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Formulation, Development and Evaluation of Herbal Antifungal Nanoemulgel Containing Neem Seed Oil, Tulsi Oil and Aloe-Vera Gel

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Abstract: *India has rich tradition of plant based knowledge of healthcare. Modern pharmaceutical technology is being combined with traditional health medicines to increase the efficacy. Fungal infection is now the fourth most common infection in the world. For topical delivery, poor permeability of drugs leads to high cost of therapy and decreased patient compliance. This problem can be overcome by preparing lipid based colloidal sub-micron drug delivery. Due to this technology high concentration of drug can be penetrate into the skin as the lipophilic intracellular pathway of skin allows penetration of materials of less than 20nm, hence drug depot is created in the stratum corneum and epidermis. The present study was aimed to formulate herbal nanoemulgel containing neem oil extract and aloe-vera gel for the treatment of cutaneous fungal infection against the Candida albicans. Nanoemulsion formulations were prepared by spontaneous emulsification method and characterization of the prepared nanoemulsion formulations were done and optimized NE formulation was incorporated into gel base to obtain nanoemulgel. From the results it can be concluded that nanoemulgel formulation is potential and effective topical drug delivery system for neem oil and aloe-vera gel for the topical treatment of fungal infections.*

Keywords: Aloe-vera gel, Fungal infection, Nanoemulgel, Nanoemulsion, Neem oil, tulsi oil

I. INTRODUCTION

For topical delivery, poor permeability of drugs leads to high cost of therapy and decreased patient compliance. This problem can be overcome by preparing lipidbased colloidal sub-micron drug delivery. Due to this technology high concentration of drug can be penetrate into the skin as the lipophilic intracellular pathway of skin allows penetration of materials of less than 20nm, hence drug depot is created in the stratum corneum and epidermis. Nano emulsions with uniform distribution of particle size offers several advantages for topical and transdermal delivery of drugs.Reduction in the globule size as compared to conventional gel helps to cross the barrier membrane (Stratum corneum) of skin which helps in increased efficacy and permeability and reduced treatment time.

1.1 Nano emulsions

Nano emulsions are nano-sized emulsions which are manufactured for improving the delivery of active pharmaceutical ingredients. Nano emulsions are thermodynamically stable dispersions of oil and water having a droplet size of less than 100nm stabilized by an interfacial film of surfactant and co-surfactant molecules

There are 3 types of nano emulsions

1. Oil in water nano emulsions
2. Water in oil nano emulsions
3. Bio-continuous nano emulsions

Formulation techniques of nano emulsions

A) High Energy Methods

1. High-pressure homogenization
2. Micro fluidization

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3. Ultrasonication

B) Low Energy Methods

1. Phase inversion method
2. Spontaneous emulsification
3. Solvent evaporation
4. Hydrogel method

1.2 Nanoemulgel

Formulation containing Nanoemulsion in gel base are called nanoemulgel, is the addition of nanoemulsion system integrated into gel matrix which influences a better skin permeation. This mixture of nanoemulgel acts as drug reservoirs, influencing the release of drug from inner phase to outer phase and further. Nnaoemulgel on intact with skin release the oil droplets from the gel and this oil droplets penetrate into the SC of the skin and deliver the drug to intended site. Nanoemulsion-gel have a good adhesion property and high solubilizing of drug in oil phase leads to larger concentration gradient towards the skin that further increase skin penetration of drug. Also patient compliance is increased due to improved spreadability compare to ointments and creams and decreased stickiness.

II. MATERIALS

Neem seed oil, tulsi oil, Tween 80, Carbopol934 and PEG 400, Aloe-vera gel, Triethanolamine, double distilled water

III. METHODS

3.1 Preparation of Nanoemulsion

Nanoemulsion formulations are prepared by low energy emulsification method. In this method oil phase containing neem oil,tulsi oil and Smix are mixed together in conical flask according to the formulae mentioned below. Then to this mixture water phase is added dropwise, and the above mixture containing both the phases is homogenised by using laboratory homogenizer at 3500 rpm for 30 minutes. All the formulated nanoemulsions are kept overnight to check the stability

3.2 Preparation of Carbopol Gel

Carbopol gel was prepared by incorporating 3% w/v of carbopol 934 in distilled water. Weighed amount of carbopol was taken and dispersed over in distilled water for 2 hours till all the carbopol is soaked, triethanolamine is added after soaking and homogenized for 2hr at 600rpm. After homogenization carbopol gel was subjected for two cycles of sonication for 15 min to expel out the entrapped air bubbles from the prepared gel.

3.3 Preparation of nanoemulgel

Nanoemulgels are prepared by spontaneous emulsification method. Optimised nanoemulsions are incorporated into the gel base to obtain the nanoemulgels. Neem Oil nanoemulsion was then combined with the aloe-vera gel in different concentrations for the synergistic effect of aloe-vera gel against the fungal infection.

IV. EVALUATION PARAMETERS

4.1 Evaluation Parameters of Nanoemulsions

a) Particle size measurement – Particle size of nanoemulsions were measured by scattering light intensity at scattering angle 900. Viscosity of the dispersant is 0.8872 and the count rate is 382.1 kcps.

b) Zeta potential measurement- Zeta potential of the formulations were measured at 25 0C temperature.

c) Thermodynamic stability studies- The nanoemulsions were subjected to following thermodynamic stability tests.

1) Heating-cooling cycle- The prepared nanoemulsions were subjected to 6 heating cooling cycles between 40 c and 450 c by storing at each temperature for 48 hours. Samples of nanoemulsions were then observed for separation or precipitation.

2) Centrifugation- Formulae which were stable after heating-cooling cycle were then subjected to centrifugation at 3500

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rpm for 30 minutes. Those which did not show any phase separation were subjected to freeze-thaw cycle.

3) Freeze-thaw cycle- The temperature range selected was in between -210 c and +250 c for 48 hours at each temperature then the formulae were observed for phase separation.

d) Viscosity determination- Brookfield viscometer is used to determine the viscosity of nanoemulsion formulations at 10rpm for 3 minutes with spindle 62.

e) Drug content measurement- 0.01 ml of formulation was dissolve in 10 ml of dichloromethane. Make sure to dissolve it completely to obtain the stock solution. 1ml from the stock solution is further diluted with dichloromethane upto 10ml and absorbance was measured spectrophotometrically at 243nm. Drug content was then calculated.

f)pH determination- pH of the formulations were determined by using digital pH meter. The formulation was taken into the beaker, then pH meter is immersed into the formulation and reading were recorded. Same process was repeated three times with the same formulations and average of three was taken as pH. Similar procedure was used for the determination of pH of all formulations.

g) In-vitro release through cellophane membrane- The in-vitro permeation studies were done using Franz Diffusion cell with the help of cellophane membrane. Cellophane membrane was clamped between donor compartment and receiver compartment. 150mg of the nanoemulsion formulation was kept evenly in the donor compartment. The receiver compartment was filled with the 60ml of phosphate buffer 7.4. It was stirred continuously at 100rpm using Teflon coated magnetic bead and temperature was maintained at 370 ±0.5 0C throughout the experiment. 2ml of the receiver fluid was withdrawn at each one hour interval and replace with same amount to maintain sink condition. The samples were analysed for drug content using UV- spectrophotometer at 243nm.

4.2 Evaluation Parameters of Gel

a) Rheology study of gel- Brookfield viscometer was used to determine the viscosity of gel at 10 rpm for 3min with spindle 64.

b) pH determination- pH of the gel was determined by using digital pH meter. The formulation was taken into the beaker, then pH meter is immersed into the formulation and reading was recorded. Same process was repeated two times with the same formulation and average of two was taken as pH.

4.3 Evaluation Parameters of Nanoemulgel

a) Physical Appearance

- Colour- The colour of the formulations were checked against black and white background.
- Odour- The odour of the gels were checked by mixing a little amount of gel in water and by taking smell of it.
- Consistency- Consistency of the formulations were checked by applying the gel on to the skin.
- Homogeneity- All the formulations were tested for occurrence of any aggregate by visual inspection after the gels have been set in the container.
- Greasiness- Greasiness were checked by applying the formulations on to the skin.
- Phase separation- Phase separation was observed by visual inspection.

b) Drug content- 10 gm of each gel formulation were transferred in the volumetric flask containing 20ml of dichloromethane and stirred for 30 minutes. The volume was made up to 100ml and filtered. 1ml from the stock solution is further diluted with dichloromethane upto 10ml, and absorbance was measured spectrophotometricaly at 243nm. Drug content was then calculated.

c) pH determination- pH of the gel was determined by using digital pH meter. The formulation was taken into the beaker, then pH meter is immersed into the formulation and reading was recorded. Same process was repeated three times with the same formulation and average of three was taken as pH.

d) Viscosity determination- Brookfield viscometer is used to determine the viscosity of nanoemulsion formulations at 10rpm for 3 minutes with spindle 63.

e) Spreadability-Spreadability is determined by apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of ‘Slip’ and ‘Drag’ characteristics of emulgels. A ground glass slide is fixed on this block. An excess of Nanoemulsion Gel (about 2 gm) under study is placed on this ground slide. The

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Nanoemulsion Gel was sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the Nanoemulsion Gel between the slides. Excess of the Nanoemulsion Gel was scrapped off from the edges. The top plate was subjected to pull of 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula. S = M.L /T Where, S = spreadability, M = Weight tied to upper slide, L = Length of glass slides T = Time taken to separate the slides completely from each other.

f) Extrudability-The extrudability test was carried out using hardness tester. A 5 gm of Nanoemulsion Gel was filled into the aluminum collapsible tubes. The plunged is subjected to hold the tube properly. The 1gm/cm2 applied for the 30 sec. Then measured the quantity of Nanoemulsion Gel extruded from the tube repeat procedure for three times.

g) SwellingIndex-To determine the swelling index of prepared Nanoemulsion Gel 1 gm of gel was taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaoH. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index was calculated as follows.

Swelling Index (SW) % = [(Wt – Wo) / Wo] ×100

Where, (SW) % = Equilibrium percent swelling.

Wt = Weight of swollen emulgel after time t.

Wo = Original weight of emulgel at zero time.

h) Antifungal activity

Fungal strains:The fungal strain employed in the study was obtained from the Dr. VikhePatil Memorial Hospital, Ahmednagar. Candida albicans is used to assess susceptibility patterns against the phytochemical extracts.

Preparation of inoculum: Stock cultures were maintained at 40 C on slant of nutrient agar. Active cultures for experiment were prepared by transferring a loopfull of cells from the stock cultures to test tubes of nutrient broth for fungi that were incubated for 24 hours at 370C. The assay was performed by agar disc diffusion method

4.4 Determination of Zone of Inhibition

Antifungal and Antibacterial activity was checked by agar well diffusion method. In this method a previously liquefied medium was inoculated with 0.2 ml of Fungal and Bacterial suspension having a uniform turbidity at temperature of 40 0 C. 20 ml of culture medium was poured into the sterile petri dish having an internal diameter of 8.5cm. Care was taken for the uniform thickness of the layer of medium in different plates. After complete solidification of liquefied inoculated medium, the wells were made aseptically with cork borer having 6mm diameter. In each of these plate gel was placed carefully. Plates were kept for pre diffusion for 30 minutes. After it normalized to room temperature; the plates were incubated at 270C for 48 hours in case of fungi. After incubation period was over, the zone of inhibition was measured with the help of Hi-antibiotic zone scale

In-vitro release through cellophane membrane

The in-vitro permeation studies were done using Franz Diffusion cell with the help of cellophane membrane.Cellophane membrane was clamped between donor compartment and receiver compartment. 150mg of the nanoemulsion formulation was kept evenly in the donor compartment. The receiver compartment was filled with the 60ml of phosphate buffer 7.4 pH. It was stirred continuously at 100rpm using Teflon coated magnetic bead and temperature was maintained at 370 ±0.5 0C throughout the experiment. 2ml of the receiver fluid was withdrawn at each one hour interval and replace with same amount to maintain sink condition. The samples were analysed for drug content using UV- spectrophotometer at 243nm.

V. RESULT AND DISCUSSION

Preformulation study

- Colour- Neem seed oil was found to be yellowish brown in colour.
- Boilingpoint- Boiling point of neem seed oil was found to be 226^{o}C.

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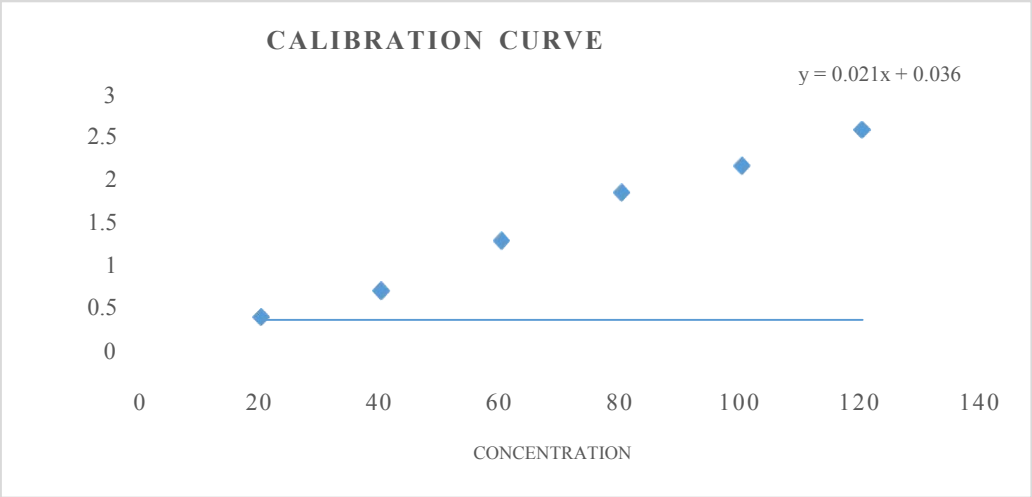
- Solubility study- Neem oil shows maximum solubility in Tween 80 and PEG 400 hence they were selected as surfactants and co-surfactants for further experiments. Ratio of Smix (5:1) is selected as the optimised ratio for the preparation of nanoemulsion formulations depending on the solubility studies.
- Lambda max and calibration curve – lambda max is obtained at 243nm



Compatibility study (FT-IR) -- FTIR characteristics of Neem Seed Oil are also observed in the spectra of physical mixtures of drug and excipient indicating no modification for interaction between the drug and excipients. This proves that there is no potential incompatibility with the drug and the excipients used in the nanoemulgel formulations

5.1 Evaluation of Nanoemulsion

Physical Appearance

Formulations were examined for appearance which shows transparent yellowish brown coloured formulations. They do not show any turbidity or phase separation.

Drug content

Table 4: Drug content of nanoemulsion formulations

Sr. no.	Formulation code	Drug Content (%)
1	NE1	94.5±0.213
2	NE2	96.6±0.314
3	NE3	93.7±0.420
4	NE4	97.1±0.129
5	NE5	95.4±0.265
6	NE6	92.8±0.203
7	NE7	95.9±0.386

Values are expressed in mean ± SD, where n=3

Viscosity

Table 5: Rheology Study of nanoemulsion formulations

Sr. no.	Formulation code	Viscosity (cps)
1	NE1	10220±3.26
2	NE2	9829±4.10
3	NE3	10846±4.62
4	NE4	10425±2.39
5	NE5	9692±4.82
6	NE6	9487±3.96
7	NE7	9875±5.13

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Values are expressed in mean ± SD, where n=3

Droplet Size and Polydispersity Index

Table 6: Droplet size and polydispersity index

Formulation code	Particle Size(nm)	Polydispersity Index	Zeta potential (mV)
NE1	491.5	0.666	-3.26
NE2	488.8	0.534	-15.2
NE3	317.7	0.840	-3.85
NE4	55	0.999	-0.635
NE5	73.96	0.357	-1.58
NE6	144.6	1.000	-15.2
NE7	538.9	1.000	0.144

Thermodynamic stability studies

Table 7: Thermodynamic stability studies

Sr. no.	Formulation code	Heating- Cooling Cycle	Centrifugation	Freeze-thaw cycle
1	NE1		×	-
2	NE2			
3	NE3			
4	NE4			
5	NE5			
6	NE5	×	-	-
7	NE7	×	-	-

Cumulative drug release of nanoemulsion formulations

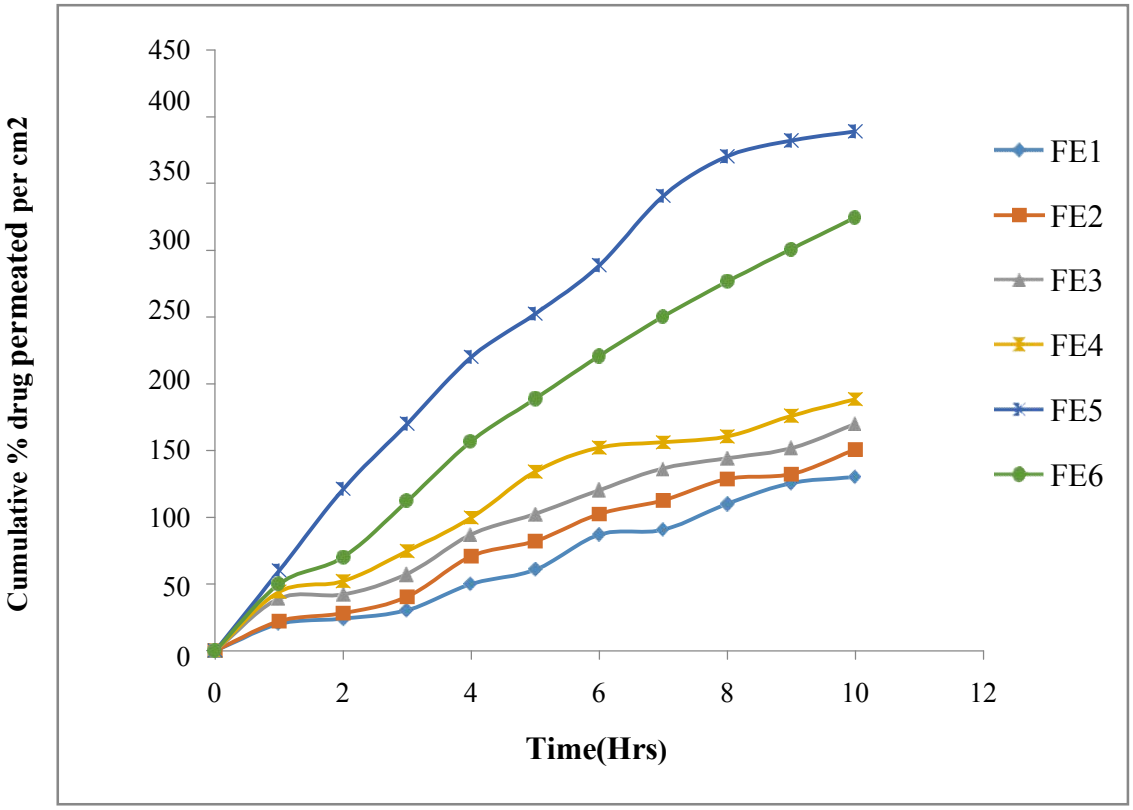

Figure 2: Cumulative drug release study of nanoemulsion formulations

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5.2 Evaluation of Gel

Table 8: Evaluation of gel

Sr. no.	Evaluation parameter	Results
1	pH	6.7±0.546
2	Viscosity	50880±0.422

Values are expressed in mean ± SD, where n=3

5.3 Evaluation of nanoemulgel

A. Physical Appearance

Table 9: Physical appearance

Sr. no	Formulation code	Colour and appearance	Phase separation	Grittiness	Homogeneity
1	NG	Pastle pale yellow	None	None	Homogeneous

Values are expressed in mean ± SD, where n=3

Antifungal activity study of nanoemulgel formulations

Table 10: Antifungal activity study of nanoemulgel formulations

Sr. No.	Formulation code	Name of the cultured Strain	Zone of inhibition (mm)
1	NG1		161±0.34
2	NG2		167±0.23
3	NG3	*Candida albicans*	188±0.42
4	NG4		196±0.22
5	NG5		143±0.13
6	NG6		128±0.26
7	NG7		158±0.22
8	Marketed formulation(Ketoconazole 2% cream)		195±0.11

Values are expressed in mean ± SD, where n=3

5.4 Evaluation Parameters of Nanoemulgel

Table 11: Evaluation parameters of nanoemulgels

Sr. No.	Formulation Code	pH	Viscosity (cps)	Spreadability (mm)	Extrudability (gm)	Flux (µg/cm^2/hr)
1	NG1	6.51	41980	4.87	0.61	30.2
2	NG2	6.55	45361	5.89	0.63	28.9
3	NG3	6.58	47820	6.12	0.58	24.4
4	NG4	6.54	48980	6.34	0.66	37.2
5	NG5	6.59	49813	6.43	0.54	32.6
6	NG6	6.48	46546	6.29	0.59	29.5
7	NG7	6.43	49310	6.84	0.63	30.1

Table 12: Evaluation of nanoemulgel as compared to marketed formulation (0.2% ketoconazole cream)

Sr. No.	Evaluation Parameters	Nanoemulgel	Marketed formulation
1	pH	6.54±0.432	6.34±0.546
2	Viscosity(cps)	48980±3.75	51876±7.62
3	Extrudability (gm)	0.66±0.126	0.54±0.214
4	Swelling Index	13±0.571	15±0.723
5	Spreadability (mm)	6.34 ± 0.765	4.88 ± 0.675
6	Drug Content (%)	93.03 ± 0.723%	90.2±0.672%
7	Zone of Inhibition (mm)	196±0.22	195±0.11

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8	Flux (µg/cm^2/hr)	37.23±0.733	16.35±0.52

Values are expressed in mean ± SD, where n=3

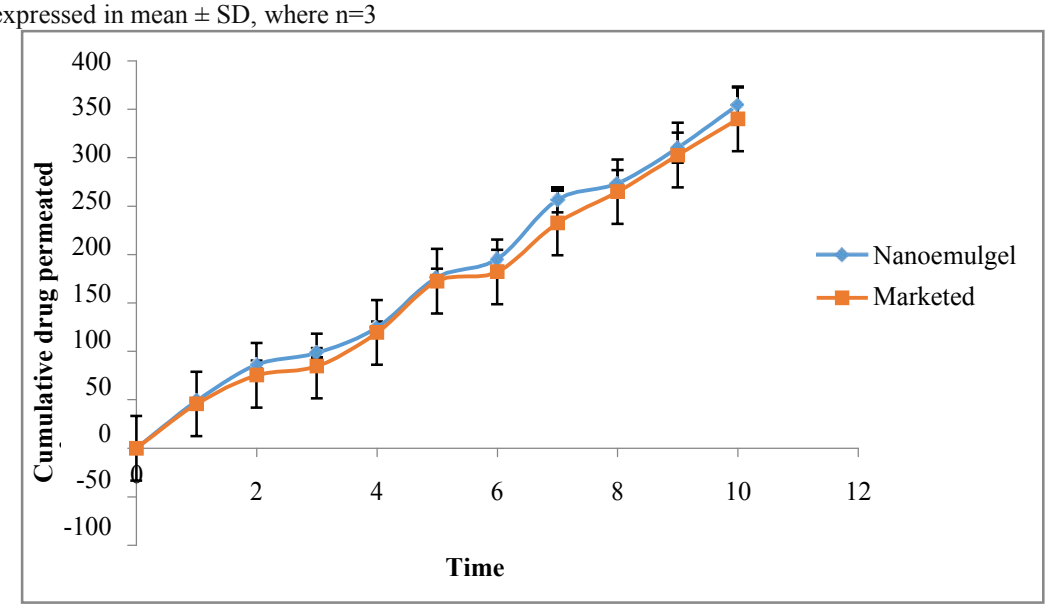

Figure 3: In-vitro skin permeation study of nanoemulgelvs marketed formulation (0.2% ketoconazole cream)

VI. CONCLUSION

In present research work, nanoemulsion of neem oil was formulated by spontaneous emulsification method and characterized for vesicle size, polydispersity index, zeta potential, drug content and viscosity. Droplet size of all the formulated nanoemulsions are found to be satisfactory in the nanoemulsion range. Polydispersity index indicates homogeneous population of nanoemulsion droplet in formulation.NE5 formulation showed highest transdermal flux across cellophane membrane. From the characterization study of nanoemulsions NE5 was selected as the optimized formulation whch was formulated into nanoemulgel by using carbopol-934 hydrogel and aloe-vera gel in diffeerent concentrations and antifungal activity is determined by petri-plate method and zone of inhibition was calculated. NEG4 shows maximum zone of inhibition which was then compared with marketed (0.2% ketoconazole cream) for various parameters i.e. viscosity, extrudability and drug content. It was observed that nanoemulgel formulation (37.23 ±0.733µg/cm^2/hr) show two fold increase in transdermal flux as compared to marketed (161.35 ± 0.52µg/cm^2/hr). From the results it can be concluded that nanoemulgel formulation is potential and effective transdermal drug delivery system for neem oil,tulsi oil and aloe-vera gel. indicates homogeneous population of nanoemulsion droplet in formulation.

NE5 formulation showed highest transdermal flux across cellophane membrane. From the characterization study of nanoemulsions NE5 was selected as the optimized formulation whch was formulated into nanoemulgel by using carbopol- 934 hydrogel and aloe-vera gel in diffeerent concentrations and antifungal activity is determined by petri-plate method and zone of inhibition was calculated. NEG4 shows maximum zone of inhibition which was then compared with marketed (0.2% ketoconazole cream) for various parameters i.e. viscosity, extrudability and drug content. It was observed that nanoemulgel formulation (37.23 ±0.733µg/cm^2/hr) show two fold increase in transdermal flux as compared to marketed (16.35 ± 0.52µg/cm^2/hr). From the results it can be concluded that nanoemulgel formulation is potential and effective transdermal drug delivery system for neem oil and aloe-vera gel. indicates homogeneous population of nanoemulsion droplet in formulation.

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