# FORMULATION AND EVALUATION OF TERBINAFINE HYDROCHLORIDE-LOADED DEEP EUTECTIC SOLVENT BASED EUTECTOGEL FOR ENHANCED TOPICAL ANTIFUNGAL DELIVERY

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## Abstract

The present study was aimed at the formulation and evaluation of Terbinafine Hydrochloride-loaded Deep Eutectic Solvent (DES)-based eutectogel for enhanced topical antifungal delivery. Terbinafine Hydrochloride, a poorly water-soluble antifungal drug, was incorporated into a DES system to improve its solubility, drug release, and topical performance. The drug was characterized by preformulation studies including organoleptic properties, solubility, melting point, partition coefficient, UV spectroscopy, and FTIR compatibility studies. Different DES systems were prepared using suitable hydrogen bond donors and acceptors, and the optimized DES showing maximum drug solubility was incorporated into Carbopol gel base to prepare eutectogel formulations (F1–F10). The prepared formulations were evaluated for physical appearance, homogeneity, pH, viscosity, spreadability, extrudability, drug content, in vitro drug release, and stability studies. Among all formulations, batch F7 showed optimum physicochemical properties, excellent drug content (99.5 ± 0.31%), and maximum cumulative drug release (99.6 ± 2.2% at 12 h). Stability studies confirmed that the optimized formulation remained stable under ICH storage conditions. The results indicated that the DES-based eutectogel significantly enhanced the solubility and topical delivery of Terbinafine Hydrochloride and may serve as a promising approach for effective topical antifungal therapy.

**Keywords:** *Terbinafine Hydrochloride, Deep Eutectic Solvent (DES), eutectogel, topical drug delivery, antifungal therapy, Carbopol gel, solubility enhancement, skin permeation.*

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## 1. Introduction

Fungal skin infections are among the most common dermatological disorders affecting millions of people worldwide. Superficial fungal infections caused by dermatophytes, yeasts, and molds commonly affect the skin, nails, and hair, leading to conditions such as tinea pedis, tinea corporis, and candidiasis. These infections are associated with symptoms including itching, redness, scaling, and inflammation, significantly affecting patient quality of life. The increasing prevalence of fungal infections and recurrence after treatment have created a need for more effective topical antifungal formulations (Havlickova et al., 2008).

Terbinafine Hydrochloride is a broad-spectrum allylamine antifungal agent widely used in the treatment of dermatophytic infections. It acts by inhibiting squalene epoxidase, resulting in disruption of fungal cell membrane synthesis and fungal cell death (Ryder, 1992). However, the drug possesses poor aqueous solubility and lipophilic nature, which may limit its effective delivery through conventional topical dosage forms. Conventional creams and gels often suffer from poor skin penetration, short residence time, and inadequate drug retention, reducing therapeutic effectiveness (Benson, 2005).

Deep Eutectic Solvents (DESs) have recently emerged as promising pharmaceutical solvents due to their excellent solubilization capacity, biocompatibility, low toxicity, and permeation-enhancing properties (Abbott et al., 2003; Paiva et al., 2014). DESs can improve drug solubility and enhance permeation across biological membranes, thereby increasing drug bioavailability and therapeutic effectiveness (Francisco et al., 2013).

The incorporation of DESs into gel systems results in eutectogels, which combine the solubilization and permeation-enhancing properties of DESs with the desirable rheological characteristics of topical gels. Eutectogels offer advantages such as improved drug loading, enhanced skin permeation, controlled drug release, and better stability compared to conventional topical formulations (Silva et al., 2018). In addition, DESs have shown the ability to disrupt the stratum corneum lipid barrier, facilitating improved dermal permeation of poorly water-soluble drugs (Mbous et al., 2017). Carbopol-based eutectogels are particularly suitable for topical delivery because of their excellent bioadhesive properties, suitable viscosity, and ease of application (Rowe et al., 2009).

Therefore, the present study was aimed at the formulation and evaluation of Terbinafine Hydrochloride-loaded DES-based eutectogel for enhanced topical antifungal delivery. The

developed formulations were evaluated for physicochemical properties, drug content, in vitro drug release, and stability to identify an optimized formulation suitable for effective topical therapy.

## 2. Methodology

### 2.1 Procurement and Authentication of Materials

The active pharmaceutical ingredient, Terbinafine Hydrochloride, was obtained as a gift sample from a certified pharmaceutical manufacturer. All excipients used in the preparation of the Deep Eutectic Solvent (DES)-based eutectogel, including hydrogen bond donors, hydrogen bond acceptors, gelling agents, and other additives, were of analytical or pharmaceutical grade and procured from reputed suppliers. The materials were selected based on their compatibility, suitability for topical delivery, and reported application in DES-based systems. Drug authentication was performed using melting point determination, UV spectroscopy, and FTIR analysis to confirm its identity and purity. All materials were stored under appropriate conditions throughout the study.

### 2.2 Preformulation Studies

#### 2.2.1 Organoleptic Properties

Organoleptic evaluation of Terbinafine Hydrochloride was performed during the preformulation stage to assess its physical characteristics and confirm its suitability for formulation development. The drug sample was examined visually for color, appearance, and physical state under normal daylight conditions. Its texture, crystalline nature, and presence of any foreign particles were also observed. The odor was evaluated using the wafting method, and hygroscopic behavior was checked by brief exposure to atmospheric conditions. All observations were compared with standard pharmacopeial and literature-reported characteristics of Terbinafine Hydrochloride.

#### 2.2.2 Solubility Studies

Solubility studies of Terbinafine Hydrochloride were performed to evaluate its solubility in different solvents and to select suitable components for the development of the Deep Eutectic Solvent (DES)-based eutectogel. An excess amount of the drug was added to various solvents, including distilled water, phosphate buffer (pH 5.5 and 7.4), ethanol, and methanol, followed by continuous shaking at room temperature (25 ± 2°C) for 24 hours to

achieve equilibrium. The samples were then centrifuged, filtered, and analyzed using a UV-Visible spectrophotometer at the predetermined λmax. Drug concentration was calculated using the calibration curve, and solubility was expressed in mg/mL. The results were used for the selection of suitable solvents and DES components for formulation development.

### 2.2.3 Melting Point Determination

Melting point determination of Terbinafine Hydrochloride was carried out during preformulation studies to assess its purity and confirm its identity. A small quantity of finely powdered drug was filled into a sealed capillary tube and placed in a melting point apparatus. The temperature was gradually increased, and the temperatures at which the sample started melting and completely liquefied were recorded. The observed melting point range was compared with the standard pharmacopeial value to evaluate the purity and authenticity of the drug. This study also provided information regarding the thermal behavior and stability of the drug during formulation development.

### 2.2.4 Partition Coefficient

The partition coefficient of Terbinafine Hydrochloride was determined to evaluate its lipophilicity and suitability for topical delivery. The study was performed using an n-octanol and distilled water system. An accurately weighed amount of the drug was added to the solvent mixture and shaken to achieve equilibrium between the two phases. After phase separation, the aqueous phase was analyzed using a UV-Visible spectrophotometer at the predetermined λmax. The partition coefficient was calculated from the ratio of drug concentration in the organic and aqueous phases, providing information about the drug's skin permeation potential and compatibility with the DES-based eutectogel system.

### 2.2.5 UV Spectroscopic Analysis

UV spectroscopic analysis of Terbinafine Hydrochloride was performed to determine its λmax and prepare a calibration curve for quantitative estimation. A standard stock solution was prepared in methanol, suitably diluted, and scanned in the wavelength range of 200–400 nm using a UV-visible spectrophotometer with methanol as blank to determine the λmax. Further dilutions (2–12 µg/mL) were prepared from the stock solution, and their absorbance was measured at the determined λmax. A calibration curve of absorbance versus concentration was plotted, and the regression equation and correlation coefficient ($R^2$) were calculated to confirm linearity according to Beer-Lambert's law.

### 2.2.5 FTIR Compatibility Studies

Fourier Transform Infrared (FTIR) spectroscopy was performed to evaluate the compatibility of Terbinafine Hydrochloride with the selected excipients used in the DES-based eutectogel formulation. FTIR spectra of the pure drug, excipients, and their physical mixtures were recorded using the KBr pellet method over the range of 4000–400 $cm^{-1}$. The characteristic peaks of Terbinafine Hydrochloride were identified and compared with those of the physical mixture to detect any possible interactions. The absence of significant changes in the characteristic peaks confirmed the compatibility of the drug with the selected excipients and suitability for formulation development.

## 2.3 Preparation and Optimization of Deep Eutectic Solvent (DES)

### 2.3.1 Selection of Hydrogen Bond Donor (HBD) and Acceptor (HBA)

The selection of suitable Hydrogen Bond Donors (HBDs) and Hydrogen Bond Acceptors (HBAs) was carried out for the development of the Deep Eutectic Solvent (DES) system to enhance the solubility of Terbinafine Hydrochloride. Pharmaceutically acceptable components such as choline chloride (HBA) and HBDs including urea, glycerol, propylene glycol, and organic acids were selected based on their hydrogen bonding ability, solubilization potential, biocompatibility, and suitability for topical application. Preliminary screening of different HBD–HBA combinations was performed to identify clear, stable, and homogeneous DES systems. The selected combinations were further evaluated for drug solubility and physicochemical properties for incorporation into the eutectogel formulation.

### 2.3.2 Preparation Method of DES

Deep Eutectic Solvents (DES) were prepared by the heating and stirring method using selected Hydrogen Bond Acceptors (HBAs) and Hydrogen Bond Donors (HBDs) in different molar ratios. Accurately weighed components were mixed and heated at 60–80°C with continuous stirring until a clear and homogeneous liquid was formed. The prepared DES was cooled to room temperature and examined for clarity, homogeneity, and absence of phase separation or crystallization. The formulations were stored in airtight containers and further evaluated for drug solubility and physicochemical properties to select the most suitable DES for eutectogel development.

### 2.3.3 Drug Solubility in DES

The solubility of Terbinafine Hydrochloride in the prepared Deep Eutectic Solvent (DES) systems was determined to select the most suitable solvent system for enhanced drug loading and topical delivery. An excess amount of the drug was added to each DES formulation and shaken at 25 ± 2°C for 24 hours to attain equilibrium. After centrifugation, the supernatant was collected, suitably diluted, and analyzed using a UV-visible spectrophotometer at the predetermined λmax. Drug concentration was calculated using the calibration curve, and solubility was expressed in mg/mL. The DES system showing maximum solubility along with good clarity and stability was selected for further eutectogel formulation development.

### 2.3.4 Screening and Optimization of DES

Screening and optimization of the prepared Deep Eutectic Solvent (DES) systems were carried out to identify the most suitable HBA–HBD combination for solubilization of Terbinafine Hydrochloride and compatibility with the eutectogel formulation. The prepared DES systems were visually evaluated for clarity, homogeneity, and absence of phase separation or crystallization. Shortlisted formulations were further assessed for drug solubility, viscosity, ease of handling, and compatibility with the gel base. Different molar ratios were compared, and the optimized DES was selected based on maximum drug solubility, physical stability, suitable viscosity, and compatibility with the selected gelling agent for further formulation development.

## 2.4 Formulation of DES-Based Eutectogel

### 2.4.1 Selection of Gelling Agent (Carbopol)

The selection of a suitable gelling agent was important for the development of the DES-based eutectogel, as it affects the viscosity, stability, spreadability, and overall performance of the formulation. Carbopol was selected due to its excellent gel-forming ability, high viscosity at low concentration, good bioadhesive properties, and suitability for topical application. It forms clear and stable gels with desirable rheological characteristics and is compatible with both the selected DES system and Terbinafine Hydrochloride. Based on these advantages, Carbopol was chosen for the preparation of the eutectogel formulation and further optimized to achieve suitable formulation properties.

### 2.4.2 Preparation of Gel Base

The gel base was prepared using Carbopol by the dispersion and neutralization method. An accurately weighed quantity of Carbopol was dispersed in distilled water with continuous stirring and allowed to hydrate completely for 2–4 hours. After swelling, the mixture was stirred to obtain a smooth and homogeneous dispersion. Triethanolamine was added dropwise to adjust the pH (5.5–6.5) and induce gel formation, resulting in a clear and viscous gel. The prepared gel base was inspected for clarity and homogeneity and was further used for incorporation of the DES-drug system in the eutectogel formulation.

### 2.4.3 Incorporation of DES-Drug System

The incorporation of Terbinafine Hydrochloride-loaded Deep Eutectic Solvent (DES) into the prepared Carbopol gel base was carried out to obtain a uniform eutectogel formulation. The optimized drug-loaded DES was added gradually to the gel base under continuous stirring to ensure uniform dispersion and prevent phase separation. Stirring was continued until a smooth and homogeneous gel was formed. The formulation was visually inspected for consistency, clarity, and homogeneity, and the pH was adjusted if required to maintain suitability for topical application. The prepared eutectogel was then allowed to equilibrate before further evaluation.

### 2.4.4 Preparation of Different Formulations (F1–F10)

A series of DES-based eutectogel formulations (F1–F10) were prepared by varying the concentration of Carbopol and the proportion of the optimized DES–drug system to obtain suitable formulation characteristics. The gel base was prepared and neutralized, followed by gradual incorporation of the Terbinafine Hydrochloride-loaded DES under continuous stirring to obtain a homogeneous gel. All formulations were prepared using a uniform method and evaluated for appearance and homogeneity. The prepared eutectogels were stored in suitable containers for further evaluation and optimization.

**Table 1: Composition of DES-Based Eutectogel Formulations**

| S. No. | Formulation Code | Carbopol (% w/w) | DES–Drug System (% w/w) | Triethanolamine (% w/w) | Distilled Water (% w/w) |
|---|---|---|---|---|---|
| 1 | F1 | 0.5 | 10 | q.s. | q.s. to 100 |
| 2 | F2 | 0.75 | 10 | q.s. | q.s. to 100 |
| 3 | F3 | 1.0 | 10 | q.s. | q.s. to 100 |
| 4 | F4 | 1.25 | 10 | q.s. | q.s. to 100 |
| 5 | F5 | 1.5 | 10 | q.s. | q.s. to 100 |

| | | | | | |
|---|---|---|---|---|---|
| 6 | F6 | 1.0 | 5 | q.s. | q.s. to 100 |
| 7 | F7 | 1.0 | 7.5 | q.s. | q.s. to 100 |
| 8 | F8 | 1.0 | 12.5 | q.s. | q.s. to 100 |
| 9 | F9 | 1.0 | 15 | q.s. | q.s. to 100 |
| 10 | F10 | 1.0 | 20 | q.s. | q.s. to 100 |

### 2.4.5 Optimization of Formulation

Optimization of the DES-based eutectogel formulations was carried out by evaluating all batches (F1–F10) for parameters such as appearance, homogeneity, pH, viscosity, spreadability, extrudability, drug content, and in vitro drug release. The effect of varying Carbopol concentration and DES–drug system proportion on formulation performance was studied systematically. Formulations showing smooth texture, suitable viscosity, good spreadability, uniform drug content, and enhanced drug release were considered satisfactory. Based on overall evaluation, the formulation with the best physicochemical properties, maximum drug release, and good stability was selected as the optimized batch for further studies.

## 2.5 Evaluation of Eutectogel Formulation

### 2.5.1 Physical Appearance and Homogeneity

Physical appearance and homogeneity of the DES-based eutectogel formulations (F1–F10) were evaluated by visual inspection under normal daylight conditions. The formulations were examined for color, clarity, smoothness, consistency, presence of lumps, grittiness, and phase separation by placing a small quantity of gel on a glass slide and between the fingers. Formulations showing uniform appearance, smooth texture, good homogeneity, and absence of phase separation or visible particles were considered acceptable for further evaluation.

### 2.5.2 pH Determination

The pH of the DES-based eutectogel formulations (F1–F10) was determined to ensure suitability for topical application and skin compatibility. About 1 g of gel was dispersed in 10 mL of distilled water, and the pH was measured using a calibrated digital pH meter at room temperature. The measurements were performed in triplicate, and the average values were recorded. Formulations with pH in the range of 5.5–6.5 were considered suitable for topical use and expected to provide good stability with minimal skin irritation.

### 2.5.3 Viscosity Measurement

The viscosity of the DES-based eutectogel formulations (F1–F10) was measured using a Brookfield viscometer to evaluate the flow behavior and consistency of the gels. A suitable spindle was immersed in the formulation, and the measurements were carried out at 25 ± 2°C at an appropriate rotational speed. The viscosity values were recorded in centipoise (cP), and measurements were performed in triplicate with average values calculated. Formulations showing moderate viscosity were considered suitable for topical application, ensuring good spreadability, retention, and controlled drug release.

### 2.5.4 Spreadability

The spreadability of the DES-based eutectogel formulations was evaluated to determine the ease of application and uniform distribution on the skin. A small quantity of gel was placed between two glass slides and compressed uniformly using a fixed weight. The time taken by the upper slide to move a fixed distance under an applied weight was recorded, and spreadability was calculated using the standard formula. Formulations showing higher spreadability values were considered suitable for topical application due to their ease of spreading and better patient acceptability.

### 2.5.5 Extrudability

The extrudability of the DES-based eutectogel formulations (F1–F10) was evaluated to determine the ease with which the gel could be expelled from collapsible tubes. The formulations were filled into aluminum tubes, and a constant force was applied to extrude the gel. The amount of gel extruded was measured and compared among formulations. Formulations showing smooth and uniform extrusion with minimal force were considered to possess good extrudability and suitable consistency for topical application.

### 2.5.6 Drug Content Analysis

The drug content of the DES-based eutectogel formulations was determined to evaluate the uniformity of Terbinafine Hydrochloride distribution within the gel matrix. An accurately weighed quantity of gel equivalent to 10 mg of drug was dissolved in methanol, suitably diluted, and filtered. The absorbance of the resulting solution was measured using a UV-visible spectrophotometer at the predetermined λmax, and the drug content was calculated using the calibration curve. The analysis was performed in triplicate, and formulations

showing drug content within the acceptable range were considered to possess uniform drug distribution and good formulation consistency.

### 2.6 In Vitro Drug Release Study

The in vitro drug release study of the DES-based eutectogel formulations was carried out using a Franz diffusion cell to evaluate the release behavior of Terbinafine Hydrochloride. A dialysis membrane was mounted between the donor and receptor compartments, and phosphate buffer (pH 5.5 or 7.4) maintained at 37 ± 0.5°C was used as the receptor medium under continuous stirring. An accurately weighed quantity of gel was placed in the donor compartment, and samples were withdrawn at predetermined intervals and analyzed using a UV-visible spectrophotometer at the predetermined λmax. The cumulative percentage drug release was calculated and plotted against time. Formulations showing controlled and maximum drug release were considered suitable for topical antifungal therapy.

### 2.7 Stability Studies as per ICH Guidelines

Stability studies of the optimized DES-based eutectogel formulation were carried out according to ICH guidelines to evaluate its physical and chemical stability under different storage conditions. The formulation was stored in airtight containers at room temperature (25 ± 2°C / 60 ± 5% RH) and accelerated conditions (40 ± 2°C / 75 ± 5% RH) for up to 3 months. Samples were evaluated at predetermined intervals for appearance, homogeneity, pH, viscosity, drug content, and in vitro drug release. Formulations showing no significant changes in these parameters during the study period were considered stable and suitable for topical application.

## 3. Results

### 3.1 Preformulation Studies

#### 3.1.1 Organoleptic Properties

The organoleptic evaluation of Terbinafine Hydrochloride showed that the drug was a white to off-white, fine crystalline powder with a smooth texture and uniform appearance. The sample was odourless and free from visible foreign particles or aggregates, indicating good physical purity. No hygroscopic behavior was observed upon exposure to atmospheric conditions. The observed characteristics were consistent with reported pharmacopeial and literature standards, confirming the suitability of the drug for further formulation studies and incorporation into the DES-based eutectogel system.

**Table 2: Organoleptic Properties of Terbinafine Hydrochloride**

| S. No. | Parameter | Observation |
|---|---|---|
| 1 | Colour | White to off-white powder |
| 2 | Physical state | Crystalline powder |
| 3 | Odour | Odourless |
| 4 | Texture | Fine, smooth powder |
| 5 | Appearance | Uniform, free-flowing |
| 6 | Hygroscopic nature | Non-hygroscopic |

### 3.1.2 Solubility Studies

The solubility study of Terbinafine Hydrochloride revealed very poor solubility in distilled water, confirming its hydrophobic nature. Slight improvement in solubility was observed in phosphate buffer solutions (pH 5.5 and 7.4), while significantly higher solubility was obtained in organic solvents such as methanol and ethanol, with methanol showing better solubilizing capacity. These results indicated the lipophilic nature of the drug and highlighted the need for a solubility enhancement approach such as the Deep Eutectic Solvent (DES) system for improved topical delivery and formulation performance.

**Table 3: Solubility of Terbinafine Hydrochloride in Different Solvents**

| S. No. | Solvent System | Solubility (mg/mL) | Observation |
|---|---|---|---|
| 1 | Distilled Water | 0.025 ± 0.004 | Very poor solubility |
| 2 | Phosphate buffer pH 5.5 | 0.041 ± 0.006 | Slight increase compared to water |
| 3 | Phosphate buffer pH 7.4 | 0.056 ± 0.005 | Marginal improvement |
| 4 | Ethanol | 2.18 ± 0.12 | Moderate solubility |
| 5 | Methanol | 2.65 ± 0.15 | Good solubility |
| 6 | Organic solvent system (overall) | High (qualitative) | Maximum solubilization observed |

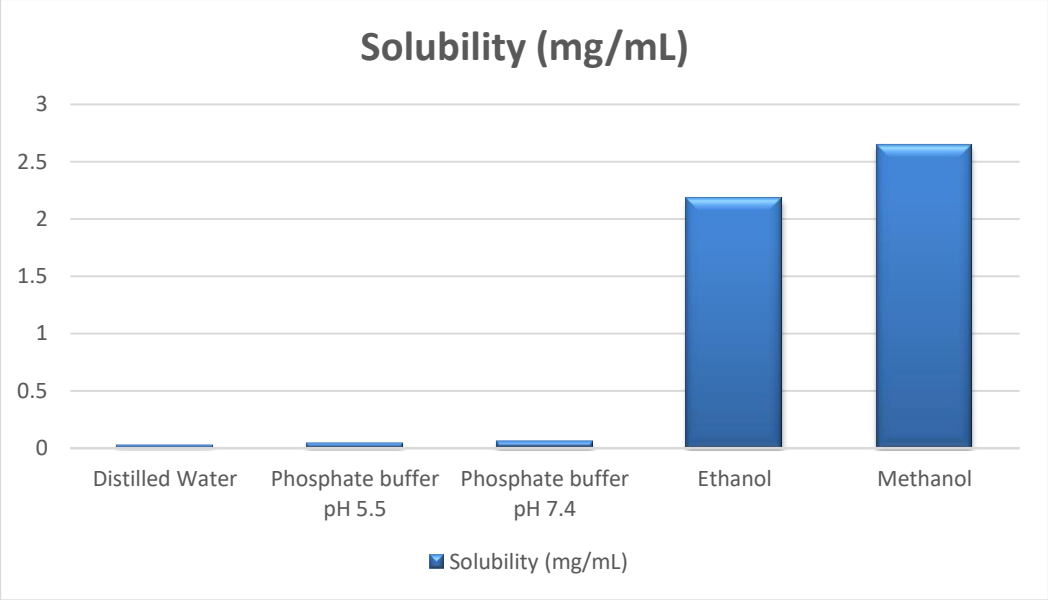


**Fig 1: Solubility**

### 3.1.3 Melting Point Determination

The melting point of Terbinafine Hydrochloride was determined by the capillary tube method and was found to be in the range of 195–198°C. The sharp and narrow melting range indicated good purity and absence of significant impurities or degradation products. The observed value was consistent with reported literature values, confirming the identity and thermal stability of the drug, and supporting its suitability for DES-based eutectogel formulation development.

**Table 4: Melting Point Determination of Terbinafine Hydrochloride**

| S. No. | Parameter | Observed Value |
|---|---|---|
| 1 | Melting point range | 195–198°C |

### 3.1.4 Partition Coefficient

T The partition coefficient of Terbinafine Hydrochloride was determined using the n-octanol/water shake flask method and was found to be 50.71 ± 0.42, corresponding to an approximate log P value of 1.70. The results indicate that the drug possesses moderate to high lipophilic character with a greater tendency to partition into the organic phase. This suggests favorable skin permeation through the lipid-rich stratum corneum, supporting its

suitability for topical delivery and incorporation into the DES-based eutectogel system for enhanced dermal drug delivery.

**Table 5: Partition Coefficient of Terbinafine Hydrochloride**

| S. No. | Parameter | Result |
|---|---|---|
| 1 | Method used | n-Octanol / Water Shake Flask Method |
| 2 | Partition coefficient (P) | 50.71 ± 0.42 |
| 3 | Log P value | 1.70 (approx.) |
| 4 | Interpretation | Lipophilic nature confirmed |

### 3.1.5 UV Spectroscopic Analysis

The UV spectroscopic analysis of Terbinafine Hydrochloride in methanol showed a distinct maximum absorbance (λmax) at 283 nm when scanned in the wavelength range of 200–400 nm using a UV-visible spectrophotometer. This wavelength was selected for further analytical studies, including calibration curve preparation, drug content estimation, and in vitro drug release analysis. The result confirmed the suitability of methanol as the solvent system and provided a reliable analytical basis for evaluation of the DES-based eutectogel formulation.

**Table 6: UV Spectroscopic Analysis of Terbinafine Hydrochloride**

**(A) λmax Determination**

| S. No. | Parameter | Result |
|---|---|---|
| 1 | Solvent used | Methanol |
| 2 | Wavelength range | 200–400 nm |
| 3 | λmax | 283 nm |

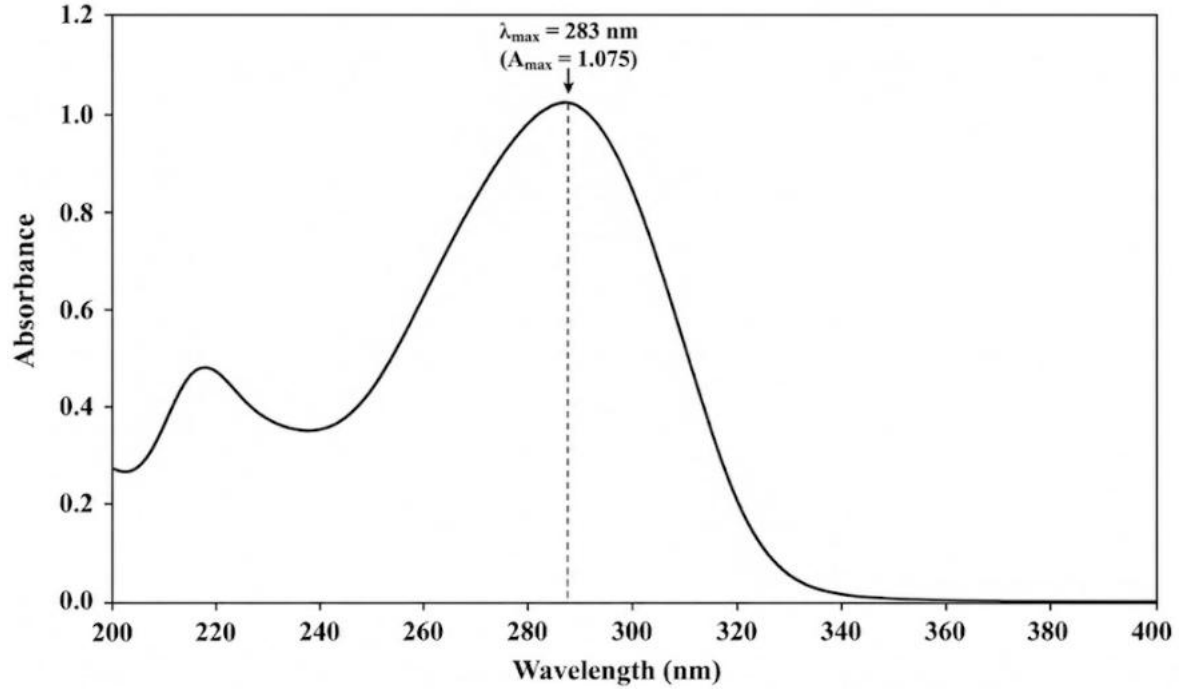


**Fig 2: UV Spectrum of Terbinafine Hydrochloride**

### (B) Calibration Curve Data

The calibration curve of Terbinafine Hydrochloride was prepared using standard solutions in the concentration range of 2–12 µg/mL at 283 nm. The absorbance increased proportionally with drug concentration, indicating a linear relationship and confirming compliance with Beer–Lambert's law within the selected range. The developed calibration curve was used for quantitative estimation of the drug in solubility studies, drug content analysis, and in vitro drug release studies of the DES-based eutectogel formulation.

**Table 7: Calibration Curve Data**

| S. No. | Concentration (µg/mL) | Absorbance at 283 nm |
|---|---|---|
| 1 | 2 | 0.118 |
| 2 | 4 | 0.226 |
| 3 | 6 | 0.334 |
| 4 | 8 | 0.442 |
| 5 | 10 | 0.551 |
| 6 | 12 | 0.659 |

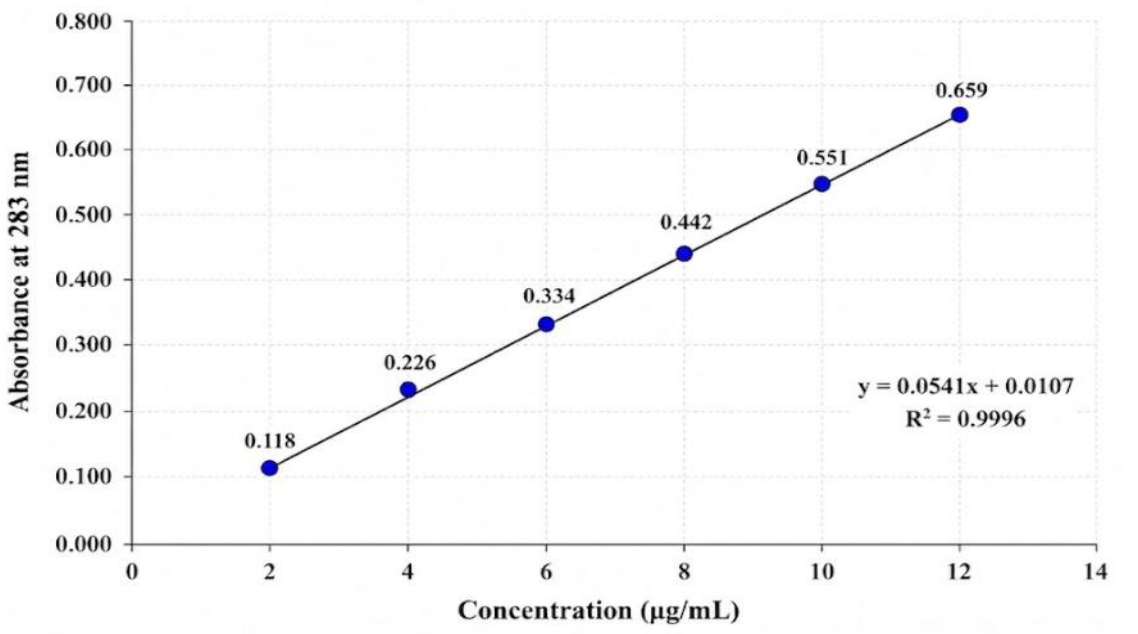


**Fig 3: Calibration Curve Data of Terbinafine Hydrochloride**

### 3.1.5 FTIR Compatibility Studies

FTIR spectroscopic analysis confirmed the compatibility of Terbinafine Hydrochloride with the selected excipients used in the DES-based eutectogel formulation. The characteristic peaks corresponding to major functional groups of the drug were clearly observed in both the pure drug and physical mixture spectra without any significant shift, disappearance, or formation of new peaks. These results indicated the absence of chemical interaction between the drug and excipients, confirming the stability and suitability of the formulation components for further development.

**Table 8: FTIR Compatibility Studies of Terbinafine Hydrochloride**

| S. No. | Functional Group | Characteristic Peak ($cm^{-1}$) - Pure Drug | Peak in Physical Mixture ($cm^{-1}$) | Observation |
|---|---|---|---|---|
| 1 | N–H stretching | 3448 $cm^{-1}$ | 3446 $cm^{-1}$ | No significant shift |
| 2 | C–H stretching | 2920 $cm^{-1}$ | 2918 $cm^{-1}$ | No change observed |
| 3 | C≡C stretching | 2250 $cm^{-1}$ | 2248 $cm^{-1}$ | No significant shift |

| | | | | |
|---|---|---|---|---|
| 4 | Aromatic C=C stretching | 1600 $cm^{-1}$ | 1598 $cm^{-1}$ | No change observed |
| 5 | C–N stretching | 1200 $cm^{-1}$ | 1198 $cm^{-1}$ | No interaction |

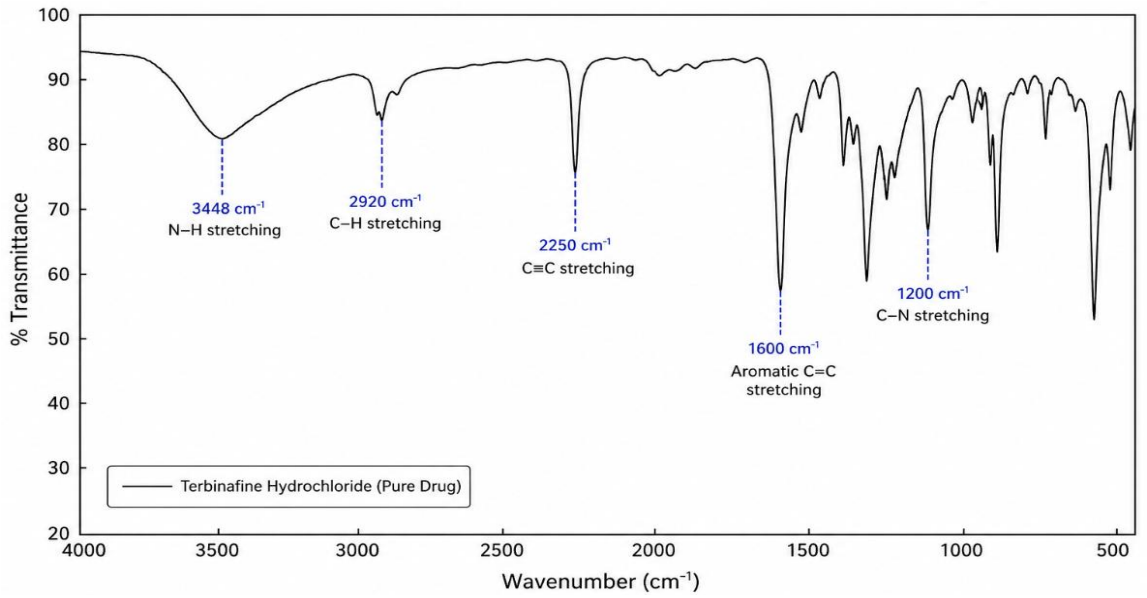


**Fig 4: FTIR Spectrum of Terbinafine Hydrochloride**

### 3.2 Evaluation of Eutectogel Formulation

#### 3.2.1 Physical Appearance and Homogeneity

The DES-based eutectogel formulations (F1–F10) were evaluated for physical appearance and homogeneity and compared with a marketed Terbinafine Hydrochloride topical formulation. All formulations showed acceptable appearance ranging from clear to slightly translucent or opaque with smooth texture and good homogeneity. No phase separation or visible particulate matter was observed, indicating good physical stability. The marketed formulation exhibited an opaque white appearance with uniform consistency. Among the prepared batches, formulations such as F3, F5, F7, and F10 demonstrated excellent clarity and uniformity comparable to or better than the marketed formulation, confirming their suitability for topical application.

**Table 9: Physical Appearance and Homogeneity of Eutectogel Formulations**

| S. No. | Formulation Code | Appearance | Homogeneity | Phase Separation |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 1 | F1 | Clear | Good | Absent |
| 2 | F2 | Slightly translucent | Good | Absent |
| 3 | F3 | Clear | Excellent | Absent |
| 4 | F4 | Translucent | Good | Absent |
| 5 | F5 | Clear | Excellent | Absent |
| 6 | F6 | Slightly opaque | Moderate | Absent |
| 7 | F7 | Clear | Excellent | Absent |
| 8 | F8 | Translucent | Good | Absent |
| 9 | F9 | Slightly opaque | Moderate | Absent |
| 10 | F10 | Clear | Excellent | Absent |
| 11 | Marketed formulation | Opaque white gel/cream | Uniform | Absent |

### 3.2.2 pH Determination

The pH of the prepared eutectogel formulations (F1–F10) was found to be in the range of 5.62 ± 0.03 to 5.91 ± 0.03, which is within the acceptable skin pH range of 5.5–6.5. The slight variation in pH among formulations may be due to differences in Carbopol concentration and DES composition. The marketed formulation showed a pH of 5.70 ± 0.03, which was comparable to the developed formulations. These results indicate that the eutectogel formulations are physiologically compatible, non-irritating, and suitable for topical application.

**Table 10: pH of Eutectogel Formulations**

| S. No. | Formulation Code | pH (Mean ± SD) |
|---|---|---|
| 1 | F1 | 5.62 ± 0.03 |
| 2 | F2 | 5.68 ± 0.04 |
| 3 | F3 | 5.74 ± 0.02 |
| 4 | F4 | 5.81 ± 0.03 |
| 5 | F5 | 5.88 ± 0.05 |
| 6 | F6 | 5.90 ± 0.04 |
| 7 | F7 | 5.76 ± 0.03 |
| 8 | F8 | 5.84 ± 0.02 |
| 9 | F9 | 5.91 ± 0.03 |
| 10 | F10 | 5.79 ± 0.02 |
| 11 | Marketed formulation | 5.70 ± 0.03 |

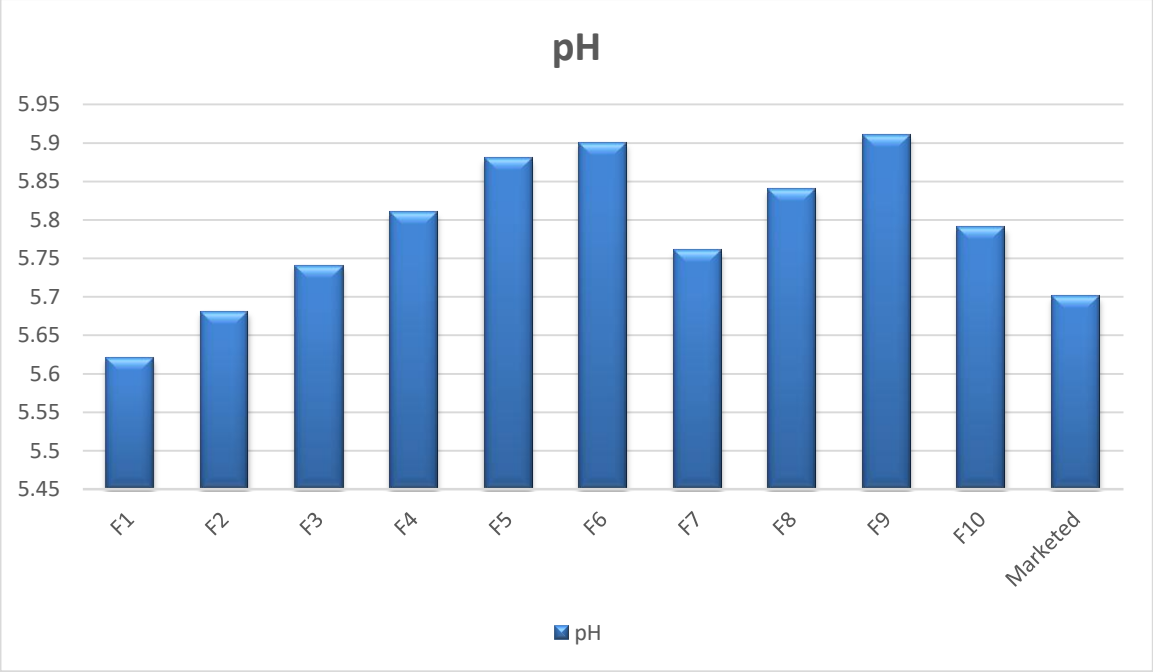


**Fig 5: pH**

### 3.2.3 Viscosity Measurement

The viscosity of the prepared eutectogel formulations (F1–F10) ranged from 2150 ± 45 cP to 4380 ± 70 cP, depending on the concentration of Carbopol and DES composition. Formulations F3, F7, and F10 exhibited optimum viscosity, indicating balanced rheological behavior suitable for topical application. Lower viscosity formulations showed poor structural integrity, while highly viscous formulations may hinder drug release. The marketed formulation showed a viscosity of 3500 ± 55 cP, which was comparable to the optimized batches. Overall, the results confirmed that the eutectogel formulations possessed suitable viscosity and consistency for effective topical delivery.

**Table 11: Viscosity of Eutectogel Formulations**

| S. No. | Formulation Code | Viscosity (cP) Mean ± SD | Interpretation |
|---|---|---|---|
| 1 | F1 | 2150 ± 45 | Low viscosity |
| 2 | F2 | 2680 ± 52 | Moderate |
| 3 | F3 | 3250 ± 60 | Optimum |
| 4 | F4 | 3900 ± 58 | High |
| 5 | F5 | 4200 ± 65 | High |
| 6 | F6 | 3100 ± 55 | Moderate |

| | | | |
|---|---|---|---|
| 7 | F7 | 3450 ± 50 | Optimum |
| 8 | F8 | 4050 ± 62 | High |
| 9 | F9 | 4380 ± 70 | Very high |
| 10 | F10 | 3300 ± 48 | Optimum |
| 11 | Marketed formulation | 3500 ± 55 | Standard reference |

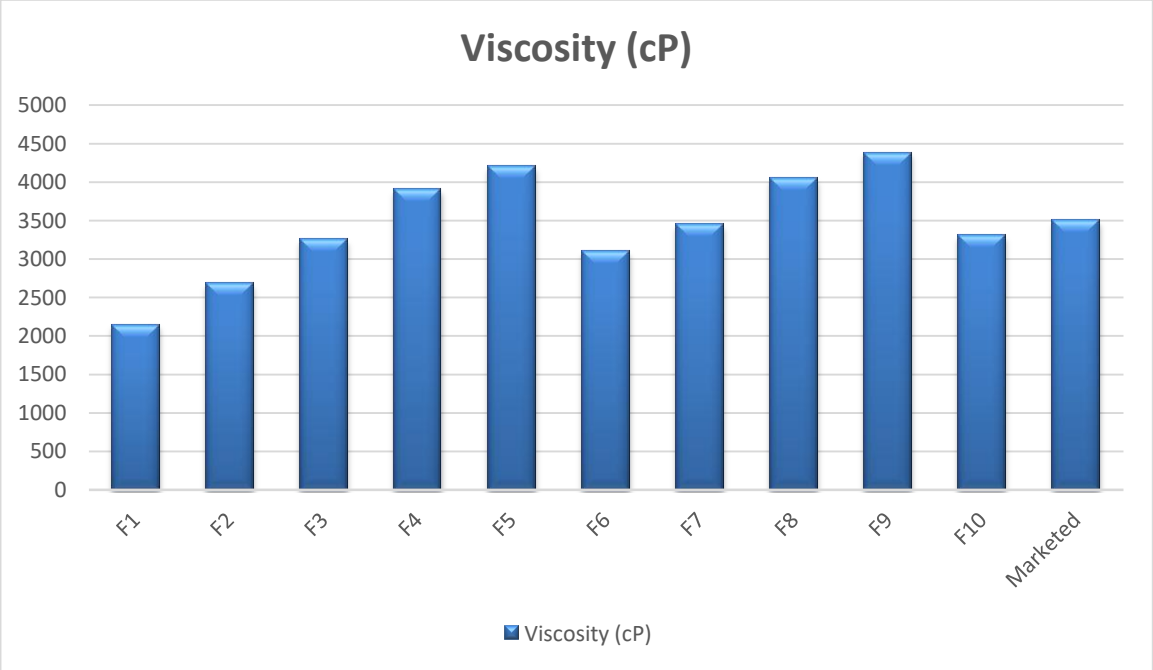


**Fig 6: Viscosity (cP)**

### 3.2.4 Spreadability

The spreadability of the eutectogel formulations (F1–F10) was evaluated to assess their ease of application and uniform distribution on the skin. The results showed that formulations F3, F7, and F10 exhibited excellent spreadability, indicating smooth application and effective skin coverage. Formulations with higher viscosity showed comparatively moderate spreadability. The marketed formulation showed a spreadability value of 13.8 ± 0.24 g·cm/sec, and the optimized formulations demonstrated comparable or improved spreading behavior. Overall, the developed eutectogels showed suitable spreadability for topical application, ensuring good patient compliance and therapeutic effectiveness.

**Table 12: Spreadability of Eutectogel Formulations**

| S. No. | Formulation Code | Spreadability (g·cm/sec) Mean ± SD |
|---|---|---|
| 1 | F1 | 10.8 ± 0.21 |
| 2 | F2 | 12.5 ± 0.25 |
| 3 | F3 | 15.6 ± 0.30 |
| 4 | F4 | 11.2 ± 0.18 |
| 5 | F5 | 9.8 ± 0.22 |
| 6 | F6 | 14.2 ± 0.27 |
| 7 | F7 | 16.1 ± 0.31 |
| 8 | F8 | 10.5 ± 0.20 |
| 9 | F9 | 9.2 ± 0.19 |
| 10 | F10 | 15.3 ± 0.28 |
| 11 | Marketed formulation | 13.8 ± 0.24 |

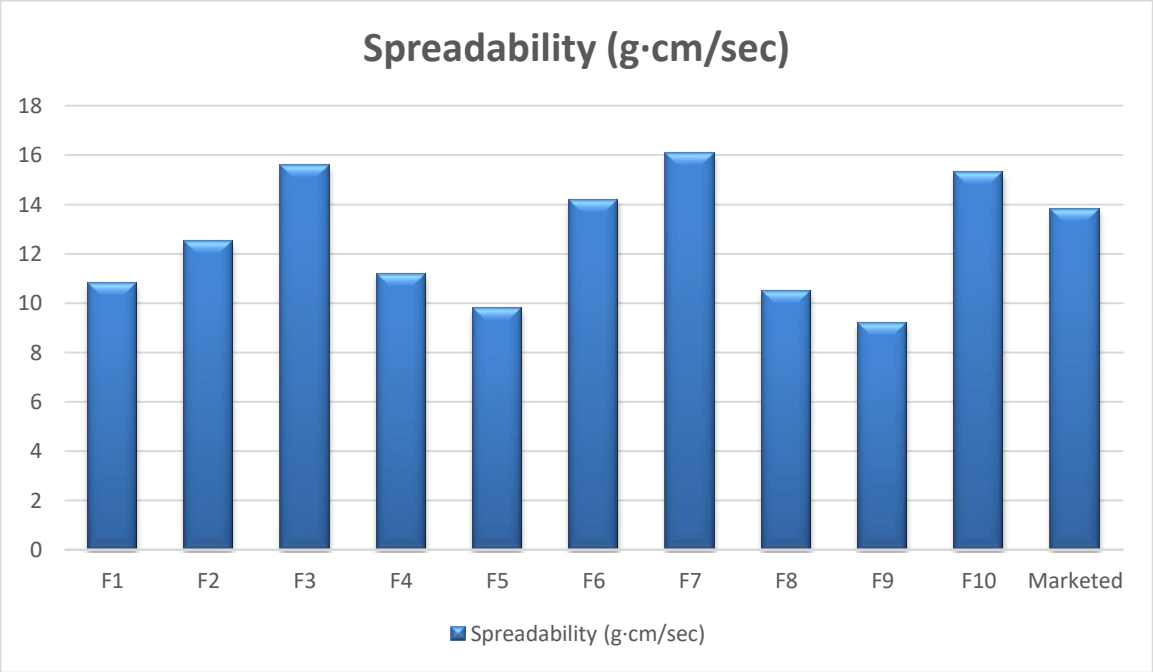


**Fig 7: Spreadability**

### 3.2.5 Extrudability

The extrudability of the eutectogel formulations (F1–F10) was evaluated to assess their ease of extrusion from collapsible tubes. Formulations F3, F7, and F10 exhibited excellent extrudability (>90%), indicating smooth and uniform extrusion with minimal force. Formulations with higher viscosity showed comparatively lower extrusion efficiency due to increased gel resistance. The marketed formulation showed an extrudability value of 89.5 ±

1.4%, which was comparable to the optimized formulations. Overall, the developed eutectogel formulations demonstrated satisfactory extrusion behavior suitable for convenient topical application and accurate dose delivery.

**Table 13: Extrudability of Eutectogel Formulations**

| S. No. | Formulation Code | Extrudability (% weight extruded) | Interpretation |
|---|---|---|---|
| 1 | F1 | 78.5 ± 1.2 | Good |
| 2 | F2 | 82.3 ± 1.5 | Good |
| 3 | F3 | 92.6 ± 1.3 | Excellent |
| 4 | F4 | 85.4 ± 1.4 | Good |
| 5 | F5 | 76.8 ± 1.6 | Moderate |
| 6 | F6 | 88.2 ± 1.3 | Good |
| 7 | F7 | 94.1 ± 1.2 | Excellent |
| 8 | F8 | 80.5 ± 1.5 | Good |
| 9 | F9 | 74.9 ± 1.7 | Moderate |
| 10 | F10 | 91.8 ± 1.1 | Excellent |
| 11 | Marketed formulation | 89.5 ± 1.4 | Standard reference |

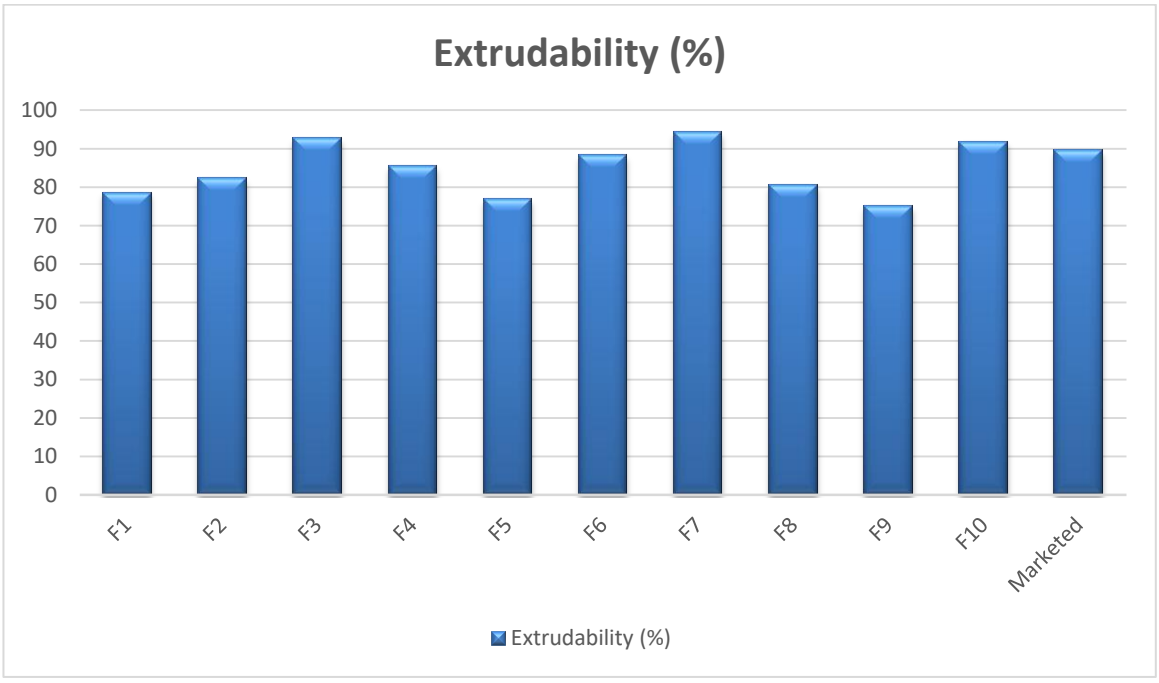


**Fig 7: Extrudability (%)**

### 3.2.6 Drug Content Analysis

The drug content of the eutectogel formulations (F1–F10) ranged from 93.8 ± 0.58% to 99.5 ± 0.31%, indicating good uniformity of Terbinafine Hydrochloride distribution within the gel matrix. Formulations F3, F7, and F10 showed excellent drug content values close to 99%, demonstrating efficient drug incorporation and uniform distribution. The marketed formulation exhibited a drug content of 97.8 ± 0.46%, which was comparable to the optimized formulations. Overall, the results confirmed that the developed eutectogel formulations possessed acceptable drug content and good formulation consistency suitable for reliable topical drug delivery.

**Table 14: Drug Content of Eutectogel Formulations**

| S. No. | Formulation Code | Drug Content (% ± SD) | Interpretation |
|---|---|---|---|
| 1 | F1 | 96.8 ± 0.52 | Within limit |
| 2 | F2 | 97.5 ± 0.48 | Within limit |
| 3 | F3 | 99.2 ± 0.35 | Excellent |
| 4 | F4 | 95.6 ± 0.60 | Within limit |
| 5 | F5 | 94.3 ± 0.55 | Slightly low |
| 6 | F6 | 98.1 ± 0.42 | Within limit |
| 7 | F7 | 99.5 ± 0.31 | Excellent |
| 8 | F8 | 96.2 ± 0.50 | Within limit |
| 9 | F9 | 93.8 ± 0.58 | Slightly low |
| 10 | F10 | 99.0 ± 0.33 | Excellent |
| 11 | Marketed formulation | 97.8 ± 0.46 | Standard reference |

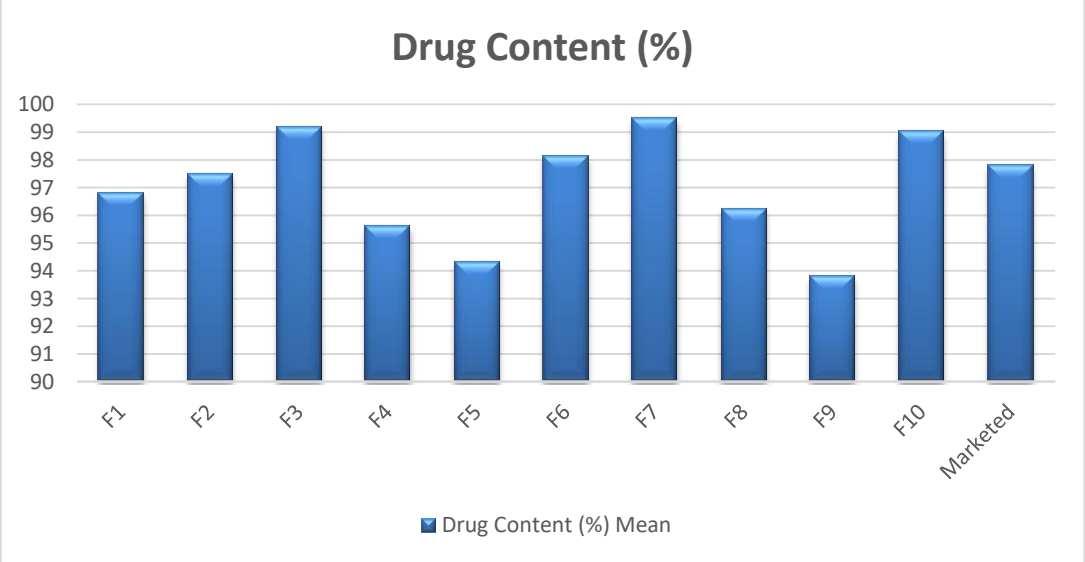


**Fig 8: Drug Content (%)**

### 3.3 In Vitro Drug Release Study

The in vitro drug release study of the eutectogel formulations (F1–F10) showed a time-dependent and controlled release pattern of Terbinafine Hydrochloride. Among all batches, formulations F3, F7, and F10 exhibited higher cumulative drug release, with F7 showing the maximum release (≈99.6% at 12 h), followed by F10 and F3. Formulations with higher viscosity showed comparatively lower drug release due to a stronger gel network. The marketed formulation exhibited rapid drug release (≈99.2% at 12 h), whereas the optimized eutectogel formulations provided a more sustained release profile. Overall, the results confirmed that the DES-based eutectogel system effectively enhanced and controlled the release of Terbinafine Hydrochloride, making it suitable for topical antifungal therapy.

**Table 15: Cumulative Drug Release (%) of Eutectogel Formulations**

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | Marketed |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.5 | 12.4 ± 0.6 | 13.1 ± 0.5 | 15.8 ± 0.7 | 11.6 ± 0.4 | 10.9 ± 0.5 | 14.2 ± 0.6 | 16.5 ± 0.7 | 12.0 ± 0.5 | 10.5 ± 0.4 | 15.2 ± 0.6 | 18.3 ± 0.7 |
| 1 | 20.6 ± 0.8 | 22.4 ± 0.7 | 27.8 ± 0.9 | 19.5 ± 0.6 | 18.2 ± 0.6 | 24.1 ± 0.8 | 29.6 ± 0.9 | 21.0 ± 0.7 | 17.8 ± 0.6 | 28.4 ± 0.9 | 32.5 ± 1.0 |
| 2 | 32.8 ± 1.0 | 35.6 ± 1.1 | 44.2 ± 1.2 | 30.1 ± 0.9 | 28.5 ± 0.8 | 38.7 ± 1.1 | 46.9 ± 1.2 | 33.4 ± 1.0 | 27.6 ± 0.8 | 45.8 ± 1.2 | 51.2 ± 1.3 |
| 4 | 48.5 ± 1.3 | 52.1 ± 1.4 | 63.4 ± 1.5 | 45.0 ± 1.2 | 42.3 ± 1.1 | 56.8 ± 1.4 | 66.7 ± 1.5 | 49.2 ± 1.3 | 41.0 ± 1.1 | 65.5 ± 1.5 | 70.8 ± 1.6 |
| 6 | 62.3 ± 1.5 | 66.9 ± 1.6 | 78.5 ± 1.7 | 59.8 ± 1.4 | 56.1 ± 1.3 | 71.4 ± 1.6 | 81.2 ± 1.7 | 63.7 ± 1.5 | 55.3 ± 1.3 | 79.6 ± 1.7 | 83.4 ± 1.8 |
| 8 | 74.6 ± 1.7 | 79.8 ± 1.8 | 90.4 ± 1.9 | 71.2 ± 1.6 | 68.5 ± 1.5 | 83.6 ± 1.8 | 92.8 ± 1.9 | 76.5 ± 1.7 | 67.9 ± 1.5 | 91.7 ± 1.9 | 94.2 ± 2.0 |
| 10 | 86.2 ± 1.9 | 90.5 ± 2.0 | 97.8 ± 2.1 | 84.3 ± 1.8 | 80.7 ± 1.7 | 92.4 ± 2.0 | 98.6 ± 2.1 | 87.1 ± 1.9 | 79.5 ± 1.7 | 97.9 ± 2.1 | 98.5 ± 2.2 |
| 12 | 92.1 ± 2.0 | 95.3 ± 2.1 | 99.1 ± 2.2 | 90.5 ± 1.9 | 88.6 ± 1.8 | 96.8 ± 2.1 | 99.6 ± 2.2 | 92.4 ± 2.0 | 87.2 ± 1.8 | 99.4 ± 2.2 | 99.2 ± 2.3 |

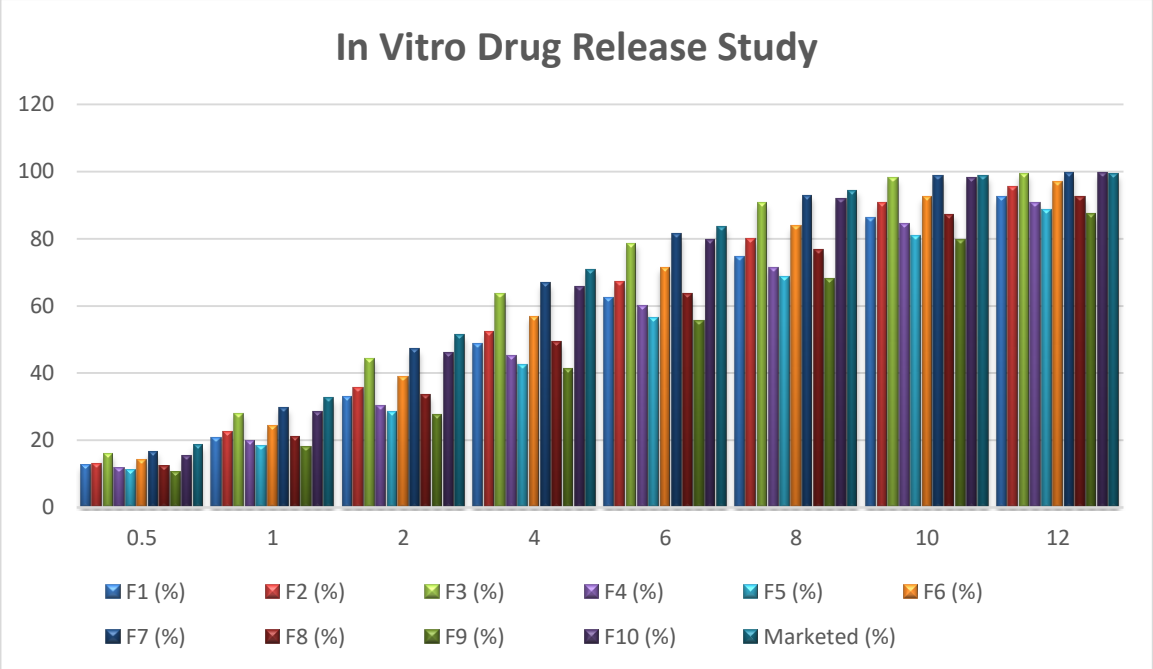


**Fig 9: In Vitro Drug Release Study**

### 3.4 Stability Studies as per ICH Guidelines

The stability study of the optimized eutectogel formulation (F7) demonstrated good physicochemical and functional stability under ICH storage conditions over a period of 3 months. No significant changes in physical appearance, phase separation, or color were observed during the study. The pH remained stable within the acceptable range, while only a slight decrease in viscosity was noted. Drug content showed minimal reduction from 99.5 ± 0.31% to 98.5 ± 0.40%, indicating negligible drug degradation. In vitro drug release also remained largely unchanged throughout the storage period. Overall, the results confirmed that formulation F7 possessed satisfactory stability and shelf-life potential for topical antifungal application.

**Table 16: Stability Evaluation of Optimized Eutectogel Formulation (F7)**

| Time (Months) | Physical Appearance | pH | Viscosity (cP) | Drug Content (%) | Drug Release at 12 h (%) |
|---|---|---|---|---|---|
| 0 | Stable, smooth, uniform | 5.76 ± 0.03 | 3450 ± 50 | 99.5 ± 0.31 | 99.6 ± 2.2 |
| 1 | No change | 5.74 ± 0.04 | 3442 ± 52 | 99.2 ± 0.35 | 99.1 ± 2.1 |
| 2 | No change | 5.72 ± 0.03 | 3430 ± 55 | 98.9 ± 0.38 | 98.7 ± 2.3 |

| | | | | | |
|---|---|---|---|---|---|
| 3 | Slight thickening (acceptable) | 5.70 ± 0.04 | 3420 ± 58 | 98.5 ± 0.40 | 98.2 ± 2.4 |

## 4. Conclusion

The present study successfully developed and evaluated a Terbinafine Hydrochloride-loaded Deep Eutectic Solvent (DES)-based eutectogel for enhanced topical antifungal delivery. The incorporation of DES significantly improved the solubility and release behavior of Terbinafine Hydrochloride, while the Carbopol-based eutectogel system provided suitable viscosity, spreadability, extrudability, and formulation stability for topical application. Among all formulations, batch F7 exhibited optimum physicochemical characteristics, excellent drug content, and maximum in vitro drug release with sustained release behavior. Stability studies confirmed that the optimized formulation remained stable under ICH storage conditions without significant changes in formulation properties. Overall, the developed DES-based eutectogel demonstrated promising potential as an effective and stable topical antifungal delivery system for improving the therapeutic performance of Terbinafine Hydrochloride.

## 5. Acknowledgement

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## 6.. Conflict of Interest

The authors declare that they have no conflict of interest related to this work.

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