Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Formulation, Development and Evaluation of Ciclopirox Olamine Nanogel for the Treatment of Cutaneous Candidiasis

Nivrutti A. Kotsulwar[1], Dr. Shivappa N. Nagoba[1*], Rachita B. Malshette[1], Gaurav G. Girwalkar[2], Anjali R. Alande[1]

[1]Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Latur.

[2]Department of Pharmaceutics, Shivlingeshwar college of pharmacy, Almala, Latur.

[*]**Corresponding author:**

Prof. Dr. Nagoba Shivappa N.

M. Pharm, Ph.D., Professor and Head, Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree), Kava Road, Latur - 413512, Dist. Latur. (MS)

Email ID: nagobashivraj@gmail.com / Email ID: nshivraj11@rediffmail.com

Cite this paper as: Nivrutti A. Kotsulwar, Dr. Shivappa N. Nagoba, Rachita B. Malshette, Gaurav G. Girwalkar, Anjali R. Alande, (2025) Formulation, Development and Evaluation of Ciclopirox Olamine Nanogel for the Treatment of Cutaneous Candidiasis. *Journal of Neonatal Surgery*, 14 (32s), 7848-7860.

ABSTRACT

Background: Cutaneous candidiasis is a superficial fungal infection predominantly caused by *Candida albicans*, often affecting moist skin areas. To overcome limitations of conventional topical antifungal treatments, such as poor skin penetration and frequent application, this study aimed to formulate, develop, and evaluate a nanogel containing Ciclopirox Olamine for improved topical delivery.

Methods: Nanogels (F1–F4) were prepared using the emulsion-solvent diffusion method, incorporating Carbopol 934 as gelling agent, PEG-600 and propylene glycol as co-solvents, Tween 80 as surfactant, and triethanolamine as a pH adjuster.

Results: All formulations were evaluated for physicochemical properties. F4 demonstrated optimal performance: pH 5.67, spreadability 6.9 g·cm/s, viscosity 22200 cps, drug content 92.93%, and entrapment efficiency 92.1%. The drug and excipient compatibility was verified by FTIR.. UV analysis showed a λmax at 256 nm with linearity between 2–8 µg/mL. SEM revealed spherical particles; DLS showed Z-average particle size of 115.8 nm with PDI 0.828; zeta potential was -19.7 mV, indicating moderate stability. In vitro drug diffusion studies showed maximum drug release for F4 at 93.68% over 8 hours. Antifungal efficacy via well diffusion showed a 17 mm zone of inhibition for F4 against *Candida albicans*, compared to 24 mm for the standard (Miconazole). MIC was determined at 31.2 µg/mL, and MFC analysis confirmed effective fungal eradication at higher concentrations.

Conclusion: The optimized nanogel (F4) thus offers improved penetration, sustained release, effective antifungal action, and better patient compliance, making it a promising candidate for the topical treatment of cutaneous candidiasis.

Keywords: *Ciclopirox Olamine, Nanogel, Cutaneous Candidiasis, Antifungal, Topical Gel, Entrapment Efficiency, Diffusion, Particle Size, Zeta Potential, MIC, MFC.*

1. INTRODUCTION

Nanogels are small, three-dimensional hydrogel structures composed of crosslinked polymers that absorb water(1). They can be customized in terms of size, shape, charge, and biodegradability, and they have the capacity to store huge volumes of water without dissolving. Nanogels can be created in a variety of shapes and architectures, such as core-shell kinds, although they are usually spherical. Nanogels are biocompatible and highly effective for drug and diagnostic delivery because of their hydrophilic nature. They allow for targeted distribution, shield their contents from deterioration, and release medications in reaction to temperature or pH changes(2). They can transport both big and small molecules, such as proteins, DNA, and nanoparticles, thanks to their adaptable structure. Nanogels can be administered orally, nasally, pulmonaryly, parenterally, or intraocularly, and they are useful for drug administration, particularly in gene therapy. In biomedical applications, their clever design allows for excellent therapeutic efficiency and regulated release(3).

Ciclopirox olamine is a synthetic, broad-spectrum antifungal agent used primarily for treating skin, nail, and mucosal fungal infections. It is the ethanolamine salt of ciclopirox, improving its solubility and stability. It acts by chelating metal ions (like Fe^{3+}), inhibiting enzymes critical to fungal metabolism, leading to cell death. In addition to antifungal effects, it also has antibacterial and anti-inflammatory properties. It is effective against dermatophytes, yeasts (e.g., *Candida*, *Malassezia*), molds, and some bacteria like *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Ciclopirox olamine is typically applied topically (creams, gels, nail lacquers, shampoos) and has minimal systemic absorption[4]. Its common uses include tinea infections, seborrheic dermatitis, and onychomycosis. Oral administration is unsuccessful because of limited solubility and permeability (BCS Class IV). However, advanced formulations like nanogels can enhance skin penetration, improve drug bioavailability, reduce dosing frequency, and increase patient adherence[5].

Candida albicans is the primary cause of candidiasis, a fungal infection that affects the mouth, skin, nails, vagina, lungs, and in extreme cases, can result in systemic problems including meningitis or sepsis. The most frequent cause is Candida albicans, which is followed by species such as Candida glabrata, Candida krusei, and the less common Candida kefyr[6]. When the immune system is compromised, the infection frequently happens. Pregnancy, obesity, diabetes, long-term illnesses, immunosuppression, poor personal cleanliness, and environmental variables are risk factors. Both sexes are susceptible to candidiasis, which is more prevalent in young children and the elderly[7].

2. MATERIALS

Ciclopirox Olamine obtained from labware chemicals, Nashik. Carbopol 934, Tween 80 from HI media Laboratories Pvt. Ltd, Mumbai, Propylene Glycol from COSMO Chem, Pune, Polyethylene Glycol 600 (PEG) from COSMO Chem, Pune, Methyl paraben from COSMO Chem, Pune, Triethanolamine from COSMO Chem, Pune,

3. METHODS

Emulsion – Solvent Diffusion Method

Accurately weighed quantity of drug dissolve in PEG along with Propylene Glycol, add Tween 80 to help blend the mixture later with water. The aqueous phase prepared using Carbopol-934 dissolve in water, add Methylparaben as stabilizer. An ultrasonicator was used to sonicate the drug-containing phase. The drug containing phase was sonicated on ultra-sonicator. The drug phase was added drop by drop into aqueous phase while mixing at high speed around 6000 rpm for 30 minutes to form emulsion. Triethanolamine is added to adjust the pH, stir the mixture on 8000 rpm for 1-hour continuous stirring to form nanogel. The prepared nanogel was further evaluated[8,9].

Table no:1 Formulation Table

Batch / Ingredients	F1	F2	F3	F4
API	50mg	50mg	50mg	50mg
Carbopol 934	0.5gm	0.75gm	1gm	1.25gm
Polyethylene Glycol (600)	0.45ml	0.45ml	0.45ml	0.45ml
Tween 80	0.9ml	0.7ml	0.5ml	0.3ml
Propylene Glycol	5ml	5ml	5ml	5ml
Methyl Paraben	0.1 gm	0.1 gm	0.1 gm	0.1 gm
Water	Up to 50ml	Up to 50ml	Up to 50ml	Up to 50ml
Triethanolamine	QS	QS	QS	QS

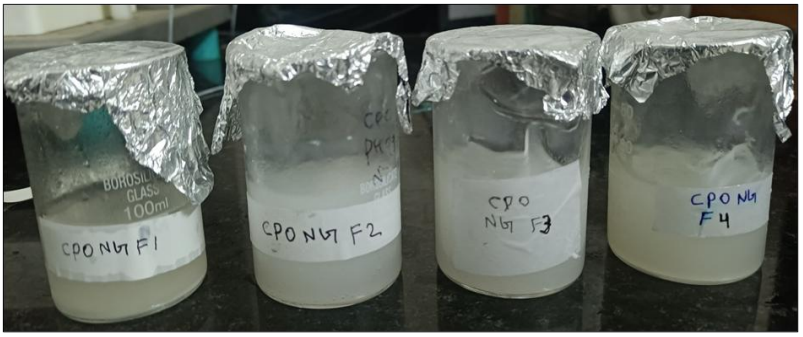

Fig. no. 1 Formulation of Nanogel

4. EVALUATION OF NANOGEL

Appearance: The formulations were examined visually to assess their appearance and ensure clarity, which is considered a key quality parameter.

pH: The pH of the developed topical formulations, ideally maintained between 5-5.67 for skin compatibility, was measured using a digital pH meter.

Homogeneity: The homogeneity of the gel determined by visual inspection after gels have been set in the container for the presence of any aggregates, any particles present in formulation.

% Drug Content: To determine the drug content, 1 gm of nanogel was dispersed in 10ml of methanol, the sample was filtered. The supernatant layer was diluted with methanol and sample was analysed by UV spectroscopy at 231 nm. The methanol was used as a blank solution.

% Drug loading = Amount of entrapped drug/Total weight ×100

Viscosity: The viscosity of formulated nanogel of all batches were measured by using Brookfield viscometer, the reading was noted at 60 rpm using spindle no. 6 and viscosity was measured three times and average viscosity was noted[10].

Spreadability: A wooden block and pulley mechanism was employed in a spreadability apparatus. One gram of gel was placed between two glass slides of identical dimensions. After placing a 1 kg weight for five minutes to ensure uniform spreading and removal of excess gel, the upper slide was pulled using a string. The time taken for the slide to move a fixed distance was recorded. A shorter time indicates better spreadability.

$S = (M \times L) / T$ is the formula for spreadability.

Where S stands for spreadability, M for mass applied (upper slide weight), L for distance traveled by the upper slide (in centimeters), and T for time spent (in seconds).

In vitro Diffusion Study: Diffusion tests were performed on the developed nanogels in a Franz diffusion cell using a cellophane membrane. A 1g sample was introduced in a cellophane membrane, and 100 ml of pH 7.4 phosphate buffer was used as the diffusion medium for the diffusion studies, which were conducted at 37± 1º. At 1,2, 3…, 8hr, 5ml of each sample were taken out and replaced with an equivalent volume of fresh diffusion media. The sample were then examined using UV spectroscopy to determine the drug content, using phosphate buffer as a blank at 231 nm[11].

Particle size analysis and zeta potential: Particle size and zeta potential of selected formulations were analysed using dynamic light scattering. Measurements were done using a zetasizer nano series after diluting the samples in double-distilled water. The system tracked droplet motion based on Brownian movement.

SEM- Scanning Electron Microscopy: Scanning Electron Microscopy, or SEM, was utilized to examine the nanogels' surface morphology. Samples were placed on brass stubs using double-sided adhesive tape and vacuum-coated with platinum for 120 seconds at 15 kV. Imaging was performed at temperatures ranging from 25°C to 30°C under a nitrogen atmosphere at a flow rate of 100 mL/min.

X-ray Diffraction (XRD) Analysis: To assess the physical condition of ciclopirox oleamine in both its pure and nanogel forms, XRD analysis was performed**.** A Shimadzu XRD-7000 diffractometer with Cu–Kα radiation (λ = 1.5406 Å) was used, scanning from 5° to 50° 2θ at a rate of 5°/min. Pure drug showed sharp peaks, confirming crystallinity. In contrast, the nanogel displayed reduced or absent peaks, indicating the drug was converted to an amorphous or dispersed form within the gel matrix[12].

Differential Scanning Calorimetry (DSC): DSC was used to assess the thermal properties of Ciclopirox Olamine and its nanogel. About 2–5 mg of each sample was sealed in aluminium pans and heated from 30 °C to 300 °C at 10 °C/min under nitrogen. The pure drug showed a sharp melting peak, indicating crystallinity, while the nanogel showed a reduced or absent peak, suggesting an amorphous or dispersed state.

Stability Study: Stability studies were conducted as per ICH guidelines. The formulations were kept in a chamber at 40°C ± 2°C and 75% ± 5% relative humidity after being packed in stability containers. Samples were analysed at 0, 1, 2, and 3 months for changes in physical characteristics, drug content, and in-vitro drug diffusion[13].

Well diffusion method: The well diffusion method is a qualitative assay used to assess the antifungal potential of a substance. Agar plates inoculated with a fungal strain (e.g., *Candida albicans*) are prepared, and wells are filled with the test compound. After incubation, the compound diffuses into the agar, and antifungal activity is indicated by a clear zone of inhibition around the well. This zone's size indicates how effective the agent is. This method is widely used for preliminary antifungal screening.

Minimum Inhibitory Concentration (MIC): The Minimum Inhibitory Concentration (MIC) refers to the smallest concentration of an antimicrobial substance required to prevent visible growth of a microorganism after incubation. It provides a quantitative measure of antimicrobial effectiveness and is commonly determined through broth or agar dilution

techniques. MIC values, typically expressed in µg/mL, are essential for assessing microbial sensitivity and guiding appropriate drug dosing in clinical and research settings.

The percentage of Inhibition was calculated by following formula:

% of Inhibition = Control-Test/Control*100

Minimum Fungicidal Concentration (MFC): The Minimum Fungicidal Concentration (MFC) is the lowest concentration of an antifungal agent that kills a fungal organism, rather than just inhibiting its growth. It is determined by subculturing from MIC test samples onto fresh media. MFC is expressed in µg/mL and is used to evaluate the fungicidal strength of a compound[14].

5. RESULT AND DISCUSSION

Organoleptic study:

Table No.2: Organoleptic Property

Sr no	Parameters	Ciclopirox Olamine
1	Nature	Crystaline
2	Appearance	White to off-white
3	Odour	Odorless

Solubility Profile

Table No.3: Solubility study

Sr no	Solvents	Solubility results
1	Methanol	Soluble
2	Ethanol	Soluble
3	Water	Partially soluble
4	DMSO	Soluble
5	Acetone	Partially soluble

Melting point: The melting point of ciclopirox olamine was found to be between 130 and 139°C using a glass capillary technique.

FTIR spectrum interpretation:

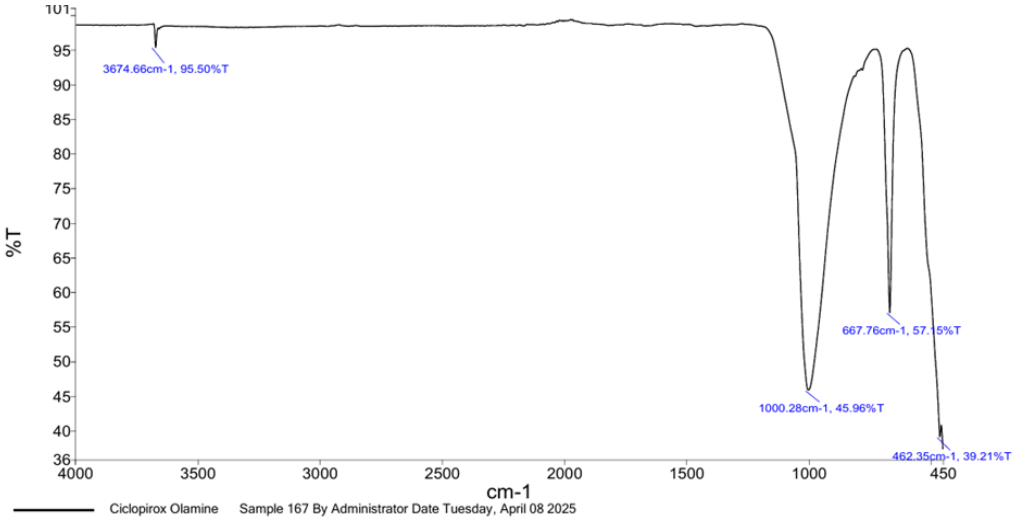

Fig.No.2 FTIR of ciclopirox olamine (API)

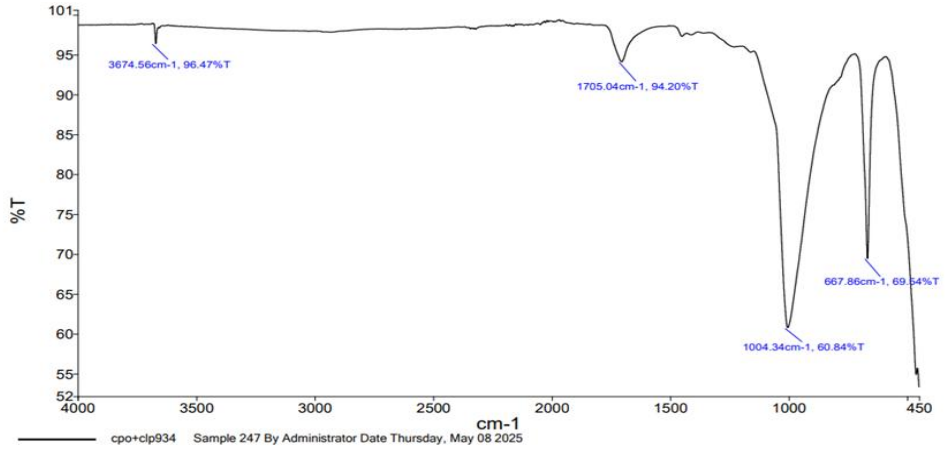

Fig.No.3 FTIR ciclopirox olamine & Carbopol 934

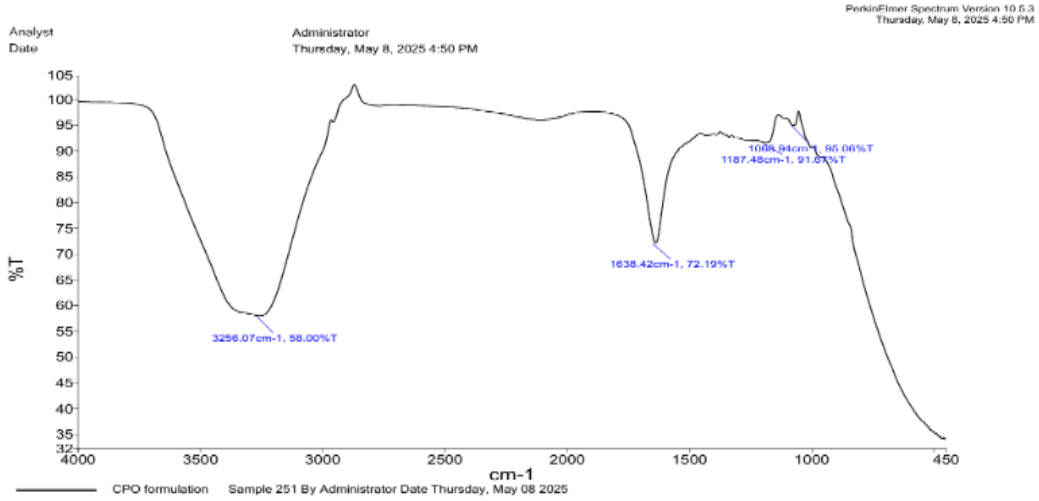

Fig.No.4 FTIR of formulation

Wavelength interpretation:

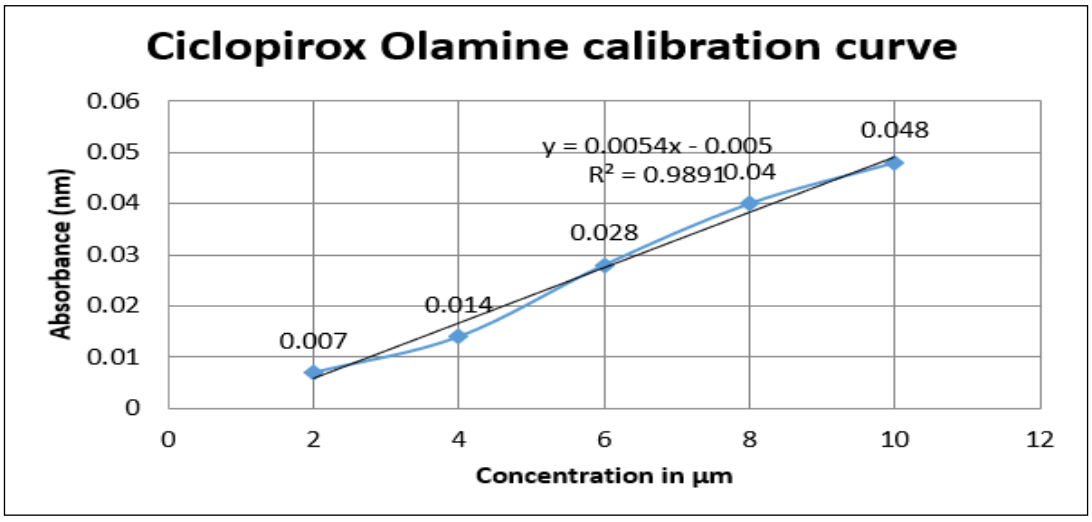

Fig.No.5 Calibration curve in methanol

Table No.4 Absorbance of ciclopirox olamine

Sr No	Conc.µg/ml	Absorbance at 231nm
1	2	0.07
2	4	0.014
3	6	0.028
4	8	0.040
5	10	0.048

Evaluation of Nanogel

Table.No.5 Evaluation Parameters of nanogel

Sr No	Formulation code	Appearance	Viscosity (CPS)	pH	Spreadability (g/sec)
1	NG1	White to off-white gel	4500	5.0	5.5
2	NG2	White to off-white gel	5000	5.64	5.2
3	NG3	White to off-white gel	6500	5.62	6.8
4	NG4	White to off-white gel	8480	5.67	6.9

Microscopic Study

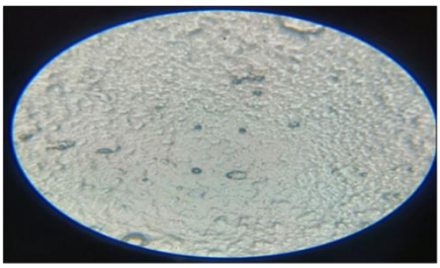

Fig.No.6Image A

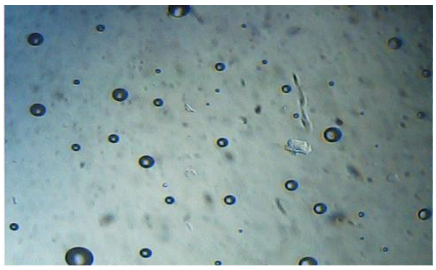

Fig.No.7 Image B

DSC (Differential Scanning Colorimetry): A melting or phase transition is probably the cause of the noticeable exothermic peak in the DSC thermogram of nanogel F4 at about 121°C.

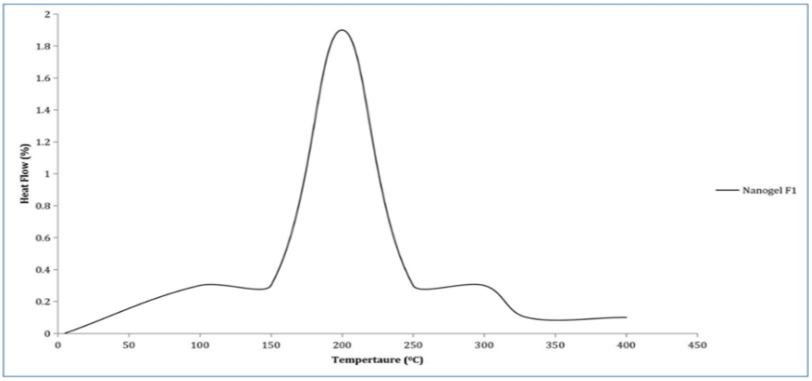

Fig. No.8 DSC graph

XRD (X-ray diffraction): The XRD pattern of nanogel F4 exhibit a broad hump without sharp diffraction peaks, indicating the amorphous nature of the formulation.

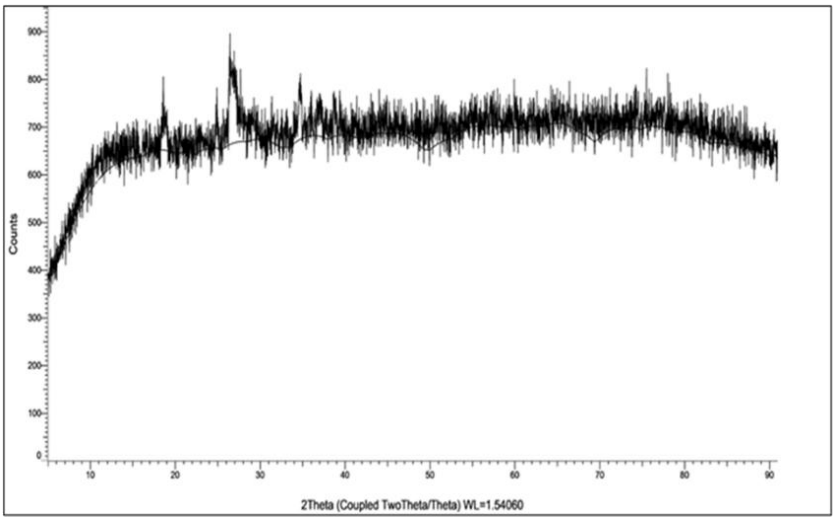

Fig.No.9 XRD graph

Scanning Electron Microscopy: The nanogel particles in batch F4 are mostly nano-to-micro-sized, irregular or slightly spherical, and form clusters. The surface seems porous, which is beneficial for drug delivery. Drug distribution benefits from the surface's apparent porosity.

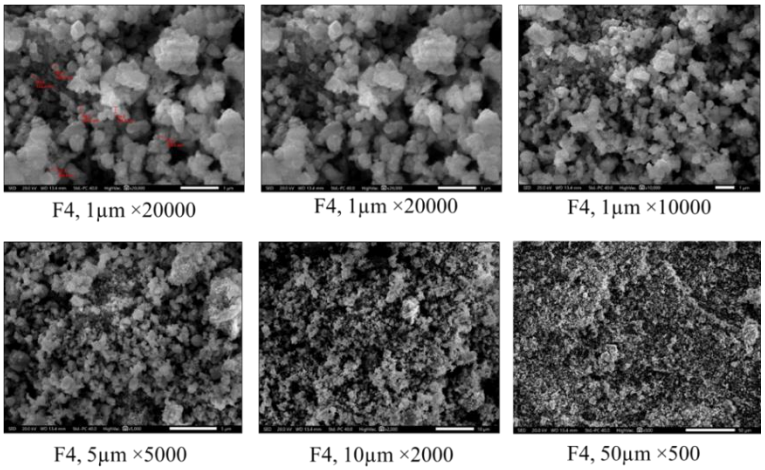

Fig.No.10 Scanning electron microscopy

Zeta potential: Nanogel F4 was found to have a zeta potential of -19.7 mV.

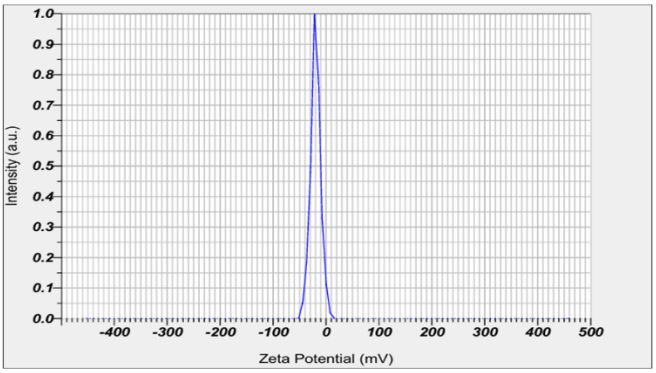

Fig. No.11. Zeta potential

Particle Size Analysis: The Z-average particle size was found to be 115.8nm, while the peak analysis revealed a mean diameter of 256.1nm.

The polydispersity Index (PDI) was recorded as 0.828.

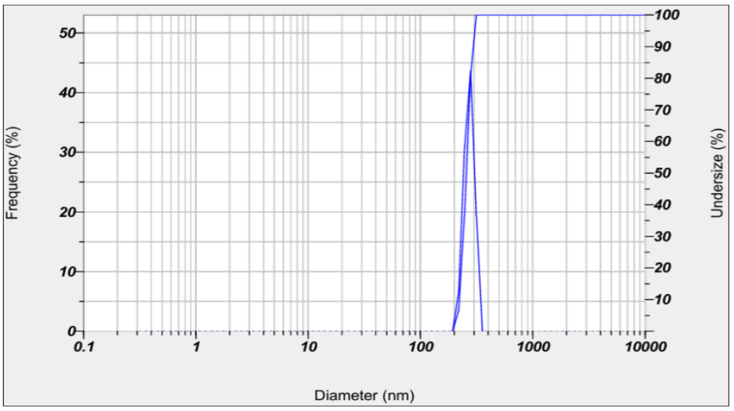

Fig.No.11. Particle size analysis

% Drug Content

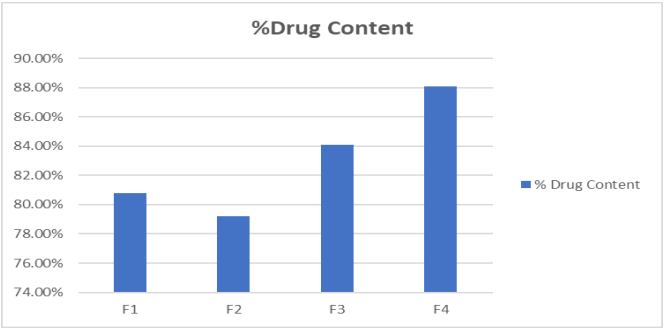

Fig.No.12. Drug Content

Table.No.6. Determination of drug content

Batch	F1	F2	F3	F4
% Drug Content	80.79%	79.20%	84.10%	88.1%

% Entrapment Efficiency

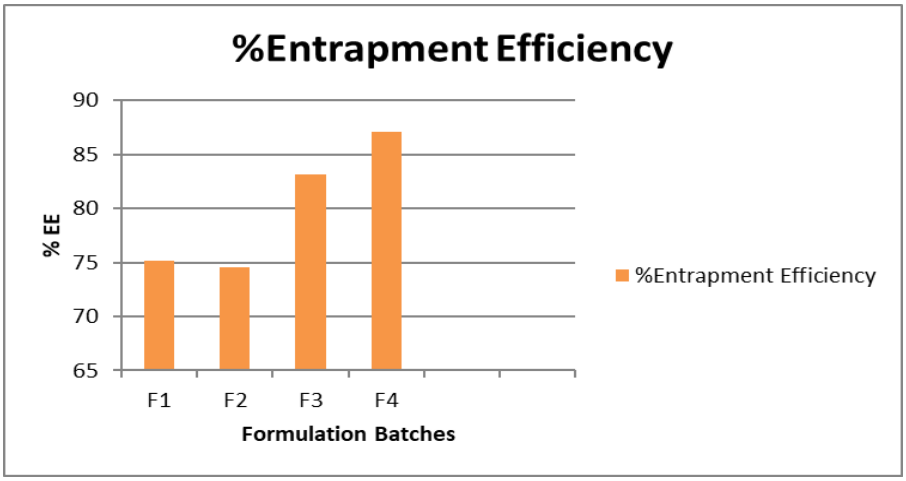

Fig.No.13. Entrapment Efficiency

Table No. 7 Determination of entrapment efficiency

Batch	F1	F2	F3	F4
% Entrapment Efficiency	75.15%	74.55%	83.1%	87.1%

***In-Vitro* drug diffusion**

Table No. 8 In-vitro diffusion of nanogel

Time/Hr	F1	F2	F3	F4
0	0	0	0	0
1	7.89	8.77	7.19	8.42
2	15.96	17.19	15.08	17.71
3	27.89	29.12	26.66	28.77
4	42.80	44.73	41.05	44.03
5	59.82	61.92	57.54	60.87
6	75.96	75.24	73.68	77.36
7	79.78	78.08	83.50	87.19
8	82.92	80.38	85.61	89.68

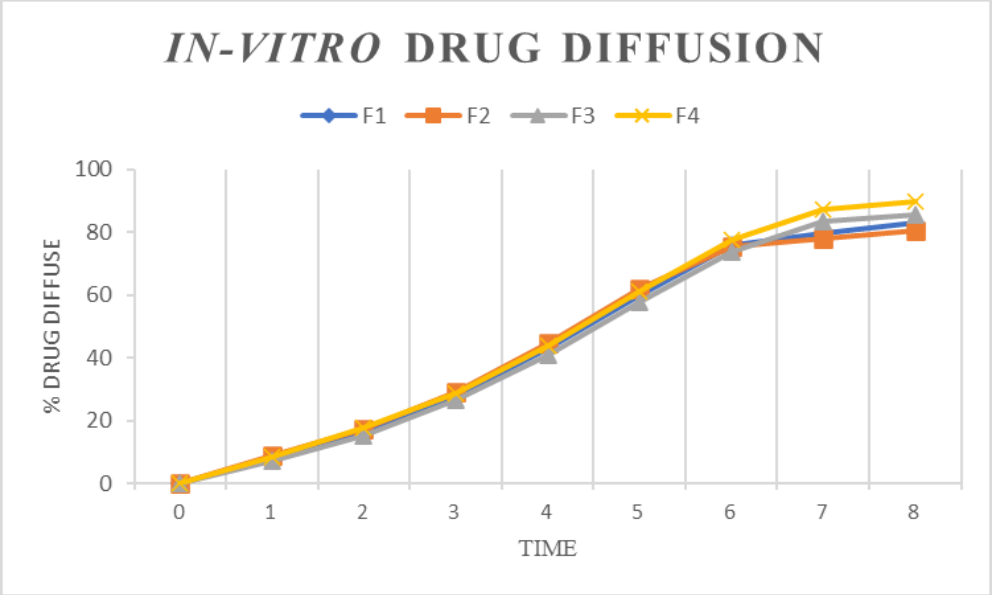

Fig No. 14 In vitro drug diffusion of nanogel

Stability study: The optimized formulation F4 was subjected to a stability testing for the period of 90 days as per ICH norms temperature of 40℃±2℃ and 75%±5%RH. The nanogel retained its initial appearance, exhibiting no changes in colour, texture, or phase separation. It remained white to off-white colour, indicating that the formulation was physically stable under conditions.

Table No. 9 Results of stability study of nanogel

After storage (40°C±2°C and 75%±5%RH)

Sr No	Number of month	Physical Appearance	pH	*In-vitro* Drug diffusion%
1	Initial	White to off white	5.67	89.68%
2	1 month	No change		88.92%
3	2 month	No change		88.56%
4	3 month	No change		87.61%

Antifungal assay: The zone of inhibition against fungal strains C was measured in order to assess Nanogel F4's antifungal profile. *albicans* (ATCC 10231) via well diffusion method. The compounds Nanogel F4 exhibited good activity as compared to the standard Miconazole

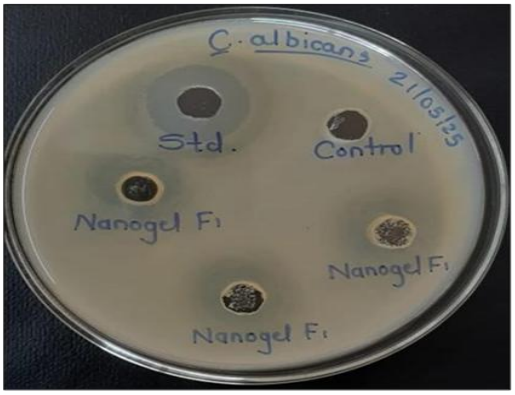

Fig No.15 Antifungal assay

Table No.10 Result of antifungal assay

Sr No	Samples	Zone in diameter (mm)
1	Control	00
2	Standard (Miconazole)	24
3	Nanogel F4	17

Minimum Fungicidal Concentration: Top section Standard drug (Miconazole). Bottom section Nanogel F4

Fig No 16 MFC by using 96 well plate method against *C. albicans*

The section where fungal growth disappears completely indicates the MFC- the lowest dose needed to kill the fungi

Fig No.17 MFC test

Minimum Inhibitory Concentration: Growth control (no drug) shows the highest turbidity (1.603), means full fungal growth as the concentration increases, turbidity decreases, indicating reduced fungal growth. Nanogel F4 shows 76.16% growth inhibition at the highest concentration (1000µg/ml). At 31.2 µg/ml, Nanogel F4 already starts inhibiting fungal growth (6.86% inhibition)

Table No.11 Effects of compound against *C. albicans*

Sr. No	Sample Code	Conc Entra Tion (µl/ml)	Absorbance at 600nm	Mean	% of Growth Inhibition
			Test 1 Test 2 Test 3		
1	**Growth C**		1.603 1.603 1.063	**1.603**	-
2	**Standard**	7.8	- - -	-	-
	(Metronidazole)	15.6	1.538 1.538 1.538	**1.538**	**4.05%**
		31.2	1.421 1.421 1.421	**1.421**	**11.35%**
		62.5	1.397 1.398 1.397	**1.397**	**12.85%**
		125	0.834 0.834 0.834	**0.834**	**47.97%**
		250	0.611 0.611 0.611	**0.611**	**61.88%**
		500	0.531 0.531 0.531	**0.531**	**66.87%**
		1000	0.422 0.422 0.422	**0.422**	**73.67%**

3	**Nanogel F4**	7.8	-	-	-	-	-
		15.6	-	-	-	-	-
		31.2	1.491	1.492	1.496	**1.493**	**6.86%**
		62.5	1.313	1.310	1.312	**1.311**	**18.21%**
		125	0.881	0.883	0.884	**0.882**	**44.97%**
		250	0.691	0.692	0.693	**0.692**	**56.83%**
		500	0.413	0.412	0.410	**0.411**	**74.36%**
		1000	0.382	0.384	0.381	**0.382**	**76.16%**

6. CONCLUSION

Concluded that the present research work was successfully designed, developed and evaluated the nanogel containing ciclopirox olamine. In formulation process successful encapsulation of ciclopirox olamine into a nanogel matrix. The optimization of formulation parameters such as polymer concentration, surfactant type, and homogenization technique was crucial in achieving a stable and uniform nanogel dispersion.

Comprehensive characterization studies, including particle size analysis, zeta potential measurement, and morphology examination, confirmed the nanoscale dimensions and colloidal stability of the nanogel. The presence of Ciclopirox Olamine compounds within the nanogel matrix was verified through spectroscopic analysis. The successful development and characterization of the nanogel containing Ciclopirox Olamine open avenues for further research and development.

Therefore, the further work will be carried out as follows,

- *In-vivo* pharmacokinetic study
- *In-vivo, In-vitro* correlation study.

REFERENCES

[1] Srivastava S, Verma NK, Agrawal N, Srivastava S. A Brief Study on Nanogel: A Review. Sch Acad J Pharm. 2024;13(05):163–8.

[2] a N, Jahangir Alam M, Kumar N. Nanogels: a Mini-Review of a Future Perspective Novel Drug Delivery System. Int J Adv Res. 2020;8(6):1081–92.

[3] Neamtu I, Rusu AG, Diaconu A, Nita LE, Chiriac AP. Basic concepts and recent advances in nanogels as carriers for medical applications. Drug Deliv. 2017;24(1):539–57.

[4] Keshavshetti GG, Shirsand SB, Gel N. Ciclopirox Olamine - Loaded Niosomal Gelas a Topical Drug Delivery System for Fungal. 2019;2(1):25–32.

[5] Tests P. Ciclopirox Topical Solution Ciclopirox Olamine » Ciclopirox Olamine contains not less than USP Monographs » Ciclopirox Olamine Cream contains not less than 90 . 0 percent and not more than 110 . 0 per-. 2018;2(2):926–7.

[6] Sri R, Nurdin C, Vitayani S, Amin S, Kadir D, Djamaluddin W, et al. Cutaneous candidiasis caused by candida kefyr. Pan Afr Med J. 2021;38(178):2.

[7] Ray TL, Wuepper KD. Experimental cutaneous candidiasis in rodents. J Invest Dermatol [Internet]. 1976;66(1):29–33. Available from: http://dx.doi.org/10.1111/1523-1747.ep12478053

[8] Atul A P, Praveen D C. Development and Evaluation of Nanogel as a Carrier for Transdermal Delivery of Aceclofenac. Asian JPharmTech. 2012;2(4):125–32.

[9] Srivastava S, Saha S, Jakhmola V. Nanogel: Types, Methods of Preparation, Limitation, Evaluation and

Application-A Systematic Review. Vol. 13, International Journal of Drug Delivery Technology. Dr. Yashwant Research Labs Pvt. Ltd.; 2023. p. 1631–9.

[10] Aparna DC, Manisha B, Sirisha DK. Formulation and Evaluation of Etoricoxib Nanogel. Int J Pharm Sci Rev Res. 2023;78(1):113–8.

[11] Aparna C. A Review on Nanogels Aparna C*, Prasanna N. Int J Drug Dev Res [Internet]. 2022;14(9):973. Available from: https://www.itmedicalteam.pl/

[12] Rasul A, Imran Qadir M, Mehmood Y, Pharm Sci PJ, Farooq U, Sher M, et al. Development, characterization and evaluation of anti-fungal activity of miconazole based nanogel prepared from biodegradable polymer. Artic Pakistan J Pharm Sci [Internet]. 2020;33(1):449–57. Available from: https://www.researchgate.net/publication/338937316

[13] Sanganabhatla D, Sunder RS. A novel nanogel formulation of finasteride for topical treatment of androgenetic alopecia: Design, characterization and in vitro evaluation. Int J Appl Pharm. 2021;13(4):228–40.

[14] Pathan IB, Dwivedi R, Ambekar W. Formulación y evaluación de ketoprofeno cargado de nanogel de quitosán para el manejo del dolor: estudio ex vivo e in vivo. Ars Pharm. 2019;60(2):101–8.