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Formulation, Development and Evaluation of Topical Ketoconazole Nanoemulgel.

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ABSTRACT
Over the years, the use of topical drugs has been a standard method for treating various skin disorders. A new generation of drug delivery system known as nanoemulgel combines the advantages of both nanoemulsion and gel. Its dual control release method allows for sustained and direct drug delivery to a target site. The present research aimed to develop a nanoemulgel that can deliver ketoconazole, a lipophilic drug, to the targeted area. The formulation was made using various excipients, such as propylene glycol, glycerine, water, methylparaben, ethanol, and oleic acid. The physical properties of the nanoemulgel were evaluated by conducting a comprehensive analysis that included a kinetic modelling study and a stability evaluation. The optimization batch F8 was selected for this study, which will allow the researchers to gain long-term insight into its effectiveness.
Keywords: *Nanoemulsion, gelling agent, Dermatophytes, Spreadability, Viscosity, Stability*

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INTRODUCTION:

Topical drug administration refers to a localized method of delivering drugs to easily accessible organs or areas of the human body. It is a primary approach in the field of topical drug delivery. This delivery system involves applying a drug-containing formulation directly to the skin to treat skin-related conditions like acne or skin manifestations of general diseases such as dermatophytosis. The main goal is to confine the pharmacological effects of the drug either to the surface of the skin or to the skin itself. Tropical drug delivery systems encompass a wide range of pharmaceutical dose types, including liquid preparations, semisolids, and solid and spray powders. Among the commonly used semisolid preparations for topical drug delivery are creams, gels, and ointments [1-3].

NANOEMULGEL

The specialized formulation combines nanoemulsion within a gel base, resulting in enhanced skin permeation. The integration of the nanoemulsion system into the gel matrix creates an effective drug reservoir, facilitating the drug release from the inner to outer phase and beyond. when applied to the skin, nanoemulgel releases oil droplets that effectively penetrate the skin's outer layer (stratum corneum) to deliver the drug precisely to the intended site. The combination of nanoemulsion and gel offers excellent adhesion properties and allows for high drug solubility in the oil phase. This high solubility leads to a significant concentration gradient towards the skin, thereby boosting drug penetration. Additionally, the use of nanoemulgel improves patient compliance due to its increased spreadability compared to conventional creams and ointments, and it reduces stickiness [5, 6].

Advantages of Nanoemulgel [19,20]:

a) The incorporation of oil droplets into the gel base enhances the stability of nanoemulsion, with the drug's affinity towards the oil phase playing a crucial role in determining its stability.
b) These formulations are particularly advantageous for delivering lipophilic and poorly water-soluble drugs, ultimately leading to improved patient compliance.
c) Nanoemulgel also enables the controlled release of drugs with shorter half-lives.
d) Nanoemulgel provides higher spreadability compared to conventional creams.
e) Moreover, nanoemulgel formulations are known for their non-toxic and non-irritating properties.

f) Overall, nanoemulgel enhances skin permeability and facilitates effective drug deposition.

MATERIAL AND METHODS

Ketoconazole was gifted by Aarti Drugs Limited, Mumbai. Oleic acid, tween 20, propylene glycol, Carbopol 934, methyl paraben, propyl paraben by Research -lab Fine Chem Industry, Mumbai. Analytical-grade chemicals were employed for all other chemicals

FORMULATION AND DEVELOPMENT OF NANOEMULGEL BY 3^2 FACTORIAL DESIGN

Table 01: Composition of Nanoemulgel formulation according to 3^2 full "factorial designs

Formulation Code	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Ingredients	%								
Ketoconazole (w/w)	2	2	2	2	2	2	2	2	2
Carbopol 934 (v/v)	0.25	0.5	0.75	0.25	0.5	0.75	0.25	0.5	0.75
Oleic acid (v/v)	5	5	5	5	5	5	5	5	5
Tween 20 (v/v)	2	2	2	2	2	2	2	2	2
Propylene glycol (v/v)	0.75	0.75	0.75	1	1	1	1.25	1.25	1.25
Methyl Paraben (w/w)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propyl Paraben(w/w)	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005"
Glycerin (v/v)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
TEA	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Water (v/v)	50	50	50	50	50	50	50	50	50

METHOD OF PREPARATION [9]

1) **Preparation of aqueous Phase A:** Distilled water was taken and the appropriate amount of Tween 20 was added.
2) **Preparation of oil phase B:** Oleic acid and propylene glycol were weighed and mixed under hot conditions. The combination was then added with precisely weighed ketoconazole. Then methyl paraben, propylparaben, and glycerin were also added.
3) **Incorporation of solution A into dispersion B:** Phases A and B have been thoroughly mixed using a high-pressure homogenizer while keeping RPM.
4) **Gel preparation:** Carbopol 934 was weighed and mixed with distilled water. TEA has been added to keep the desired pH of the solution. The mixture was uniformly stirred and the gel was then refrigerated for 24 hours.
5) **Preparation of Nanoemulgel:** Moreover, the incorporation of gel into nanoemulsion comprising 1 percent drug to get nanoemulgel

Fig 1. Nanoemulgel Formulation From batches F1 to F9

CHARACTERIZATION OF NANOEMULGEL:

Appearance:

The nanoemulgel formulations' appearance was assessed through visual examination, focusing on color, uniformity, consistency, and pH. To determine the pH, 1 percent aqueous solutions of the Gellified nanoemulsion have been tested using a pH meter.

Particle Size Analysis [9,10,12]:

The hydrodynamic particle size of the formulated nanoemulsion needs to be analyzed. Typically, the dynamic light scattering method is employed for measuring the particle size and distribution of nanoparticles in the nanoemulsion.

Zeta potential measurements [8,11,12]:

The nanoemulsion's zeta potential was determined with a Microtrac S3500. Clear disposable zeta cells were used to hold the samples, and the results were recorded. Prior to each test, the cuvettes have been cleaned with methanol and then rinsed with a sample to be determined, ensuring a fresh sample for each measurement.

Entrapment efficiency: [18]

Entrapment efficiency refers to the percentage of drug amount that is unentrapped within the nanoemulsion. The unentrapped drug was separated by centrifugation for 30 minutes at 15,000 RPM to determine the effectiveness of the entrapment. The resultant solution and liquid supernatant were both collected. The collected supernatants were appropriately diluted with "methanol" and examined with a UV-visible spectrophotometer at 243nm.

Nanoemulgel Evaluation:

Determination of pH [6,7]:

A digital pH meter was utilized to measure the formulation's pH. Before each measurement, the pH meter electrode was cleaned with distilled water, and then it was immersed into the formulation to record the value of pH. This process was performed three times for accuracy and consistency.

Viscosity [6,7]:

A Brookfield Viscometer ("RVDV-I Prime, Brookfield Engineering Laboratories, USA") equipped with spindle 63 was utilized to measure the formed batches' viscosity. The formulation was introduced to a beaker and then allowed to be settled for 30 minutes at a specified test temperature (25±1°C) before measuring the viscosity. The spindle has been carefully lowered vertically into the nanoemulgel center, ensuring it did not touch the bottom of the container. The spindle rotation speed was set at 50 rpm for 10 minutes, and a reading of viscosity was recorded.

Spreadability [4]:

To evaluate the spreadibility of gel formulations, 2 standard-sized glass slides have been chosen. The formulation of the gel to be tested was applied to one slide as well as another slide was placed on top, sandwiching the gel between them. The slides have been passed together to remove any trapped air, and the excess gel was wiped off. The setup was then placed on a stand, with the lower slide securely kept with a clamp while allowing the upper slide to move freely due to the weight tied to it. A 20gm weight has been carefully linked to the upper slide. The amount of time needed for the upper slide to fully separate from the bottom slide has been recorded. The spreadability has been determined with the following expression:

$$S = \frac{M.\ L}{T}$$

Here, M represents the weight tied to the upper slide, L denotes glass slides length , T presents the time required to separate slides

Study of Drug Content [6,7,11]:

It was conducted to ascertain the quantity of drug present in a specific amount of the formulation. A 10 mg sample of the formulation was taken and placed in a 10ml volumetric flask. Methanol was added to the flask, and the mixture was thoroughly shaken to guarantee proper dissolution. The volume was then made up to mark with methanol. The volumetric flask has been allowed to stand for 2 hours and then shaken within a shaker to ensure thorough mixing. The solution was then filtered via filter paper to remove any particulate matter, and the filtered mixture was measured for absorbance using a spectrophotometer at 243 nm.

In-vitro Drug release study [6,7,17]:

The release profile of the drug from the nanoemulgel was determined using a Franz diffusion cell. His cell is comprised of two chambers, namely the donor as well as receptor compartment, separated by a cellophane membrane, which acted as the diffusion membrane. The donor compartment, with an inner diameter of 24mm, was left open to the atmosphere on one end, while the receptor compartment allowed for sampling. Phosphate buffer solution (PBS) with a pH of 6.8 served as the diffusion medium. To start the experiment, 10 mg of drug-containing nanoemulgel (1gm) was positioned in the donor compartment, directly above the drug release membrane, and separated from the receptor compartment using a pre-soaked cellophane membrane (previously soaked in PBS for 24 hrs). The donor, as well as receptor compartments, have been then clamped together securely. The donor compartment position was adjusted so that the cellophane membrane lightly touched the diffusion medium. The entire setup was placed on a magnetic stirrer. 25 ml of PBS was introduced to the receptor compartment, which was held at a constant temperature of 37±0.5°C as well as stirred at a 50-rpm speed using a thermostatically controlled magnetic stirrer. 1 ml samples were taken at predefined intervals, diluted with a solvent to a total volume of 10 ml, and then tested for drug diffusion with a UV spectrophotometer at the drug's λ max absorption wavelength of 243 nm in comparison to a blank. To maintain the sink condition the receptor phase has been supplied with an identical amount of "phosphate buffer" each time a specimen was removed. This ensured consistent and reliable results throughout the experiment.

Accelerated stability studies of nanoemulgel [3, 14]:

Stability studies were conducted following established guidelines. The prepared nanoemulgels were filled into 5g aluminium collapsible tubes. These tubes were then subjected to storage conditions at 5°C, 25°C/60

percent RH, 30°C/65 percent RH, 40°C/75 percent RH, and 60±2°C for three months. Regular testing was performed at 15-day intervals during this period, and the samples were assessed for drug content, rheological properties, pH, and physical appearance.

RESULT

Pre-formulation study:

Organoleptic Properties of Drug:

Table 02: Organoleptic Properties of Ketoconazole

Drug	Properties	Observed Results
Ketoconazole	Odour	Slight Odour
	Color	White to Creamy yellow
	Appearance	Crystalline powder

Calibration curve of Ketoconazole in Phosphate buffer 6.8 pH:

- **Stock solution:** The volume of 10ml of solvent ("Phosphate buffer 6.8 pH") was added to 10mg of ketoconazole that had been dissolved in less than 1ml of methanol to generate 1000µg per ml.
- **Solution A:** One milliliter of the sample was taken from the stock solution, diluted with solvent up to ten milliliters, and then concentrated to get 100 µg per ml.
- **Dilutions:** To determine the absorbances at 243 nm, 0.5, 1, 1.5, 2, and 2.5 ml of solution A were taken out and diluted with solvent up to 10 ml to produce 5, 10, 15, 20, and 25 ppm.

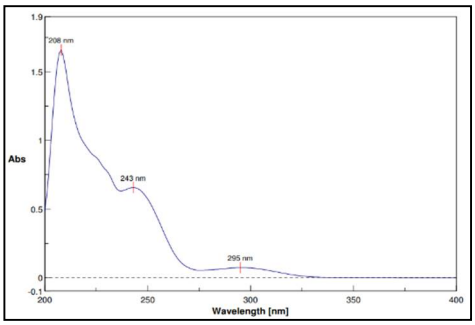
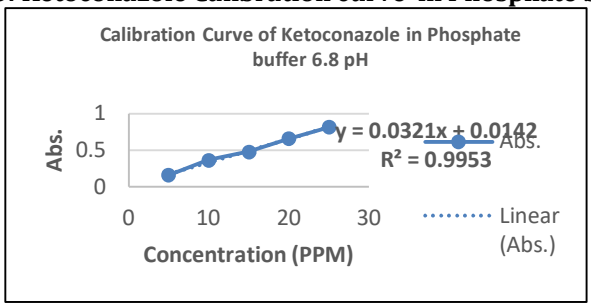


Figure 2: 20 PPM Ketoconazole in Phosphate buffer 6.8 pH

Table 5: calibration curve for ketoconazole

"Sr.no.	Concentration (ppm)	Absorbance
1.	5	0.1625
2.	10	0.3625
3.	15	0.4778
4.	20	0.6564
5.	25	0.8175"

Figure 3: Ketoconazole Calibration curve in Phosphate buffer 6.8 pH



Evaluation of Nanoemulsion:

Entrapment Efficiency:

Among the tested formulations, the maximum drug entrapment efficiency was recorded at 95.6%, while the minimum was found to be 67.7%, as depicted in the figure. Notably, the optimized batch (F8) exhibited the highest drug entrapment efficiency.

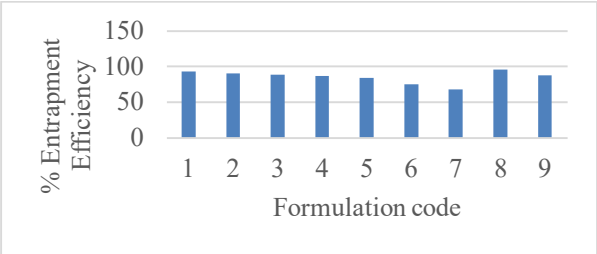


Figure 4: Entrapment efficiency of F1 to F9

Table 06: Efficiency of entrapment for formulations "F1 to F9.

Sr. No.	Formulation code	% Entrapment Efficiency
1	**F1**	93.1
2	**F2**	90.5
3	**F3**	88.3
4	**F4**	86.2
5	**F5**	84.1
6	**F6**	75.0
7	**F7**	67.7
8	**F8**	95.6
9	**F9**	87.16"

Size of particle and Zeta potential analysis:

The nanoemulsion's particle size from batches F1 to F2 was ranging from 102.2 nm to 972.0 nm. The nanoemulsion of the optimized batch exhibited a particle size of 102 nm. The nanoemulsion's polydispersity index of the optimized batch (F8) is 0.119.

Table 07: Polydispersity index and size distribution

Formulation code	Size of the particle (nm)	PDI
F1	972.0	0.532
F2	687.0	0.432
F3	578.0	0.651
F4	409.0	0.455
F5	289.0	0.213
F6	204.4	0.631
F7	144.5	0.365
F8	102.2	0.119
F9	243.0	0.612

Zeta Potential:

Zeta potential is a crucial indicator of colloidal dispersion's stability under stress testing conditions, as per ICH standards for stability analyses of pharmaceutical formulations. In this case, the zeta potential was impacted by the size of the particle, and the lowest particle size in the nano range showed a value of nanoemulsion of optimized batch and optimized nanoemulgel formulation was found to be -13.9mV and -14.5mV respectively, indicating thermodynamic instability of the dispersion.

Scanning Electron Microscopy:

Figure 3 indicates the SEM ("Scanning Electron Microscopy") images of the nanoemulsion. The nanoemulsion appeared to have a spherical shape, and its size was observed to be below the mm range. However, the SEM micrograph also showed some agglomeration of the nanoemulsion, which could be attributed to water evaporation from the formulation during the preparation of the sample before SEM analysis.

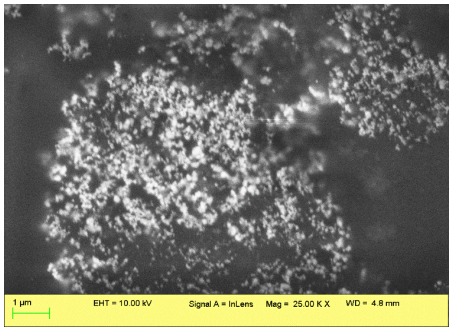


Fig 5: SEM of nanoemulsion

NANOEMULGEL EVALUATION:

1. Physical Appearance

Ketoconazole Nanoemulgel formulation from F1 to F9 batches is white in appearance. F1 to F9 Formulations are homogenous and consistent.

2. Determination of pH

Table 8: Determination of pH

Formulation	Observed pH (± SD)
"F1	6.75±0.045
F2	6.56±0.035
F3	6.37±0.036
F4	6.42±0.020
F5	6.73±0.040
F6	6.62±0.020
F7	6.55±0.015
F8	6.42±0.026
F9	6.74±0.026"

3. Spreadability test:

Table 9: Spreadability test

"Sr. No.	Formulation code	Spreadability (g.cm per sec) ± S.D.
1	F1	15.25 ± 0.079
2	F2	14.09 ± 0.030
3	F3	16.63 ± 0.025
4	F4	13.43 ± 0.020
5	F5	14.55 ± 0.025
6	F6	15.22 ± 0.020
7	F7	16.66 ± 0.036
8	F8	17.52 ± 0.025
9	F9	15.90 ± 0.025"

4. Determination of viscosity:

Table 10: Viscosity

Batches	Viscosity (cP)
F1	3841
F2	3749
F3	4632
F4	4702
F5	4138
F6	5512
F7	5689
F8	6140
F9	5099

5. Size of particle and PDI Measurement:

Table 11: Size of particle and PDI

Formulation code	Size of the particle (nm)	PDI
F1	564.2	0.542
F2	245.5	0.614
F3	757.1	0.245
F4	441.1	0.365
F5	662.2	0.475
F6	322.3	0.389
F7	268.4	0.512
F8	146.2	0.218
F9	384.2	0.568

6. Determination of Drug content:

It was conducted on all the formulated batches, and the outcomes ranged from 94.42% to 99.13%. These values are within the acceptable limit of 98.0% - 102.0% as stated in the literature.

The corresponding data has been presented in Table 07.

Table 12: Determination of Drug content

"Sr. No.	Formulation code	Drug content (%) ± SD
1	F1	95.10 ± 0.021
2	F2	99.00 ± 0.032
3	F3	96.31 ± 0.015
4	F4	97.23 ± 0.041
5	F5	98.89 ± 0.032
6	F6	94.42 ± 0.016
7	F7	95.13 ± 0.015
8	F8	99.13 ± 0.011
9	F9	96.10 ± 0.010"

7. Determination of Drug release (Drug diffusion):

Table 13: % Drug diffusion

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	11.33	12.88	10.40	12.20	13.23	13.26	12.65	11.78	11.23
2	19.91	24.21	19.10	21.43	23.91	21.72	23.98	22.67	20.88
3	38.11	37.27	35.41	38.98	41.80	38.99	40.43	39.67	38.12
4	50.22	50.12	48.47	55.01	56.11	54.31	53.12	51.77	51.22
5	61.04	63.33	59.91	67.13	67.52	62.26	66.32	64.77	64.78
6	72.65	74.36	69.10	78.98	81.14	75.26	77.35	77.34	79.55
7	84.12	84.23	81.53	87.19	91.92	85.23	87.22	89.59	88.66
8	95.98	92.34	91.02	97.95	96.43	94.35	97.95	99.13	95.26

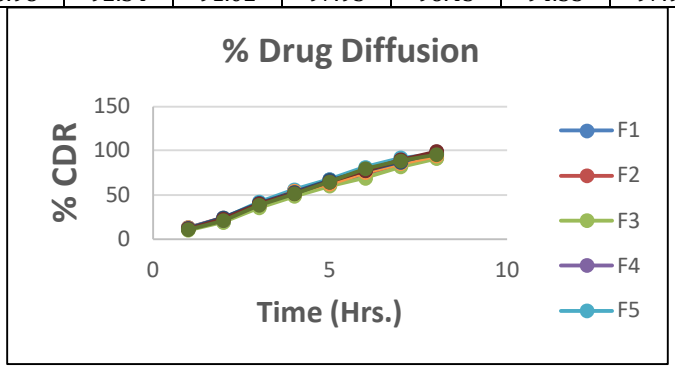


Fig 6: % CDR vs Time for drug diffusion

8. Stability Study

Table 14: Data for the F8 formulation's stability study in accelerated conditions (40°C ± 2°C, 75 percent RH ± 5 percent RH)

Sr. No	Observations	Before Accelerated Stability Testing	During study Third month
1	**Visual appearance**	Translucent	Translucent
2	**pH**	6.60±0.025	6.60±0.008
3	**% Drug content**	99.13 ± 0.011	98.89±0.010
4	**Viscosity (50rpm)**	6140cP	5855cP

DISCUSSION AND CONCLUSION

To meet the desired criteria, drug-loaded nanoemulgel formulations were prepared. The process involved the preparation of nanoemulsion through high-speed homogenization, and various parameters were studied. Issues related to nanoemulsion stability were addressed by formulating drug-loaded nanoemulgel using 3^2 full factorial designs. The independent factors chosen at three different levels were Carbopol 934 (%) and propylene glycol. Before creating these formulations, preformulation testing was conducted to characterize the drug and analyze its purity and compatibility. Several tests, including FTIR analysis, UV spectroscopy studies, solubility testing, melting point determination, and organoleptic properties were carried out on ketoconazole, and drug samples procured have been observed to be consistent with excipients utilized in the formulation. For optimization, Design Expert 7.0 software was employed.

Among all the formulations, the ketoconazole-loaded nanoemulgel prepared with tween 20 and oleic acid demonstrated better drug diffusion. The nanoemulsion of the optimized batch and optimized nanoemulgel formulation exhibited a particle size ranging from 1-300 nm and was found to be 102.2 nm and 146.2 nm respectively, indicating the potential for increased drug penetration through biological membranes. The zeta potential of the nanoemulsion of the optimized batch and optimized nanoemulgel formulation was measured at -13.9mV and -14.5mV respectively, indicating thermodynamic instability of the dispersion.

Scanning electron microscopy revealed that the nanoemulsion had a spherical shape and a size below the micrometer range. Decreasing viscosity values increased spreadability values, indicating the suitability of the formulation for external use. The drug content percentage ranged from 94.42% to 99.13%, ensuring uniformity of content. The formulation's drug release exhibited zero-order kinetic behaviour. The optimized formulation displayed a zone of inhibition measuring 24mm for antifungal activity. Accelerated stability studies indicated no significant changes in the optimized formulation (F8) over 3 months.

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