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FORMULATION DEVELOPMENT AND EVALUATION OF NANOEMULSION BASED LULICONAZOLE FORMULATIONS FOR TARGETED TREATMENT OF ONYCHOMYCOSIS THROUGH TRANSUNGUAL ROUTE

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Abstract: Onychomycosis is the most common disorder affecting the nail unit and accounts for at least 50% of all nail diseases. Nail is an important segment for effective treatment of onychomycosis and consists of a network of keratin proteins. Oleic acid, Tween 80, and Propylene glycol were selected as the oil, surfactant, and co-surfactant respectively for the construction of the phase diagram. 2:1 smix ratio was finalized due to larger nanoemulsion region in pseudo ternary phase diagram. The nanoemulsion formulations were prepared by using ultrasonication method. Luliconazole Nanoemulsions were characterized by droplet size, zeta potential, pH, viscosity, refractive index, drug content. The optimized batch of nanoemulsion was converted into nanoemulsion gel by using combination of 0.5%w/w Carbopol 934 and 0.5%w/w xanthan gum. Nanoemulsion gel was evaluated for pH, spreadability, extrudability, rheological study and in vitro drug release study.

Index Terms: Nanoemulsion, Nanoemulgel, Luliconazole, Onychomycosis

1. Introduction

Onychomycosis is the most common disorder affecting the nail unit and accounts for at least 50% of all nail diseases which is caused by fungi (dermatophytes, non-dermatophyte molds, and yeasts), presenting with discoloration of the nail, onycholysis, nail plate thickening and irregular surface occurrence on the nail site. The causative microorganisms for onychomycosis primarily include *Trichophyton rubrum*, *Trichophyton mentagrophytes,* and yeast *Candida albicans*. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected. It prevails among around 5% of the total world population and affects toe-nails much more than finger-nails. Onychomycosis has been reported as a gender- and age-related disease, being more prevalent in males and increasing with age in both genders. Predisposing factors are diabetes mellitus, peripheral arterial disease, immunosuppression due to HIV or immunosuppressive agents.

Nail is an important segment for effective treatment of onychomycosis and consists of a network of keratin proteins. Keratin filaments are aligned transversely with the plane of nail growth which imparts hardness to the nail plate. In onychomycosis, the nail becomes hyperkeratotic and this prohibits effective drug penetration at the treatment site in topical therapy. A new generation of triazole topical antifungal drug Luliconazole was developed as a 5 percent nail solution to resolve this problem. A multicenter, double blind, randomized phase III study concluded that once daily topical Luliconazole 5 percent nail solution demonstrated clinical efficacy and was well tolerated. However, the drug solution can be easily be wiped out from the nail surface after application. It can lead to reduced nail permeability from the topical solution

owing to disadvantages such as the greater concentration of the drug required to produce the therapeutic effect. Hence, there is a requirement for a drug delivery system that overcomes the problems associated with the existing conventional topical solution formulation along with nail permeability improvement and residence time on the nail surface.

In the recent era, colloidal based drug delivery has gained enormous importance in onychomycosis treatment due to its higher efficacy with fewer side effects. By formulating Luliconazole into a colloidal based drug delivery system, it is possible to reduce the drug concentration into the formulation in comparison to existing conventional topical solution formulation (reference formulation) as well as to improve the nail permeability of Luliconazole.

Nanoemulsions or sub-micron emulsions (droplet size, 20–200 nm) are used as vehicles for the delivery of active pharmaceutical ingredients (API) due to their high kinetic stability and approaching thermodynamic stability. Unlike microemulsions, which require a high surfactant concentration, nanoemulsions are formulated with reasonable surfactant concentration for the efficient topical delivery of API owing to their small droplet size, large surface area and low surface tension. They allow rapid penetration of lipophilic actives and thus improving efficacy and minimizing side effects by reducing the dose. Due to improved physical stability, and their non-toxic and nonirritant nature, they can be employed in topical drug delivery systems, providing greater absorption of solubilized lipophilic drugs. Gel can be defined as a semisolid system, which consists of dispersion of particles with interpenetration of liquid. There is a formation of a three-dimensional structure, having a two-phase system with the dispersion of inorganic/organic particles in the continuous phase.

Nanoemulsions can be converted into gel, a system designated as ‘nanoemulgel’, which prolongs the contact time of the formulation with the applied surface, in contrast to nanoemulsion, which has a tendency to flow and run off. Apart from that, for most of the lipophilic drugs (like Luliconazole, in this case), which cannot be incorporated directly into an aqueous gel base due to solubility limitation, an emulgel can provide ease of formulation and improve the therapeutic effectiveness of the existing drugs by incorporating drug molecules in the oil phase of o/w emulsion and uniformly dispersing them in aqueous phase containing the gel base.

The goal of our research was to formulate a topical nanoemulgel of KCZ with desirable characteristics for the effective treatment of onychomycosis.

2. Materials and Methods

2.1. Materials:

Luliconazole was gifted by Alaina Healthcare (Himachal Pradesh, India). Oleic acid, Arachis oil, olive oil, eucalyptus oil, polysorbate 20, 60 and 80 (tween 20, 60 and 80), sorbitan monolaurate (span 20), sorbitan monooleate (span 80), propylene glycol, Carbopol 934, xanthan gum, triethanolamine were procured from S D Fine-Chem Limited (Mumbai, India). Poly ethylene glycol 200 and 400 were provided by Loba Chemie Laboratory Reagents & Fine Chemicals (Mumbai, India). Dialysis membrane-60 was purchased from Himedia Laboratories (Mumbai, India). Analytical grade potassium dihydrogen phosphate was procured from Pallav Chemicals & Solvents (Mumbai, India). Analytical grade sodium hydroxide was provided by Research-Lab Fine Chem Industries (Mumbai, India). Analytical grade methanol was provided by S D Fine-Chem Limited (Mumbai, India). Distilled water was used as an aqueous component.

2.2. Nanoemulsion components screening according to solubility study:

The determination of Luliconazole solubility in various oils, surfactants, and co-surfactants is an utmost requirement for achieving optimum nanoemulsion components because these components finally determine the transungual penetration of Luliconazole through the nail. Various oils such as Oleic acid, Arachis oil, Olive oil and Eucalyptus oil; various surfactants such as tween 20, 60 and 80, span 20 and 80; and co-surfactants such as PEG 200 and 400, propylene glycol were selected for preliminary solubility screening study. An excess amount of Luliconazole was added to each test tube containing 2 g of the selected oils, surfactants and co-surfactants. After the mixture was sonicated using a bath sonicator (PCI, Mumbai) for 5 min in order to facilitate proper mixing of Luliconazole with the vehicles. Mixtures were then kept for 24 hrs for saturation maintained at room temperature. Then the mixture was centrifuged at 3000 rpm for 15 min using a centrifuge (Remi Mumbai, India). The 0.1ml supernatant was then pipette out and diluted in 10 ml volumetric flask upto the mark with methanol. Absorbance reading for the same was taken using a Shimadzu UV-1800 UV-Visible Spectrophotometer against a blank solution at a wavelength of 296nm. The blank solution used for UV measurement consisted of corresponding oily phase, surfactants and co-surfactants diluted with methanol in the same proportion as that of the test solution.

2.3. Preparation of nanoemulsion based formulations

2.3.1. Construction of pseudo-ternary phase diagram

The water titration method was used for the construction of pseudo-ternary phase diagrams. From the solubility study results, Oleic acid, Tween 80, and Propylene glycol were selected as the oil, surfactant, and co-surfactant respectively for the construction of the phase diagram. For the construction of each pseudo-ternary phase diagram, the surfactant was mixed with co-surfactant (Smix) in the ratio of 1:1, 1:2, 2:1, 3:1 [i.e., Smix w/w]. Then the part of each Smix has been combined with the oil in the ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9 (w/w). By vortexing with vortexer for 5 min, a transparent homogenous mixture of oil and the Smix component had been prepared. Then titration of each mixture was carried out in drop by drop method with distilled water keeping on magnetic stirrer and prominently viewed for clarity of phase and ability to flow. The volume of water at which the transitions from transparency to turbidity occurred was supposed to be the titration's endpoint. From this titration method, the ratio of surfactant/co-surfactant (Smix) has been determined. These estimated values were utilized to identify the region of the nanoemulsion formulation with the selected amount of oil and surfactant and co-surfactant. The pseudo ternary phase diagram was constructed using the chemix school software. The percent weight ratios of each component was calculated and points were plotted in the software to get the pseudo ternary phase diagram.

2.3.2. Luliconazole loaded nanoemulsion preparation

After the nanoemulsion regions in the phase diagrams were identified from the phase studies, 2:1 ratio of Smix was finalized for formulation of nanoemulsions. Luliconazole in a concentration of 1% w/w was dissolved into the selected oil and the Smix mixture was added under continuous magnetic stirring (500 rpm) at ambient temperature. The required amount of distilled water was added drop wise to the above mixture till a clear and transparent crude nanoemulsion solution was obtained. The crude nanoemulsion solution was then allowed for ultrasonication to get a nanoemulsion following a cycle of 20 min. Subsequently, the nanoemulsion formulations were stored at room temperature.

2.4. Characterization of luliconazole loaded nanoemulsion formulations

Droplet Size

For understanding or determining the behavior of nanoemulsions, mean droplet size is very important. It was determined by using Zetasizer Nano ZS90 (Malvern Instruments, Malvern, UK) based on the principle of photon correlation spectroscopy, which analyses fluctuation in light scattering due to Brownian motion of particles. Light scattering was monitored at 25°C at a scattering angle of 90°. The nanoemulsion (1–1.5 mL) was transferred to a disposable polystyrene cuvette with the help of a micropipette, and the mean droplet size was determined.

Zeta Potential

Zeta potential is the electric potential which exists at the hydrodynamic plane of shear of a particle. It was measured by applying an electric field across the dispersion. Nanoemulsions were placed in clear disposable zeta cells, and zeta potential, which indicates the surface charge of the developed nanoemulsions, was measured by Zetasizer (Malvern Instruments, Malvern, UK) at 25°C.

pH

The pH of the nanoemulsions was measured using the digital pH meter at room temperature. One gram of Nanoemulsion samples were taken and mixed with 250 ml double distilled water so as to obtain a uniform dispersion and then the electrode of the pH meter was directly immersed in the diluted formulations and the pH was noted individually under ambient temperature conditions.

Viscosity

The viscosity of nanoemulsions was measured using Brookfield viscometer LMDV-200. The measurements were performed using spindle no-4 and spindle speed-10rpm at room temperature.

Refractive Index

The refractive index can be used to identify a substance, to measure its purity, and to determine the concentration of one substance dissolved in other and for nanoemulsion to determine their clarity. The refractive indexes of the selected nanoemulsions were determined using Abbes refractometer.

Drug Content

The drug content in the drug loaded nanoemulsion were determined using a UV spectrophotometric (Shimadzu 1800, Japan.) method. 0.1 gm of nanoemulsion was dissolved in methanol AR and filtered then the volume was made upto 10 ml. 1 ml of this solution was diluted to 10 ml with phosphate buffer pH 7.4. The absorbance of the resultant solution was measured at 296 nm on a UV- visible spectrophotometer against phosphate buffer pH 7.4 as blank. Drug free nanoemulsion (blank nanoemulsion) diluted in a similar manner showed no significant absorbance at 296 nm indicating absence of any interferences. The drug content was extrapolated from the standard curve.

2.5. Luliconazole loaded nanoemulsion-gel preparation

Different formulations of nanoemulgel were prepared by the addition of Carbopol 934 and xanthan gum as gelling agent (0.5-2% w/w). The gel base was prepared by dispersing the gelling agent in purified water, with constant stirring at moderate speed using a magnetic stirrer, and then the optimized nanoemulsion was incorporated into the gel base. The prepared nanoemulgel formulations were inspected visually for their color, appearance and consistency.

2.6. Evaluation of nanoemulsion-gel

pH

The pH of the selected nanoemulsion based gel was measured using the digital pH meter at room temperature. One gram of nanoemulsion based gel sample was taken and mixed with 100 ml distilled water so as to obtain a uniform dispersion and then the electrode of the pH meter was directly immersed in the diluted formulations and the pH was noted individually under ambient temperature condition.

Spreadability

Spreadability of nanoemulsion gel was determined in triplicate as per procedure described. Apparatus used for the study consist of two glass plates which are kept one over the other. A circle of diameter 1cm is marked on lower glass plate and weights (500g) are kept on upper glass plate.

Briefly 1 g of gel was placed on within a circle of 1 cm diameter premarked on the lower glass plate of the spreadability apparatus on which was placed the upper glass plate so the gel was sandwiched between two glass slides. A weight of 500 g was allowed to rest on upper glass plate for 5 min minute to expel entrapped air between glass slides and to provide uniform film of the formulation and then removed. The increase in the diameter due spreading of the gel was noted.

Extrudability

It is a test to measure the force required to extrude the gel from the tube. On the application of weight, the amount of gel extruded from the aluminium tube was determined. The nanoemulsion gel extruded should be at least 0.5 cm ribbon in 10 s. The higher the quantity of gel extruded, the better is the extrudability. The extrudability of the optimized formulation was measured, in triplicate, and calculated by using the formula:

E = M/A

Rheological Study

Rheological characterization of sample was performed using Brookfield viscometer (LMDV-200). The measurements were performed using spindle no-4. Viscosity parameters were collected at different rpm with 1 minute equilibration time at every rpm. Different torque values at respective spindle speeds were obtained for an ascending and descending curve. Rate of shear and shearing stress were calculated by using following formula. Rheogram was constructed by plotting the shear stress verses shear rate. Results obtain are reported.

$$shear\ rate\ (y) = \frac{2\ \mathrm{W}\ R_c^2.R_b^2}{X^2\ (R_c^2 - R_b^2)} \quad (sec^{-1})$$

$$shear\ stress\ (\sigma) = \frac{\mathrm{M}}{2\Pi\ R_b^2\ L} \quad (dyne/cm^2)$$

In vitro drug release study was performed using dialysis membrane-60 (average diameter; 15.9 mm, average flat width; 25.27 mm, Himedia®, India) which was activated for about 24 h in a solvent system of phosphate buffer (pH 7.4). About 1 g of nanoemulgel and appropriate amount of aqueous drug suspension (containing the same equivalent amount of drug as contained in 1 g nanoemulgel) were placed on the artificial membrane, and the receptor compartment was filled with solvent system (25 mL). The whole assembly was maintained at 37 ± 1°C, and the speed of stirring was kept constant (100 rpm) for 24 h. Then, the aliquot of drug samples of about 1 mL were withdrawn at pre-determined time intervals, filtered through a 0.22-µm membrane filter and replaced with an equal volume of a fresh solvent. The analysis was done by using U.V Visible spectrometer.

Stability study

The present study involves investigation of the stability of the formulation of nanoemulsion based gels of Luliconazole under the influence of 40 ±2°C +75% RH storage conditions for a period of 1 month. The study was carried out to evaluate the effect of temperature on essential attributes of the nanoemulsion gel for properties such as visual appearance, pH and drug content after specified time intervals.

3. Result and Discussion

3.1. Nanoemulsion components screening according to solubility study

All excipients for the formulation were selected from among the "Generally-Recognized-as-Safe" (GRAS) category (Table I). Oleic acid was selected as the oil phase due to the highest solubility of Luliconazole (35.1 mg/mL) as compared to other experimental oils. Tween 80 and Propylene glycol were used as the surfactant and co-surfactant, respectively, since they showed the maximum drug solubility, i.e. 31.83 mg/mL and 30.8 mg/mL, respectively (Table I).

Table I: Solubility Profile of Luliconazole in Different Excipients (Oils, Surfactants and Co-surfactants)

Sr. No.	Vehicles	Solubility (mg/ml)
1.	Oleic acid	35.1
2.	Arachis oil	24.1
3.	Olive oil	6.27
4.	Eucalyptus oil	20.6
5.	Tween 20	22.55
6.	Tween 60	29.08
7.	Tween 80	31.83
8.	Span 20	17.88
9.	Span 80	13.96
10.	Propylene glycol	30.8
11.	PEG 200	23.55
12.	PEG 400	17.57

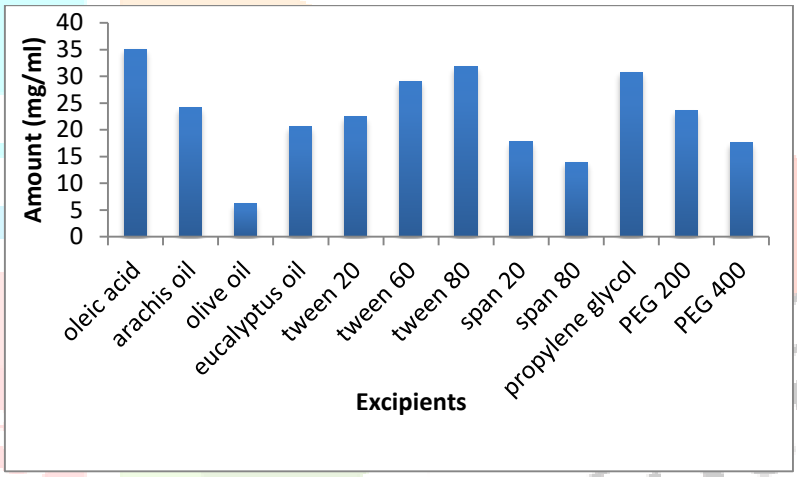
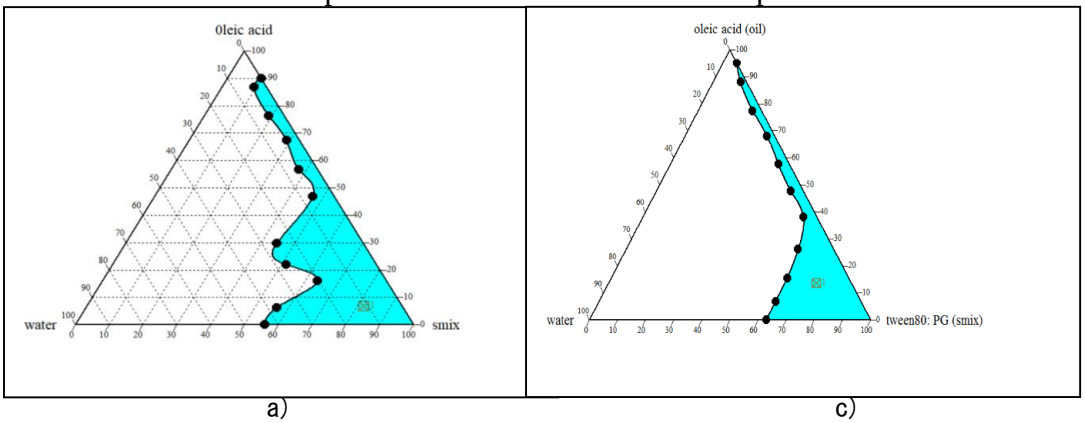


Figure I: Solubility of Luliconazole in different Excipients

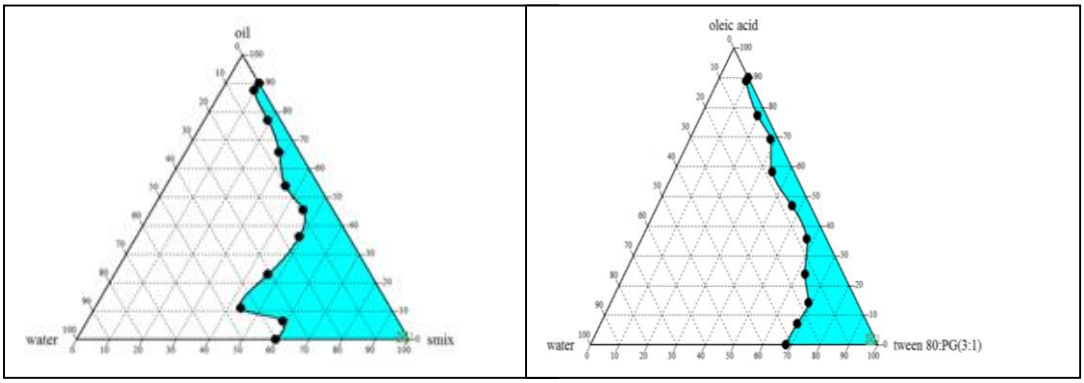
3.2. Preparation of nanoemulsion based formulations

3.2.1. Construction of pseudo-ternary phase diagram

The desired concentration range of the components in the nanoemulsion system was determined by constructing a pseudo-ternary phase diagram. The pseudo-ternary phase diagram was constructed with different ratios of Smix *viz*. 1:1, 1:2, 2:1 and 3:1. As shown in figure 1:1 and 2:1 ratios had larger areas than that of 1:2 and 3:1 ratios. From 1:1 and 2:1 ratios, large nanoemulsion area was observed for the ratio 2:1 (w/w) and the same was used to optimize the final formulation compositions.



a) c)



b) d)

Figure II: Pseudo ternary phase diagrams of Oleic acid and Smix (Tween 80:Propylene glycol) Ratios; a) 1:1, b) 2:1, c) 1:2 and d) 3:1.

3.2.2. Luliconazole loaded nanoemulsion preparation

Concentrations of the components were selected on the basis of optimized pseudo ternary phase diagram and the formulations were prepared as per procedure with addition of drug.

Table II: Composition of Nanoemulsion Formulations

Sr. No.	Formulation	Oil (Oleic acid) (% w/w)	Smix (2:1) (Tween 80:Propylene glycol) (% w/w)	Water (% w/w)	Drug (% w/w)
1.	F1	5	40	54	1
2.	F2	5	50	44	1
3.	F3	5	60	34	1
4.	F4	7.5	40	51.5	1
5.	F5	7.5	50	41.5	1
6.	F6	7.5	60	31.5	1
7.	F7	10	40	49	1
8.	F8	10	50	39	1
9.	F9	10	60	29	1

3.3.Characterization of luliconazole loaded nanoemulsion formulations

Droplet Size

Mean globule size was ranging from 93.84 to 238 nm and all system showed single peak in size distribution. The results of particle size analysis of the different formulations with Luliconazole are presented in table below. The particle size of formulation F3 was smallest i.e. 93.84 nm as compared to other formulations.

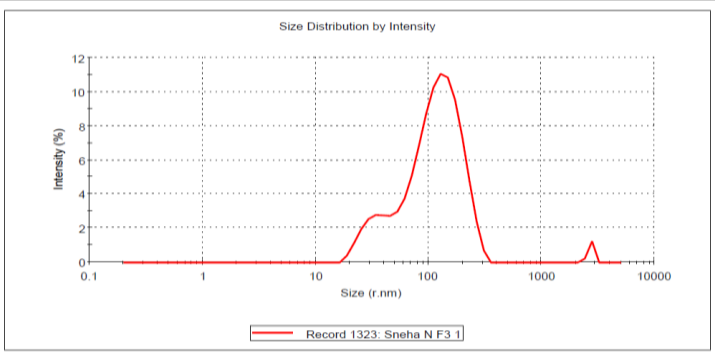


Figure III: particle size distribution graph of F3 formulation

Table III: Particle size analysis of F3 formulation

	Peak	Size (nm)	% Intensity	Width
Z-Average (nm): 93.84	Peak1	131.5	84.6	55.72
PDI: 0.512	Peak2	33.88	13.9	7.966
Intercept: 0.832	Peak3	2721	1.4	137.6

Zeta Potential

The magnitude of the zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particles in a dispersion. F3 nanomulsion has been shown to be stable due to the presence of non-ionic surfactants that impart stability to the system by steric stabilization, considering the lower zeta potential value obtained. Adsorption of these steric stabilizers decreases the zeta potential value and produces strong repulsion between particles thereby preventing aggregation during storage.

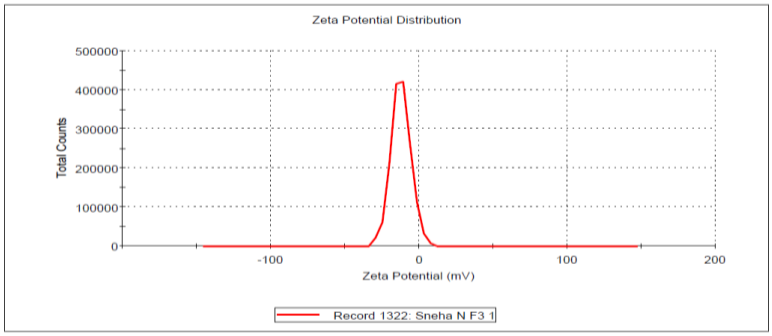


Figure IV: Zeta potential distribution of F3 nanoemulsion

Table IV: Results of zeta potential distribution of nanoemulsion

	Peak	Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -12.2	Peak 1	-12.2	100.0	6.63
Zeta Deviation (mV): 6.63	Peak 2	0.00	0.0	0.00
Conductivity (mS/cm): 0.222	Peak 3	0.00	0.0	0.00

pH, viscosity, refractive index and drug content

Table V: Characterization parameters of Luliconazole nanoemulsions

Sr. No.	Formulation	Refractive index (±SD)	pH	Drug content	Viscosity (mpa.s)
1.	F1	1.58±0.018	6.28±0.12	94.76±0.1	635.6
2.	F2	1.56±0.018	6.14±0.12	97.95±0.2	743.7
3.	F3	1.55±0.018	6.33±0.12	99.53±0.17	525
4.	F4	1.58±0.018	6.20±0.12	94.5±0.1	759.3
5.	F5	1.59±0.018	6.46±0.12	100.2±0.16	724
6.	F6	1.57±0.018	6.45±0.12	95.09±0.03	512
7.	F7	1.59±0.018	6.36±0.12	96.2±0.1	644.2
8.	F8	1.54±0.018	6.50±0.12	99.89±0.11	837.9
9.	F9	1.55±0.018	6.23±0.12	98.6±0.05	435.9

From particle size analysis and zeta potential, it was found that F3 nanoemulsion has lowest particle size 93.84nm among all the nanoemulsion formulations and the zeta potential of the F3 formulation was found to be -12.2mV showing that the respective formulation is stable due to steric stabilization of similarly charged particles. Hence, it can be concluded that F3 formulation is the optimized batch and having good and satisfactory results.

3.4. Luliconazole loaded nanoemulsion-gel preparation

From all concentrations of Carbopol 934 and xanthan gum gelling agents, Carbopol 934 (0.5%w/w) and Xanthan gum (0.5%w/w) in combination were selected as gelling agent for optimized nanoemulsion formulation (F3) as they produced clear, transparent gel and prepared as per procedure.

3.5. Evaluation of nanoemulsion-gel

pH

The pH value of prepared nanoemulsion gel was determined and found to be 7.22 which is acceptable and compatible for topical formulation.

Spreadability

The spreadability of the prepared nanoemulsion gel was determined and found to be 5.2 g.cm/s indicating that the spreadability of the nanoemulsion gel was good.

Extrudability

The extrudability of the prepared nanoemulsion gel was determined and found to be 1.2 g/cm^2 indicating that the extrudability of the gel was good.

Rheological Study

Table VI: Rheological study of nanoemulsion gel

Shear Rate (sec^{-1})	Shear Stress (dyne/cm^2)
0.033	3.014
0.066	5.2
0.166	6.36
0.332	9.48
0.399	12.36
0.665	13.89
0.399	11.31
0.332	8.2
0.166	6.02
0.066	4.1
0.033	2.11

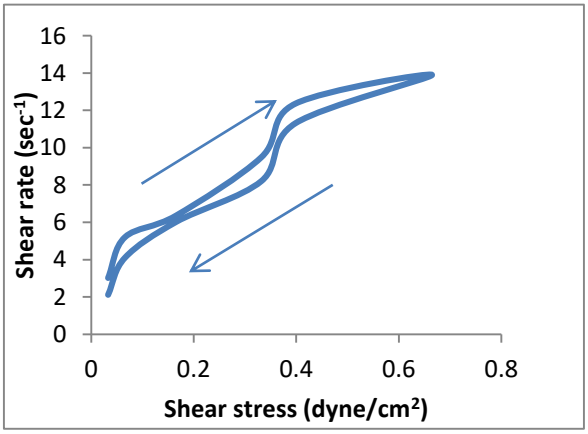


Figure V: Rheology of nanoemulsion gel

The rheological behaviour of the nanoemulsion gel was studied using a Brookfield viscometer. In the rheogram a non- linear relationship was observed between shear stress and shear strain indicating a Non-Newtonian system. From the above rheogram curve we could conclude that the nanoemulsion based gel formulation exhibited pseudoplastic flow behavior. The lower viscosity of Luliconazole nanoemulsion gel could be attributed to ease of spreading.

In Vitro Drug Release Study

In vitro release studies were carried out in using dialysis-60 membrane to assess the release of Luliconazole nanoemulsion gel and aqueous drug suspension. The diffusion cell selected was Franz-diffusion diffusion cell. Saline Phosphate buffer (pH 7.4) was selected as diffusion medium on the receptor side.

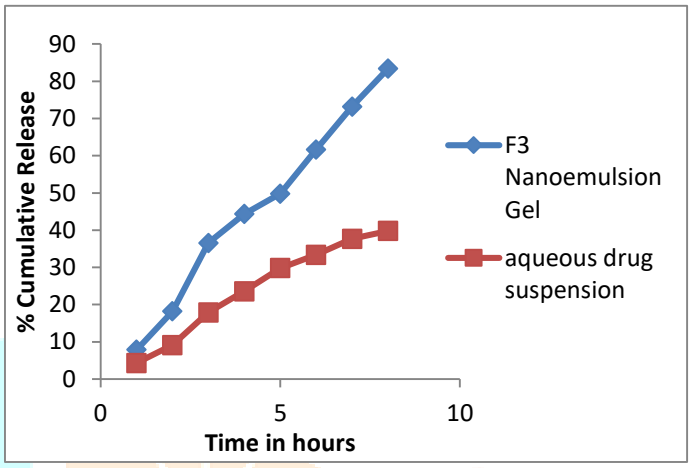


Figure VI: % Cumulative release of nanoemulsion gel and aqueous drug suspension

From the in vitro release profile, it was clear that about 83% drug release was achieved in 8 hrs from the formulation containing Carbopol 934 (0.5%) and xanthan gum (0.5%) in combination as gelling agent. And about 40% of drug was released from the aqueous drug suspension resulting that the nanoemulsion gel formulation shows better release profile than the aqueous drug suspension.

Stability study

Visual Appearance

Nanoemulsion gel appeared as clear, transparent, homogenous oily gel and no drug precipitation was observed at all the storage conditions during the entire period of study.

pH

pH of the nanoemulsion gel at different storage time points was not found to be significantly different from the initial value as shown in the table.

Table VII: pH of Nanoemulsion Gel

Parameter	Initial	10th day	20th day	30th day
Ph	7.22±0.1	7.26±0.12	7.29±0.13	7.3±0.12

Drug Content

The drug content of the nanoemulsion gel under different storage conditions are indicated in the table below. The results do not show any significant change in the drug content in comparison with initial values. Thus we can colclude that the nanoemulsion gel of Luliconazole is stable under the different storage conditions.

Table VIII: Drug Content of Nanoemulsion Gel

Storage Condition	Initial	10th day drug content (%w/w)	20th day drug content (%w/w)	30th day drug content (%w/w)
40 ºC 75%RH	99.4	99.36	99.3	99.11

4. Summary

Nanoemulsions have been in focus in topical drug delivery with the objective of improving the drug penetration. Luliconazole is a poorly water soluble drug with partition coefficient value of 4.07. Hence, the main objective of present investigation was aimed at development of nanoemulsion using Luliconazole as a model drug for topical drug delivery. . The solubility of Luliconazole in various oils, surfactant and cosurfactant was investigated. Among oils, Oleic acid showed highest solubility (35.1 mg/ml) of Luliconazole. Therefore, oleic acid was selected as oil phase. Among surfactants and co-surfactants, Tween 80 and Propylene glycol showed the highest solubility (31.83 mg/ml and 30.8 mg/ml) respectively of Luliconazole. Selected oily phase, surfactant, and cosurfactant for Luliconazole were optimized by constructing ternary phase diagram. The largest area was found at Smix value of 2:1. Due to larger nanoemulsion region, Smix value of 2:1 was selected for further optimization and formulation studies. Luliconazole was dissolved in oil with vortexing followed by ultrasonication. To this smix (tween80 and propylene glycol) were added and the mixture was mixed to yield a homogenous solution. Finally water was added to this solution to yield primary emulsion. The primary emulsions were then subjected to probe sonication for 20 minutes to yield nanoemulsions. Nanoemulsions were characterized for macroscopic appearance, pH, refractive index, drug content, viscosity, globule size and zeta potential. From particle size analysis and zeta potential, it was found that F3 nanoemulsion had lowest particle size 93.84nm among all the nanoemulsion formulations and the zeta potential of the F3 formulation was found to be -12.2mV showing that the respective formulation is stable due to steric stabilization of similarly charged particles. Hence, it was concluded that F3 formulation was the optimized batch and having good and satisfactory results. On the basis of compatibility with nanoemulsion structure, feel and ease of spreadability Carbopol 934 (0.5%w/w) and xanthan gum (0.5%w/w) in combination were selected as gelling agent. The nanoemulsion based gel was evaluated for pH, spreadability, extrudability, rheological study, drug content, in vitro diffusion and accelerated stability study. The nanoemulsion based gel formulation F3 exhibited the drug release 83.4% within 8 hrs and the aqueous drug suspension of Luliconazole exhibited 40% drug release in 8 hrs resulting that the nanoemulsion gel formulation shows better release profile than the aqueous drug suspension.

5. Conclusion

In this study, an attempt was made to formulate Nanoemulgel formulation of Luliconazole for Transungual delivery. Based upon the experimental findings it can be concluded that:

Solubility study revealed that the Luliconazole had highest solubility in Oleic acid among all the oils, tween 80 and propylene glycol among the surfactants and co-surfactants respectively. Drug excipient compatibility study showed no shift in λ_{max} of the overlay spectrum of drug and drug + excipient indicating no interaction between drug and excipients. Phase behavior investigations of selected excipients demonstrated a suitable approach to determine the ratio of smix and concentration range of various components used, over which they could form nanoemulsions. In view of current investigation, due to larger nanoemulsion region oleic acid- tween 80: propylene glycol- water system with smix ratio of 2:1 was selected for further formulation studies. Formulations of nanoemulsion containing Luliconazole in the concentration 1%w/w were prepared and characterized for pH, globule size, drug content and zeta potential. From characterization results of nanoemulsions, F3 nanoemulsion was found to have lowest globule size and hence considered to be optimized. Among the polymers screened for the preparation of gel, Carbopol (0.5%w/w) and xanthan gum (0.5%w/w) in combination were found to be suitable and utilized to prepare nanoemulsion gel of optimized formulation F3 by using overhead stirrer and evaluated for various parameters as pH, spreadability, drug content and rheological studies. Rheological study revealed the pseudoplastic behavior of nanoemulsion gel. In vitro release profile was found to be better for nanoemulsion gel. Nanoemulsion gel showed stability over different storage conditions.

6. References

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