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FORMULATION, DEVELOPMENT AND EVALUATION OF ANTIFUNGAL NANOGEL USING VORICONAZOLE AND VITAMIN-C FOR TOPICAL DRUG DELIVERY

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ABSTRACT

In the present study the formulation of nanogel was prepared by solvent evaporation method. With a aim to improve water solubility of the poorly water soluble drug Voriconazole belonging to the BCS Class-II. Total fifteen formulations of drug were prepared with varying proportion of polymer Ethyl-cellulose along with the stabilizer Poloxamer F38. The formulated nanogel is evaluated for particle size analysis, saturation, solubility, poly-dispersity index, drug entrapment, in-vitro dissolution studies, zeta potential, short term stability studies and the result showed stable The objective of the research was to design a formulation that can be easily applied onto the skin by providing relief and retention of water (the major ability of hydrogel) for a prolonged period on dermatitis-affected dried skin and able to permeate through intact skin. Voriconazole is an antifungal agent of the triazole class and a new existing drug. It overcomes all side effects of fungal other medicines like Ketoconazole, Amphotericin B, Clotrimazole, and Miconazole. Even though it has some side effects in the oral and IV dosage forms. Voriconazole remains one of the most frequently prescribed triazoles because of its excellent bioavailability, tolerability, and side effect profile. The voriconazole nanoparticle nanogels were prepared on the different concentrations of four polymers, HPMC, Methylcellulose, Carbopol, and pectin. The formulation of voriconazole nanoparticle-loaded gel with HPMC showed favorable characteristics such as a good flow index, spreadability, and viscosity. This indicated its suitability for topical application. The release profile demonstrated sustained drug release over a prolonged period, suggesting the potential for a long therapeutic effect. In the in vitro permeation studies $R^2 = 0.9046$, the nanogel exhibited efficient drug permeation through a synthetic membrane with a controlled release profile. This indicated the nanogel's ability to deliver voriconazole to the target site effectively nanogel with nanosize __. L-ascorbic acid (vit-C) is a water soluble compound and most abundant anti-oxidant in human skin, but this vitamin is unstable and loses its potency with poor formulation strategies. Nanotechnology has been effectively used to promote stability and therapeutic activity of various drug molecules. The objective of this work was set to formulate a topical delivery system of Voriconazole and Vitamin C nanoparticles incorporated into polymeric gel. Saturation solubility of such nanogel reveals that the aqueous solubility of drug is significantly increased due to decrease in particle size (80-300 nm). The short term stability studies was performed at two set of temperature 25oC and 37oC proves that the drug in nanogel can be remain stable at temperature 25oC. Zeta potential was found to be optimum which show the formulation is stable. From the above studies it is concluded that the Poloxamer F38 stabilizer (Pluronic F38) can be used for formulating stable nanogel with varying concentration in range of 0.5-1.0 %. It gives effective size as well as stability to nanogel. The ratio of Drug, polymer and stabilizer (Drug, Ethyl cellulose and Poloxamer F38) is important to obtain the stable nanogel formulation.

KEYWORDS: Development, Evaluation, Nanogel, Antifungal Drug and Topical Delivery.

1 INTRODUCTION

Novel Drug Delivery System[1-3]

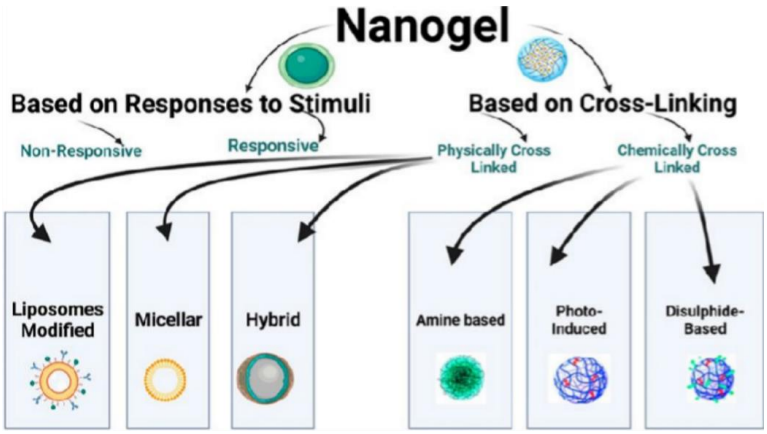
A novel drug delivery system can be defined as a new approach that combines innovative formulations, development and novel methodologies for delivering pharmaceutical compounds in the body that ensures safety and achieves its pharmacological effect. Compared to conventional drug delivery systems, novel drug delivery systems are advanced drug delivery systems. Preparing new pharmaceutical forms which having smaller particle size and increased permeability for targeted delivery is a key aspect of novel drug delivery system. The novel drug delivery system prolongs and enhances the therapeutic effect of drug which controls the distribution of drug is achieved by incorporating the drug in carrier system or changing the structure of the drug at molecular level.

Characteristics of Novel Drug Delivery System[4]

- The novel drug delivery system can enhance bioavailability.
- It ensures controlled delivery of drug.
- Transport drug to targeted site by avoiding non-diseased tissue.
- The drug delivery can be maintained under stable and different physiological conditions.
- NDDS is safe, reliable and easy to administer.
- It is cost effective

Nanogel

Nanogels are nanoparticles composed of a hydrogel with cross-linked hydrophilic polymer with 100–200 nm. Physically and chemically cross-linked synthetic or biopolymers constitute nanogels. The pores of nanogels are filled with multiple oral doses of ondansetron (3 or 4 doses of 8mg) after moderately emetogenic chemotherapy.[6-8]



2 MATERIAL AND METHODOLOGY

2.1 Selection of drug

In the present work, Voriconazole (BCS class II drug) was selected to develop antifungal nanogel as it is poorly water soluble and requires fast therapeutic action. An attempt was made to formulate Voriconazole to use in the treatment of fungal infection for enhanced topical drug delivery. Vitamin-C was used as co-drug in this formulation which gives nourishment and provides moisture to the fungal infected skin.

2.1.1 Material

Table 1: List of materials used for the preparation of Antifungal Nanogel of Voriconazole and Vitamin-C.

Name of material	Source	Use
Voriconazole	Dhamtech Pharma, Mumbai, India	A, PI
L-Ascorbic Acid	Dhamtech Pharma, Mumbai, India	API
Pluronic F38	Research Lab	Surfactant/Stabilizer
Ethyl Cellulose (EC)	Research Lab	Organic solvent
Glycerin	Research Lab	Lubricant
Triethanolamine	Research Lab	Glidant
Methylparaben	Research Lab	Lubricant
Carbopol 934	Research Lab	Gelling agent

Pre-Formulation Studies

The Physicochemical properties of the drug play a very important role in performance of the drug and the development of dosage form. Hence, in order to develop a safe, stable and effective dosage form the performulaion study of Metformin Hydrochloride was carried effectively.

Solubility

The solubility of Voriconazole was tested in different solvents like Ethanol, & Methanol at ambient temperature by dissolving a specific amount of API (10 mg) in (10 ml) of each solvent. The solubility was detected visually and also using UV- visible spectroscopy.[5]

Melting Point

For determination of melting point USP method was followed. Small quantity of Voriconazole was placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature in the apparatus was gradually increased and the observation of temperature was noted at which Voriconazole started to melt and the temperature when the entire drug gets melted. This method is also known as open capillary method.[6]

UV-Visible Spectroscopy

The UV visible spectrum of Metformin hydrochloride in Phosphate buffer pH 7.4 shows λmax 234 nm as shown in figure No.2.

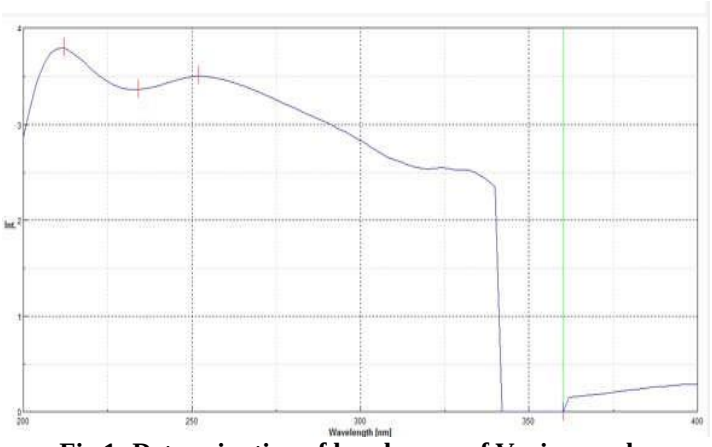


Fig 1: Determination of lamda max of Voriconazole.

Determination of lambda max

The structural information on chromophoric Voriconazole's component was obtained using a UV-Vis spectrophotometric approach. The solution was then analyzed in the range 200- 400nm using UV/Vis Spectrophotometer to measure the Absorption maxima. 10mg of Voriconazole was dissolved in 10ml Phosphate buffer (pH 7.4) and diluted up to 100ml using phosphate buffer.

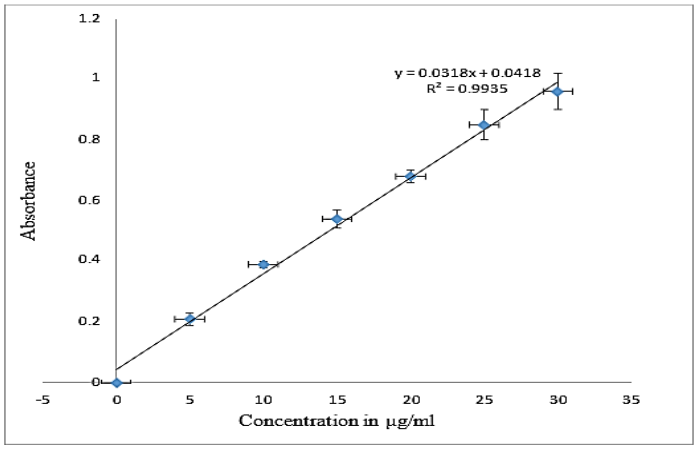


Figure 2: Calibration curve of Voriconazole.

Preparation of Calibration curve

A series of dilutions with concentration 2, 4, 6, 8, 10 ppm were prepared from Voriconazole 100 ppm stock solution in phosphate buffer (pH 7.4) and were scanned at the determined Absorption maximum. Absorbance vs. Concentration graph was plotted.

Table No. 6: Calibration Curve data of Voriconazole in Phosphate buffer pH7.4 at wavelength of 234 nm.

Sr. No.	Concentration (µg/ml)	Absorbance
1.	2	0.07
2.	4	0.135
3.	6	0.209
4.	7	0.273
5.	10	0.341

Fourier Transform Infra-Red Spectroscopy (FT-IR)

To demonstrate the chemical integrity and compatibility of the formulations, the IR spectra of the pure drug, Physical mixture of drug & Excipient, Optimized batch of Nanogel formulations were obtained. The compatibility between the medicine and excipient in Voriconazole was examined using a Fourier-transform infrared Analyzer.[9] FT-IR Spectroscopy was used to qualitatively identify the compound, providing adequate data on the groups present within these compound. The IR investigation was conducted using a Perkin Elmer Fourier Transform Infrared Spectrophotometer.[10,11]

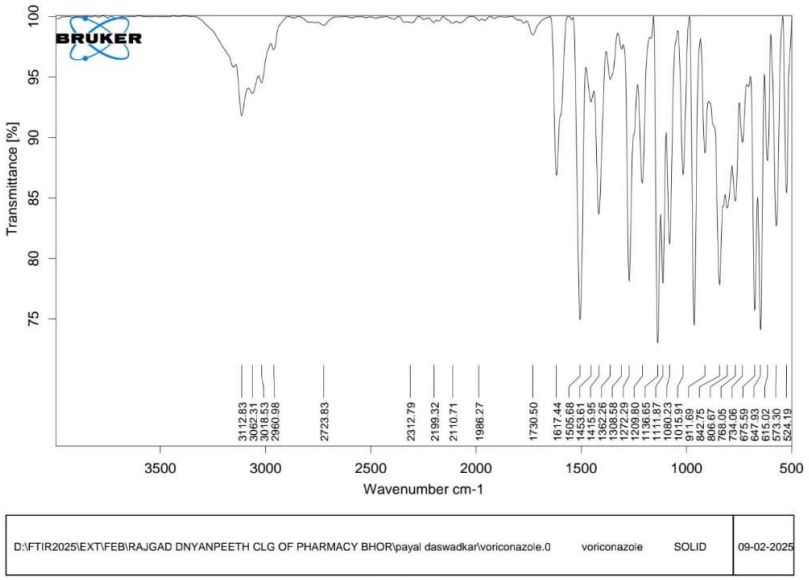


Fig. 3: FTIR of Voriconazole.

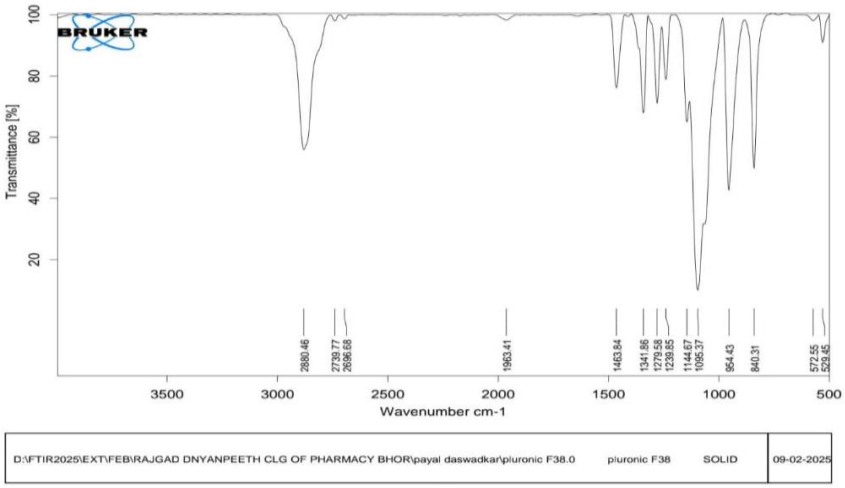


Fig. 4: FTIR of Pluronic F38.

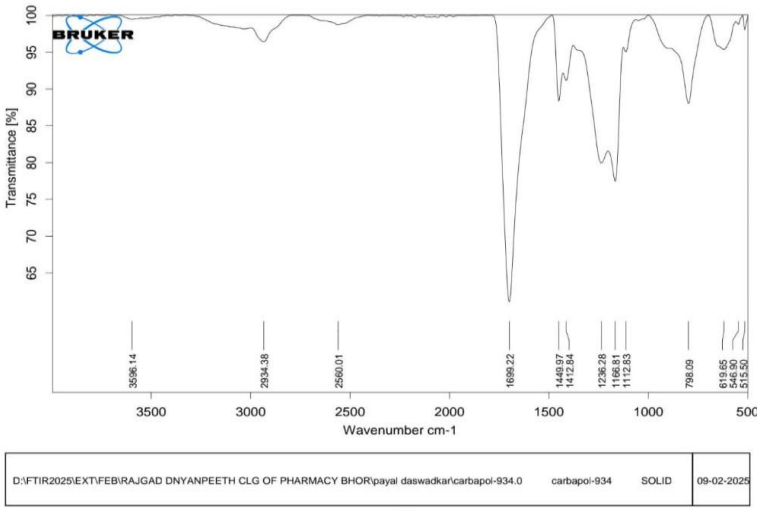


Fig. 5: FTIR of Carbapol 934.

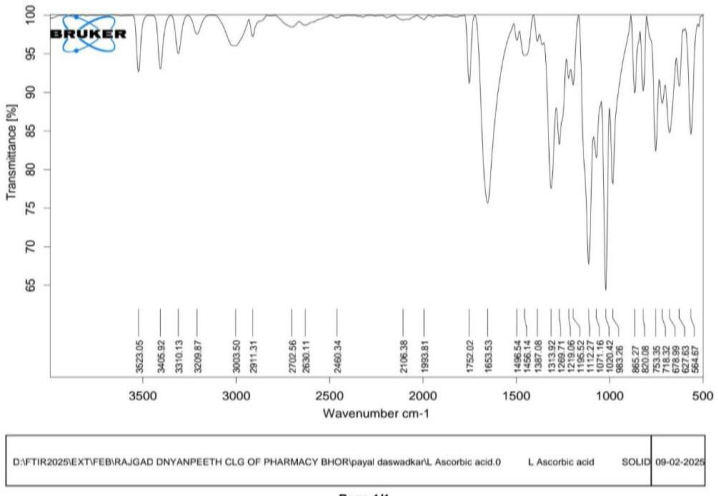


Fig. 6: FTIR of L-Ascorbic acid.

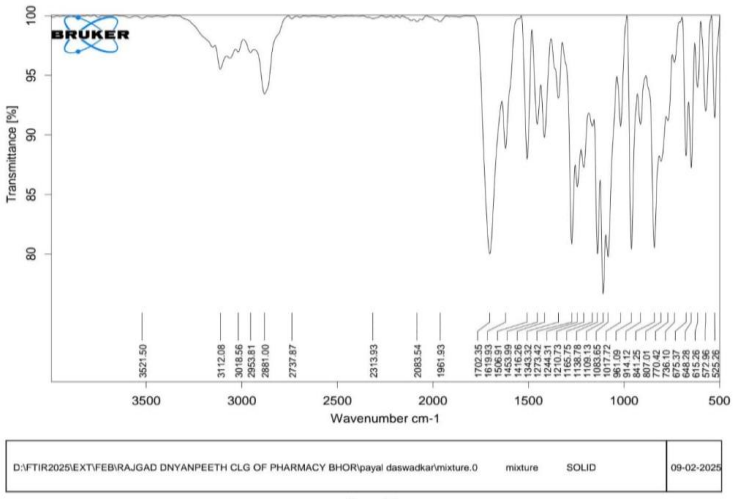


Fig. 6: FTIR of Drug-Excipient Compatibility.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimeter study of Voriconazole samples was carried out on a differential scanning calorimeter. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30–300°C. Alumina was employed as the reference standard. The onsets of melting points and enthalpies of fusion of samples were automatically calculated by the instrument.[12,13,14]

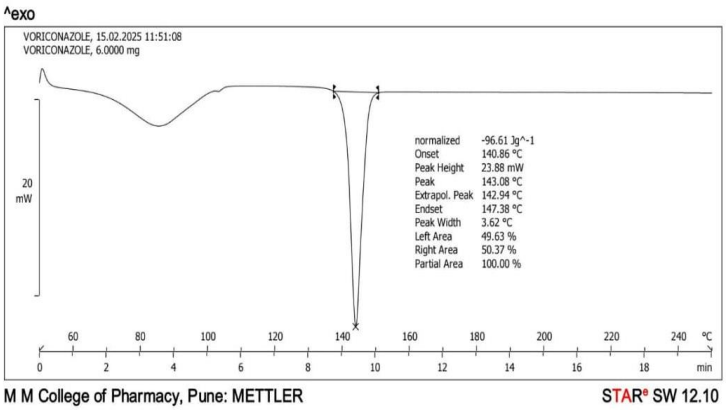


Fig. 6: DSC of Voriconazole.

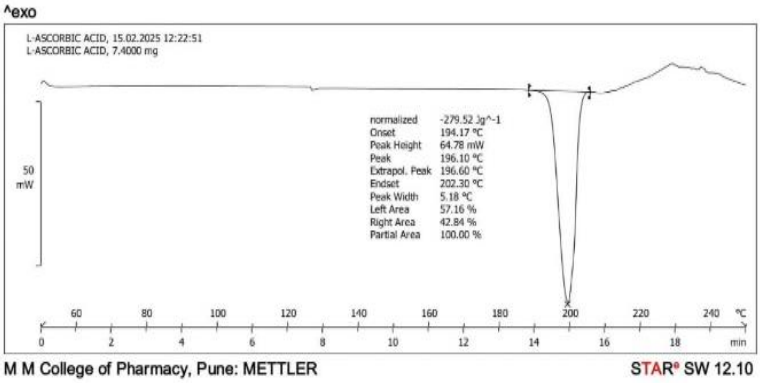


Fig. 6: DSC of L-Ascorbic Acid.

Experimental Design

Optimization of nanogel preparation procedure was done by using 3^2 full factorial design. The Concentration of Ethyl cellulose (X1) and Pluronic F38 (X2) were selected as independent variables. % Entrapment efficiency (Y1) were selected as dependent variables.

Statistical Analysis of Data

The effect of independent variables upon the response was checked by using Statistical tools, such as descriptive statistics and one way ANOVA by Design expert software (Version 13). A value of $p < 0.05$ was considered statistically significant.

Table No. 5.5: Formulation Table of antifungal Voriconazole loaded nanogel.

Sr. No.	Formulation Batch	Voriconazole (mg)	Vitamin C (mg)	Ethyl Cellulose (mg)	Carbopol 934 (mg)	Pluronic F38 (mg)
1.	F1	10	20	50	20	100
2.	F2	10	20	50	30	100
3.	F3	10	20	50	40	100
4.	F4	10	20	75	20	100
5.	F5	10	20	75	30	100
6.	F6	10	20	75	40	100
7.	F7	10	20	100	20	100
8.	F8	10	20	100	30	100
9.	F9	10	20	100	40	100

Formulation of Voriconazole loaded nanogel by Solvent Evaporation Method

The antifungal nanogel of Voriconazole and vitamin-C was prepared with solvent diffusion method with an appropriate water-miscible organic solvent such as ethanol or acetone is selected. The required quantity of **ethylcellulose,** Glycerin, Triethanolamine and methylparaben is accurately weighed and dissolved in the organic solvent under continuous stirring to obtain a clear polymeric solution. **Voriconazole**, as the drug, and **vitamin C** as the co-drug are then added to the same organic phase and stirred until complete dissolution is achieved. This organic phase acts as the internal phase containing the drug and hydrophobic polymer.

Separately, the **aqueous phase** is prepared by dissolving **Pluronic F38** in purified water under magnetic stirring. Pluronic F38 acts as a stabilizer and surfactant, helping

to prevent aggregation of nanoparticles. The aqueous phase is maintained at room temperature and stirred until a clear solution is obtained. The organic phase is then **slowly added dropwise into the aqueous phase** under continuous high-speed stirring. As the organic solvent diffuses into the aqueous medium, the solubility of ethylcellulose decreases, resulting in its precipitation and the spontaneous formation of **drug-loaded nanoparticles**. Continuous stirring is maintained for a sufficient period (usually 1–2 hours) to allow complete diffusion and evaporation of the organic solvent, leading to a stable nanodispersion.

In the next step, the **gel base** is prepared separately by dispersing **Carbopol 934** in purified water with gentle stirring. The dispersion is allowed to hydrate and swell for several hours, after which the pH is adjusted using a suitable neutralizing agent such as triethanolamine to obtain a clear and smooth gel.

The prepared nanodispersion is then **slowly incorporated into the Carbopol gel base** with gentle and uniform stirring to avoid air entrapment. Mixing is continued until a homogeneous nanogel is obtained. Finally, the pH of the formulation is adjusted to the desired range (generally pH 5.5–7.0 for topical application), and the nanogel is allowed to equilibrate before being transferred into suitable containers for storage and further evaluation.

Characterization of Drug Loaded Nanogel

Entrapment Efficiency

Centrifugation method was used to determined percentage entrapment efficiency of Nanogel. Approximately 5ml of prepared **nanogel** is accurately weighed. The nanogel is dispersed in a suitable solvent or buffer and subjected to **centrifugation** at high speed (12,000–15,000 rpm for 30–45 minutes). The **free (unentrapped) drug** remains in the supernatant, while the **drug-loaded nanoparticles** settle as sediment. The supernatant is carefully collected and analyzed for **free Voriconazole and Vitamin C** using **UV–Visible spectrophotometry** (Jasco V-530).

Zeta Potential

The charge on antifungal nanogel of Voriconazole and Vit-C surface was determined by using Zeta Potential Analyzer (Horiba SZ 100). Voriconazole being weakly basic contributes minimal surface charge, while Vitamin C and Carbopol 934 impart a negative charge to the nanogel, resulting in an overall negative zeta potential that favors formulation stability.

Scanning Electron Microscopy[29,30,31]

The Surface morphology of prepared Voriconazole antifungal nanogel were evaluated by Scanning Electron Microscopy.

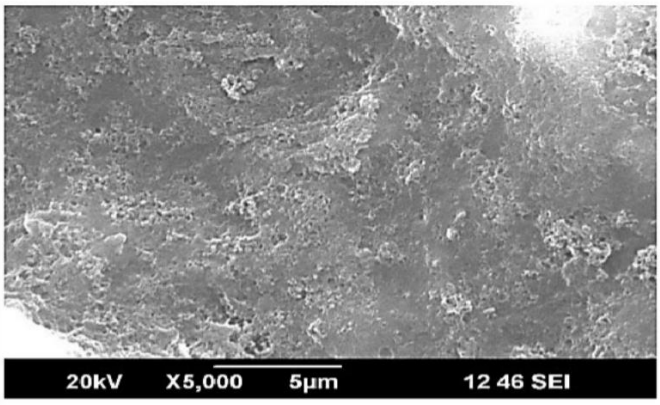


Fig. 7: SEM of F1 Formulation.

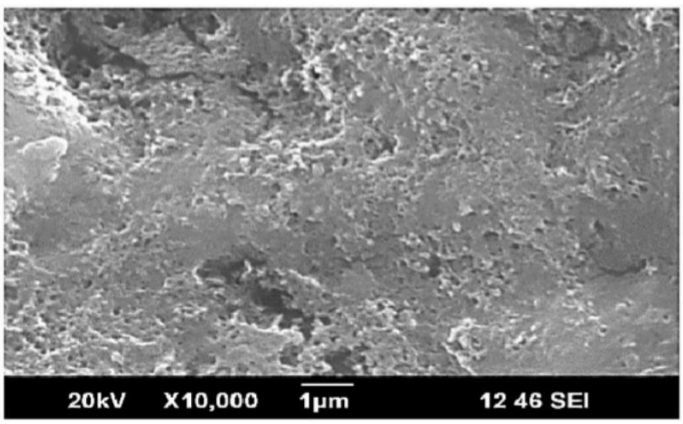


Fig. 8: SEM of F2 Formulation.

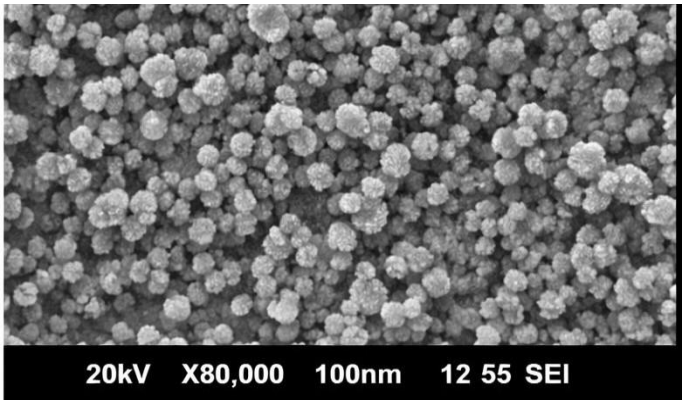
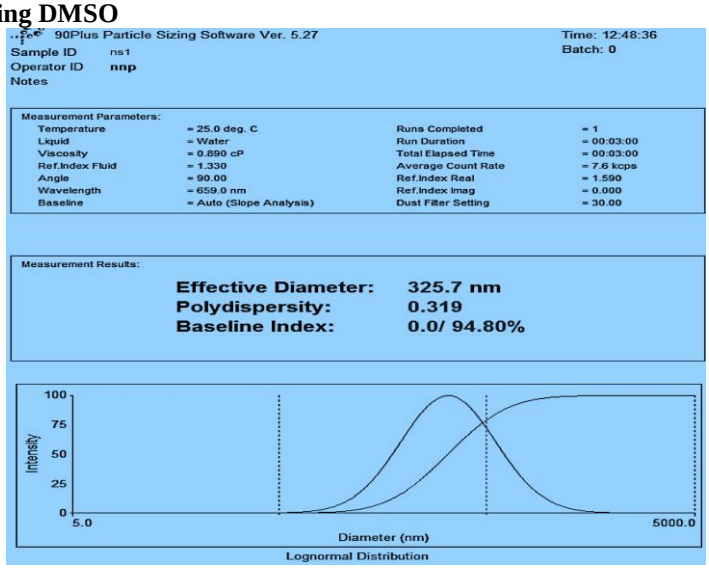
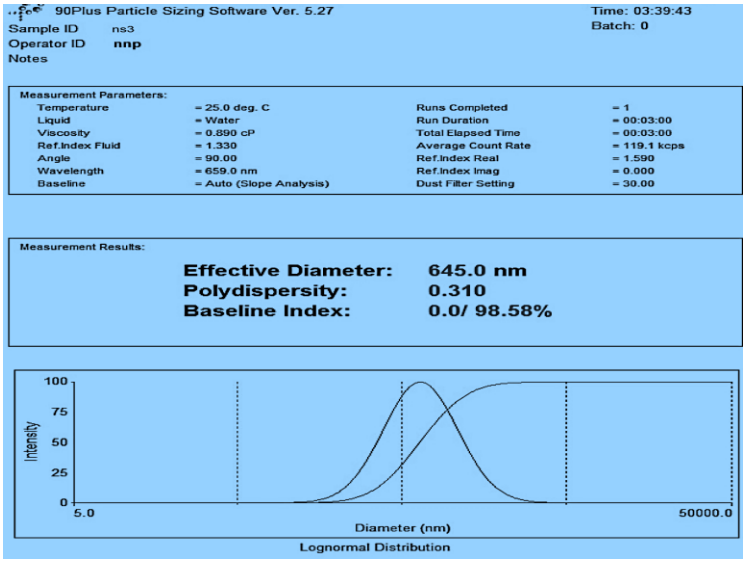


Fig. 9: SEM of F3 Formulation.

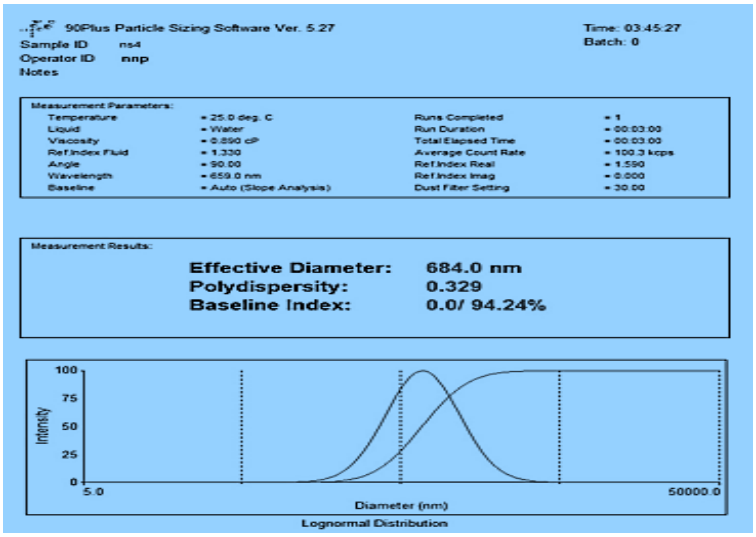
Particle Size Analysis Using DMSO



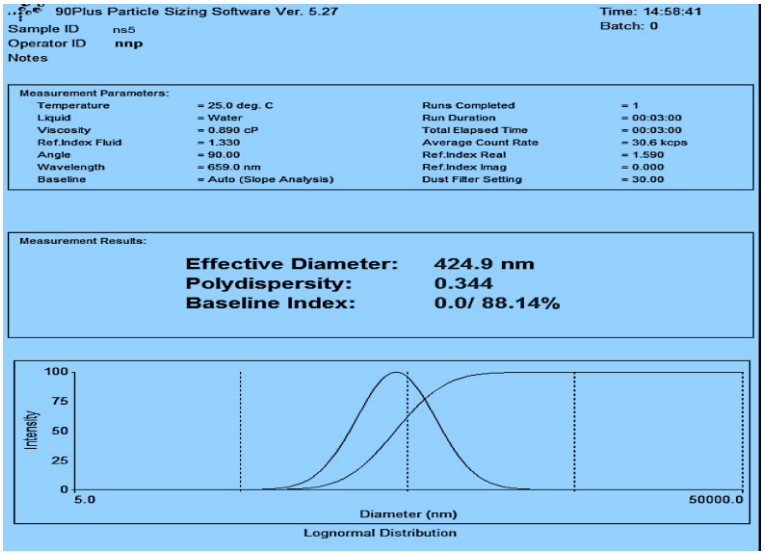
PDI using Ethanol.



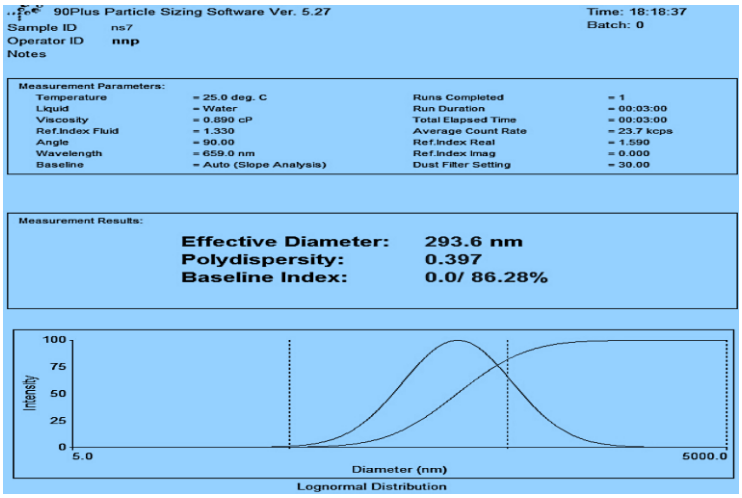
Particle size analysis of formulation using DMSO.



Particle size analysis of formulation with S: NS of 1:10.



Particle size analysis of formulation with S: NS of 1:20.



Particle size analysis of formulation with stirring time of 5min.

Evaluation parameters
Post-Evaluation Parameters
Spreadability
The nanogel exhibited good spreadability, indicating ease of application and uniform drug distribution.

Extrudability
All formulations showed satisfactory extrudability, ensuring convenient dispensing.

Skin Irritation Test
No signs of redness, edema, or irritation were observed, confirming the safety of the formulation for topical use.

3 SUMMARY AND CONCLUSION

The present study was successfully carried out to formulate and evaluate a Voriconazole–Vitamin C loaded antifungal nanogel with the objective of enhancing topical drug delivery. The major findings of the study are summarized below:

Physical characterization of Voriconazole confirmed that the drug is a white to off-white, odorless crystalline powder with poor aqueous solubility and good solubility in organic solvents. These characteristics were consistent with reported literature values and justified the need for a nano-based delivery system.

Melting point analysis showed a narrow melting range of 137–139 °C with a mean melting point of 138 °C, indicating the purity and thermal stability of the drug and its suitability for formulation processes.

Solubility studies demonstrated that Voriconazole is slightly soluble in water but freely soluble in ethanol and methanol, supporting the selection of ethanol as a suitable solvent for nanosuspension preparation.

UV–spectrophotometric analysis revealed a distinct λmax at 234 nm in phosphate buffer pH 7.4. The calibration curve exhibited excellent linearity in the concentration range of 2–10 µg/mL with a high correlation coefficient (R^2 = 0.9997), validating the analytical method for quantitative estimation.

Particle size and polydispersity index (PDI) studies showed that formulation parameters significantly influenced nanosuspension characteristics. Smaller particle sizes were obtained with ethanol as solvent, higher solvent:non-solvent ratios, and prolonged stirring times. All formulations exhibited acceptable PDI values, indicating uniform particle size distribution.

SEM analysis confirmed the formation of nanosized, spherical particles with smooth surface morphology. Among all formulations, **F4 exhibited the smallest particle size (92.20–105 nm)**, indicating optimal formulation conditions for dissolution enhancement.

Entrapment efficiency ranged from 68.88 % to 91.21 %, with formulation F4 showing the highest drug entrapment, attributed to optimal polymer concentration and effective encapsulation.

Zeta potential measurements indicated moderate electrostatic stability of the nanogel formulations, supported by steric stabilization provided by Poloxamer F38.

Post-evaluation parameters, including spreadability, extrudability, and skin irritation studies, confirmed good topical applicability, ease of administration, and dermal safety of the nanogel formulation.

Overall, the study established that the optimized Voriconazole–Vitamin C nanogel (F4) possesses desirable physicochemical properties, enhanced drug entrapment, nanoscale particle size, sustained drug release, and good topical acceptability, indicating its potential as an effective antifungal delivery system for topical application.

CONCLUSION

The present research work was successfully undertaken to develop and evaluate an **antifungal nanogel containing Voriconazole and Vitamin C** for enhanced topical drug delivery. Preformulation studies confirmed the purity, identity, and suitability of Voriconazole for formulation development, while its poor aqueous solubility justified the need for a nano-based delivery approach. The Voriconazole nanosuspension was effectively prepared using polymeric carriers and subsequently incorporated into a Carbopol-based nanogel. Systematic optimization of formulation variables demonstrated a significant influence on particle size, polydispersity index, and drug entrapment efficiency. Among all formulations, **formulation F4** emerged as the optimized formulation, exhibiting the smallest particle size in the nanometer range, highest entrapment efficiency, and uniform particle size distribution. Morphological evaluation by SEM confirmed the formation of spherical, smooth- surfaced nanoparticles, supporting effective drug encapsulation. The developed nanogel exhibited acceptable zeta potential, indicating adequate formulation stability. In-vitro drug release studies revealed an initial burst release followed by sustained release, suggesting diffusion-controlled drug release behavior that is favorable for prolonged antifungal activity at the site of application. Post-evaluation studies demonstrated good spreadability, satisfactory extrudability, and absence of skin irritation, confirming the suitability of the formulation for topical application and improved patient compliance. Overall, the findings of this study conclude that the **Voriconazole–Vitamin C nanogel** is a promising topical drug delivery system capable of enhancing solubility, providing sustained drug release, and potentially improving therapeutic efficacy in the treatment of fungal infections. Further in-vivo and clinical studies may be carried out to establish its clinical effectiveness and long-term safety.

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