ml of filtered supernatant and dilute with 50ml of distilled water. Then prepared solution was examined under the UV-spectroscope at 257nm. The calibration curve was prepared and absorption was recorded. The percentage entrapment efficiency was calculated by following equation:

$$\% EE = \frac{total\ deug - free\ drug}{total\ drug} \times 100$$

Percentage loading capacity

The tolnaftate NLC's (TNF-NLCs) dispersion was centrifuge for 30 min. at 12,000-15,000 rpm. Take 1 ml of supernatant and add 1ml of DMSO (dimethyl sulphoxide) and makeup the volume up to 10ml. the prepared solution was examined under the UV-spectroscope at 257nm and absorption of the sample was recorded. The percentage loading capacity of the sample was calculated as following equation:

$$\%\ loading\ capacity = \frac{weight\ of\ total\ drug}{weight\ of\ NLC's} \times 100$$

Particle size, Zeta potential and PDI

The mean particle size, zeta potential and polydispersive index of prepared NLC's were analysed by using zeta sizer (Malvern Instrument Ltd-©Copyright 2008) available at M.D.U (Maharshi Dayanand University).

Scanning electron microscopy

It is the method for utilization for identifying the morphology of particle surface to determined their size and shape.

Preparation of NLC's emulgel

The emulgel was formulated by dispersing the 1% of carbopol 940 in the optimized NLC's of tolnaftate formulation. The carbopol 940 was mixed into the NLC's by using the magnetic stirrer for 30min. at 40°C. After dispersing the carbopol 940 using the triethanolamine for neutralizing the formulation.

Characterization of NLC's emulgel

pH

A pH metre was used to calculate the pH of all formulations. Before use, the pH metre was calibrated with a standard buffer solution of pH 4 and pH 7. The weighted amount 1 gm of gel formulations were dissolved in 100 millilitres of distilled water and preserved for two hours. A pH metre was used to determine the pH of the suspension.

S*preadibility*

2 gm of emulgel was placed on the glass slide, and the second glass slide was placed over it. 1kg weight was placed on the both slides for removing the air. 80gm weight was placed in the pan. The separation time of the both slides and distance covered by the slide was noted. The spreadibility of the formulation was calculated by using the equation given below:

$$S = M.L/T$$

Where, M= mass placed on the upper slide, L= distance covered by glass slide, T= time taken for separation the both slides

Viscosity

The viscosity of different emulgel formulation was determined by the Brookfield viscometer (DV-E- Viscometer) with spindle no. 6 at 50 rpm at room temperature.

Extrudability

The test was measure by the amount of gel extruded from the collapsible aluminium tube by applying finger pressure. The extruded amount of gel was weighted.

In vitro penetration study

The *in vitro* studies of tolnaftate NLC's emulgel were carried out by using the dialysis membrane bag method. The dialysis membrane was activated by dipping into the ratio of ethanol and distilled water (2:1) for 24 hours. The 2mg of emulgel was dispersed into the 1ml of phosphate buffer 6.8 and fill in the dialysis membrane bag. The samples are taken at the predetermined time of intervals from the receiving cell and add the fresh solvent of equal amount taken from the receiving cell. All the taken samples were analysed by the UV spectroscopy at λ_{max} 257nm and absorption were noted.

Table 1: Preparation of TNF-NLC's.

Ingredients (%w/v)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	1	1	1	1	1	1	1	1	1	1
Stearic acid	0.5	1	1.5	2	-	-	-	-	-	-
GMS	-	-	-	-	0.5	1	1.5	2	1	1
Gelucire 44/14	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 20	1	1	1	1	1	1	1	1	1	1
Tween 80	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Carbopol 940	-	-	-	-	1	1	1	1	0.5	1.5
Triethanolamine	-	-	-	-	0.5	0.5	0.5	0.5	0.5	0.5
Methyl paraben	-	-	-	-	0.1	0.1	0.1	0.1	0.1	0.1
Propylene paraben	-	-	-	-	0.5	0.5	0.5	0.5	0.5	0.5

Table 2: Selection of lipids

S.No.	Lipid	HLB value	Melting point	Drug partition
1.	GMS	3.8	55-60	6.78±0.06
2.	Gelucire 44/14	14/11	42.5-47.5	6.89±0.12
3.	Glyceryl behenate	2	70-75	6.21±014
4	Stearic acid	15	66-70	6.52±0.04

Table 3: Screening of emulsifier

S.No.	Name of emulsifier	Particle size(nm)
1.	Tween 80	282.0
2.	Span 20	305.6
3.	Pluronic F-68	442.0
4.	Pluronic F-127	309.9

Table 4: optimization of TNF-NLC's

%EE	Particle size (nm)	Zeta potential (mV)	PDI
98.23±0.963	104.8±44.30nm	-33.0	0.446

Figure 1: Particle size report of TNF-NLCs

Figure 2: Zeta potential report of TNF-NLCs

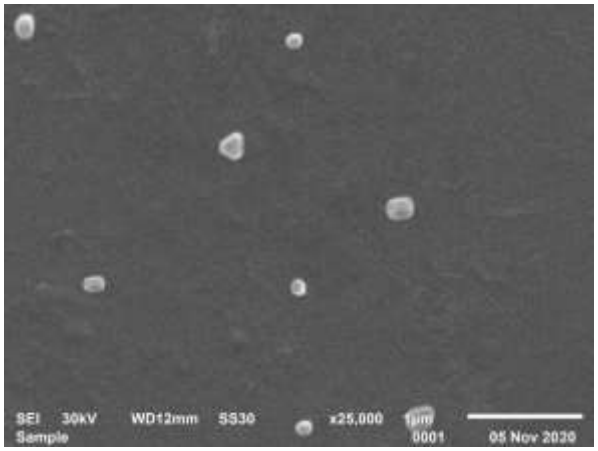

Figure 3: The optimized formulation seen through SEM

Table 5: Optimization of Gelling agent

S.no.	Quantity of carbomer 940 (gm)	Gel formation	Spreadability
1.	0.5	Gel not formed	poor
2.	1	Gel formed	good
3.	1.5	Gel formed	poor

Table 6: Spreadiability of all formulation

Formulation code	Weight (gm)	Length (cm)	Time (sec)	Spreadability coefficient
F1	80	10	29	27.58
F2	80	10	25	32
F3	80	10	32	25
F4	80	10	30	26.66
F5	80	10	26	30.76
F6	80	10	28	28.57
F7	80	10	26	30.76
F8	80	10	24	33.33
F9	80	10	20	40
F10	80	10	23	34.78

Table 7: Viscosity of all formulation

Formulation code	Spindle no.	RPM	Torque (τ)	Viscosity(cps)
F1	6	50	16.28	9280±25
F2	6	50	22.81	9360±57
F3	6	50	26.58	10737±96
F4	6	50	29.26	11484±27
F5	6	50	32.90	12840±85
F6	6	50	34.56	13426±80
F7	6	50	37.43	14263±79
F8	6	50	38.92	15670±97
F9	6	50	33.45	13470±63
F10	6	50	32.40	12890±74

Table 8: Extrudability of all formulation

Formulation code	Weight of emulgel in collapsible tube (gm)	Pressure	Weight of extruded emulgel from tube (gm)
F1	8	Figure pressure	0.47±0.1
F2	8	Figure pressure	0.25±0.2
F3	8	Figure pressure	0.38±0.2
F4	8	Figure pressure	0.36±0.1
F5	8	Figure pressure	0.38±0.3
F6	8	Figure pressure	0.37±0.1
F7	8	Figure pressure	0.35±0.1
F8	8	Figure pressure	0.39±0.2
F9	8	Figure pressure	0.48±0.2
F10	8	Figure pressure	0.50±0.1

Table 9: Drug release (*in vitro*)

Time	% Cumulative Drug Release
1	9.9±0.23
2	21.6±0.45
3	28.1±0.73
4	35.9±0.56
5	42.4±0.21
6	49.2±0.41
7	56.4±0.62
8	60.5±0.36
9	64.0±0.24
10	68.6±0.11
11	72.1±1.53
12	74.7±0.13
13	76.6±0.35
14	79.9±0.39
15	81.4±0.70
16	82.6±0.37
17	86.6±0.25
24	90.6±0.79

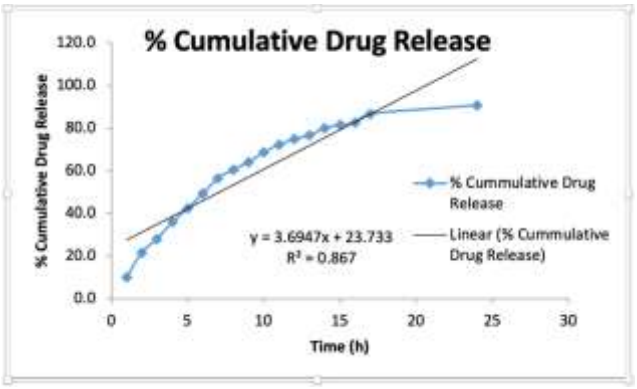

Figure 4: % Cumulative drug release vs time

Table 10: Comparison of in-vitro release profile of TNF-NLCs with marketed formulation

Time	% CDR in phosphate buffer pH 6.8 of marketed formulation	% CDR in phosphate buffer pH 6.8 of optimized formulation
1	19.33±1.27	9.9±0.23
2	27.62±1.46	21.6±0.45
3	39.47±2.01	28.1±0.73
4	47.26±1.52	35.9±0.56
5	51.62±1.12	42.4±0.21
6	58.19±1.33	49.2±0.41
7	62.92±1.42	56.4±0.62
8	65.95±1.39	60.5±0.36
9	68.07±1.67	64.0±0.24
10	71.70±1.46	68.6±0.11
11	74.35±1.35	72.1±1.53
12	75.22±1.73	74.7±0.13
13	77.32±1.91	76.6±0.35
14	80.59±1.71	79.9±0.39
15	82.40±1.32	81.4±0.70
16	83.70±1.56	82.6±0.37
17	85.70±1.34	86.6±0.25
24	86.61±1.27	90.6±0.79

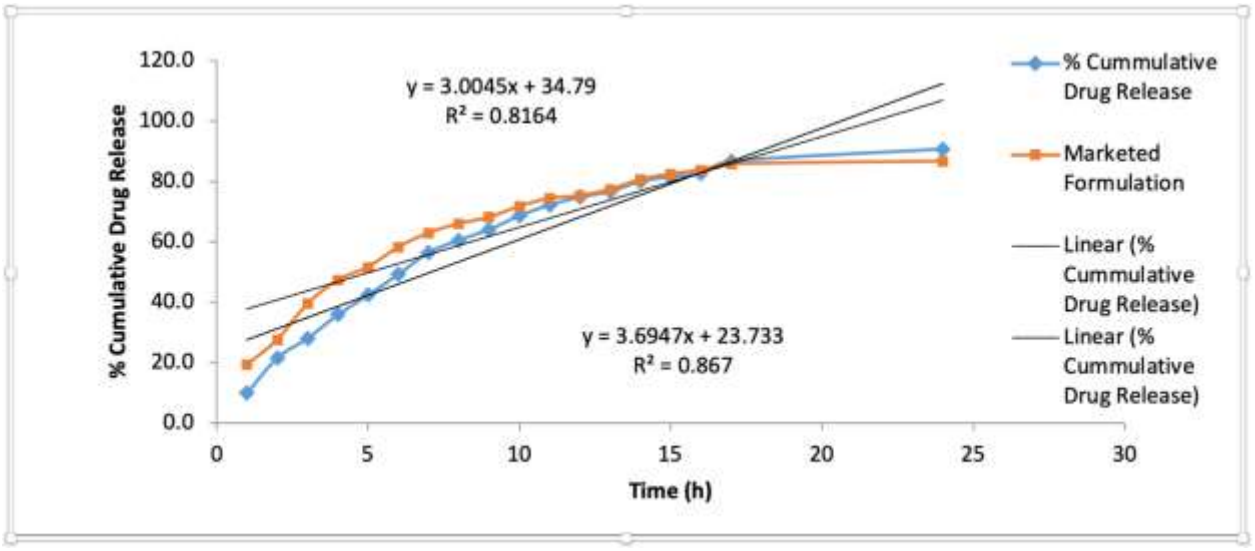

Figure 5. Comparison of optimized formulation with Marketed formulation

Table 11: Result of stability study

Evaluation parameter	Storage condition	Time intervals in months		
		1st Month	2nd Month	3rd Month
Particle size	25°C/60% RH	104.8±44.30	104.9±40	105.4±52
	45°C/75% RH	104.7±45.20	104.3±53	106.4±62
Zeta potential	25°C/60% RH	-33.0	-35.0	-36.4
	45°C/75% RH	-33.8	-34.9	-36.7
%EE	25°C/60% RH	98±69	95±34	91±25
	45°C/75% RH	85±45	84±65	80±3
pH	25°C/60% RH	5.8	6	5.9
	45°C/75% RH	5.9	6.2	6
Spreadiability	25°C/60% RH	28.57	26.45	24.52
	45°C/75% RH	21.36	24.56	25.78
Viscosity	25°C/60% RH	13426±80	14356±45	14987±56
	45°C/75% RH	13569±36	14593±78	15879±52

RESULT AND DISCUSSION

Selection of lipids

As per the literature survey, the partition coefficient and high lipid solubility can be the result of high encapsulation efficiency. The experimental data showed that partition of tolnaftate in the following order: Gelucire 44/14>GMS>Stearic acid>Glyceryl Behenate, mention in Table 2.

Screening of emulsifiers

The screening of surfactants such as Tween 80, Span 20, Pluronic F-28 and Pluronic F-127 were used for the preparation of NLCs with fixed lipid-emulsifier ratio i.e.,1.5:3.5. The results of the prepared NLCs with Tween 80 and Span 20 shows the smallest mean particle size i.e., 282.0nm and 305.6nm. However, the other emulsifiers such as Pluronic F-68 and Pluronic F-127 form larger particles size in comparison with above emulsifiers i.e., 442.0nm and 309.9nm, respectively as Table 3.

Optimization and characterization of TNF-NLC's

The TNF-NLCs that were optimised were characterised. The optimised TNF-NLCs particle size and PDI were found to be 104.8±44.30nm and 0.446, respectively, while the zeta potential was -33.0mV. The percent EE was calculated to be 98.23±0.963, and the data was shown in Table 4.

Percentage entrapment efficiency and percentage loading capacity

The %EE and %DL of optimized NLC's are 98.23% and 31.56% due to the matrix structure of NLC's in NLC's, the liquid lipid matrix insert in a small lipid section in which the drug solubility is higher that shows higher drug loading capacity. Accordingly, the present liquid lipid matrix in NLC's shows higher entrapment efficiency which provides the high drug load successfully.

Particle size, Zeta potential and polydispersity index

The optimized formulation of NLC's were in the nano-sized range 104.8±44.30nm, Zeta potential 33.0mV with low polydispersity index 0446. The presence of small amount of lipids in the NLC's lipid matrix show a small mean diameter of NLC's it was generally notice that on increasing the amount of lipid in NLC's that shows the small particle size. Also the surfaces are influenced by the small size of NLC's and show stabilization of formulation. (Figure 1 and 2)

Scanning electron microscopy

It is the method for utilization for identifying the morphology of particle surface to determined their size and shape. (Figure 3)

Preparation of tolnaftate NLC's emulgel

0.5 percent, one percent, and 1.5 percent carbomer 940 were used to formulate the optimised NLC's into a gel. Because of its consistency, the emulgel 1 percent was discovered to be appropriate for gelling the NLCs. (Table 5)

Characterization of tolnaftate NLC's emulgel

pH

A pH metre was used to calculate the apparent pH of the gel at 25 degrees Celsius, in triplicate The optimum NLC's pH was identified. 5.43 ± 0.04. The tolnaftate NLC's emulgel pH was within the acceptable range. The range of topical formulations that are suitable and compatible the skin's pH.

Spreadability

The most important criteria of emulgel was spreadability. The all emulgel formulation are showed good spreadability which is shown in the Table 6. In overall formulation the F6 formulation were shows best spreadability coefficient of the emulgel formulation.

Viscosity

The viscosity of all prepared emulgel was listed in the Table 7. The viscosity of emulgel was increase by increasing in concentration of polymer. In overall formulation the F6 formulation was shows optimum viscosity.

Extrudability

The extrudability of all emulgel formulation was determined and listed in the Table 8. In all over formulation the F6 formulation was shows optimum extrudability.

***In vitro* penetration study**

The *in vitro* release of TNF from NLCs was studied using the dialysis membrane bag process. The TNF release pattern (Figure 1) from the NLCs was evaluated over the course of 24 hours. Table 9 indicates that the percentage cumulative drug release (percent CDR) of TNF in 24 hours was found to be 92.62 percent in PBS pH 6.8. (Figure 4)

Comparison with Marketed formulation

The optimized formulation of TNF-NLC emulgel was related with marketed formulation (KT5DERM 15gm, Batch No.KTP-162, Mfg. date: 08/20/2020, Expiry date 07/2022) by Laborate pharmaceuticals India LTD for release of drug (*in vitro*) in PBS pH 6.8 (Table 10 and Figure 5). The optimized formulation of TNF-NLCs emulgel showed 9.918% CDR in PBS pH 6.8 in 1 hr, correspondingly. Although marketed formulation indicated 19.33% CDR in PBS pH 6.8 with in 1hr, correspondingly. At 24h, TNF-NLCs emulgel indicated 94.628% CDR in phosphate buffer

pH 6.8 correspondingly. Although marketed formulation (KT5DERM) showed 86.61% CDR in phosphate buffer pH 6.8 within 24 h, correspondingly (Figure 5).

Stability Studies

Stability study presented that the potential remains within the therapeutical, chemical, physical and toxicological measurement. Stability study of the current work conceded out on optimized TNF-NLCs emulgel at room temperature 25°C/60% RH and in stability chamber at room temperature 45°C/75% RH acc. To the guidelines of ICH. The optimized preparation has stability for 3 months; the readings are shown in Table 11.

CONCLUSION

The aim of this research work was to create and describe an ideal formulation of tolnaftate nano-structured lipid carriers, which would then be integrated into an emulgel. The NLCs were produced using the water-insoluble drug tolnaftate. The lipid and emulsifier were selected based on solubility studies (i.e. partitioning effects). The two variables of lipid number (Gelucire 44/14 and GMS) and emulsifier amount (Tween 80 and Span 20) were investigated in this analysis. As the concentration of lipids increased, the EE increased as well. As the concentration of lipids was increased, the particle size was found to decrease. As the volume of lipid was increased, the particle size became larger. The zeta potential improved slightly as the concentration of Gelucire 44/14 increased, but not substantially. The charge on the particle surface is insulated because Gelucire 44/14 coats the particle surface. As a result, it's likely that NLCs of tolnaftate infused into emulgel might be used as a dosage form to accomplish our goal. The goal was to create an emulgel with carbopol 940 (1%) that had improved drug entrapment, enough viscosity, good extrudability, good homogeneity, and better drug release. Emulgels may provide a more pleasant skin sensation than other traditional dosage types. Water does not dissolve emulgels. They are difficult to remove from the application site.

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