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Formulation and Evaluation of Tolnaftate Emulgel: A Novel Approach for Enhanced Topical Delivery and Antifungal Efficacy

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Abstract:- The present study focuses on developing a tolnaftate emulgel to enhance topical delivery and minimize side effects through targeted application. Utilizing an emulgel method, tolnaftate was formulated with various excipients, including Carbopol 934, propylene glycol, and clove oil as a natural penetration enhancer at different concentrations (1-5% w/w). Comprehensive evaluations were conducted, assessing parameters such as rheology, pH, drug content, skin irritation, washability, drug release, swelling index, antifungal activity against Candida albicans, and stability. Notably, formulation F2 achieved a remarkable 97.45% in vitro drug release within 8 hours and maintained stability over 3 months without significant changes. Skin irritation tests confirmed its safety, while its antifungal efficacy exceeded that of the pure drug and commercial tolnaftate creams. These findings suggest that the tolnaftate emulgel, particularly formulation F2, offers a promising strategy for improved topical delivery, combining enhanced penetration, stability, and antifungal activity.

Keywords:- *Tolnaftate, Emulgel, Topical Delivery, Penetration Enhancer, Candida Albicans.*

I. INTRODUCTION

For many years, humans have encountered numerous diseases impacting their health and well-being. Topical drug delivery systems are designed to apply formulations containing active pharmaceutical ingredients directly onto the skin, aiming for a localized drug effect. [1] This method is typically used to treat skin conditions directly, but recent advancements have enhanced its potential to exert effects throughout the entire body. [2] The key advantages of topical drug delivery include bypassing the first-pass hepatic metabolism and avoiding the risks and complications associated with intravenous therapy. Additionally, it circumvents absorption challenges such as pH variations, enzymatic activity, and gastric emptying time. Topical drug delivery is often the preferred option when other treatment methods fail, particularly in managing fungal infections. [3]

Topical delivery refers to the application of a medicated formulation directly onto the skin to treat cutaneous conditions, such as acne and psoriasis, with the goal of confining the drug's effects to the skin's surface or within the skin layers [4]. Topical drug administration, through various routes, offers a broad range of preparations for both cosmetic and dermatological purposes, targeting both healthy and diseased skin without metabolic degradation before reaching the intended site [5]. Traditional dosage forms like creams, ointments, and gels have been widely used for topical applications but often lead to inconsistent drug absorption and present certain limitations. For instance, gels are mainly suitable for hydrophilic drugs, whereas ointments are more appropriate for hydrophobic drugs. Recent advancements in topical drug delivery aim to overcome these challenges by offering more controlled and efficient drug administration, tailored to patient needs, thereby enhancing overall treatment outcomes. [6]

A fungal infection, or mycosis, is an infection caused by fungi. These organisms are commonly found in the environment, including soil, plants, and decaying organic matter. Although many fungi are harmless or even beneficial, certain types can lead to infections in humans. [7]

Tolnaftate (TNF) is a synthetic antifungal medication classified under the BCS class IV category. Research has shown that TNF is effective when used topically, but it does not demonstrate the same level of efficacy when administered orally or via the intraperitoneal route. It is available in various topical forms, including creams, powders, sprays, and liquid aerosols. Tolnaftate is effective against several fungal species, such as Epidermophyton, Microsporum, Trichophyton, Malassezia furfur, and Candida albicans. [8]

The skin is the body's largest organ and serves as an external defense system. While it covers the body's exterior, its functions extend beyond defense. It acts as a mechanical barrier, protecting the internal body from the external environment. [9]

- *Physiology of Skin and Penetration of Topical Drugs:*

The skin of an average adult covers about 2 m² and receives approximately one-third of the body's blood supply. On average, each square centimeter of human skin contains 40-70 hair follicles and 200-300 sweat ducts. The skin's surface is slightly acidic, with a pH ranging from 4 to 5.6, influenced by sweat and fatty acid secretions. The skin consists of three distinct layers: the epidermis, dermis, and subcutaneous connective tissue. [10]

➢ *Mechanism of Skin Penetration:*

Skin penetration enhancers are substances that temporarily weaken the outer layer of the skin, allowing medications to more easily penetrate into the deeper layers and ultimately reach the bloodstream. [11]

➢ *Factors Affecting Drug Absorption Through the Skin:*

- *Biological Factors:*

✓ Thickness of the skin
✓ Lipid composition and area of the skin
✓ Number of sweat glands
✓ Skin acidity
✓ Blood circulation
✓ Skin moisture
✓ Skin health and inflammation

- *Chemical Factors:*

✓ Partition coefficient
✓ Size of the molecule
✓ Level of ionization (non-ionized drugs are absorbed more effectively)
✓ Impact of additional ingredients [12]

➢ *Rationale for Emulgel as a Topical Drug Delivery System:*

An emulgel is created by combining a gel with an emulsion, offering several advantages over traditional and newer drug delivery systems. Emulgels are thixotropic, meaning they are thick at rest but flow easily when applied. They are non-greasy, easy to spread and remove, soothing to the skin, non-staining, water-soluble, have a longer shelf life, and are environmentally friendly with an appealing clear appearance. Emulgels are commonly used for delivering steroids, antibiotics, painkillers, and antifungal medications. [13]

Traditional topical treatments, such as ointments, creams, and lotions, can be sticky, uncomfortable, difficult to spread, and may require extensive rubbing. They can also be unstable. To address these issues, the use of clear gels has risen in both cosmetics and pharmaceuticals. However, gels often struggle with delivering hydrophobic drugs. Emulgels address this limitation by using an emulsion-based approach, allowing effective incorporation and delivery of even hydrophobic drugs through the gel matrix. [14]

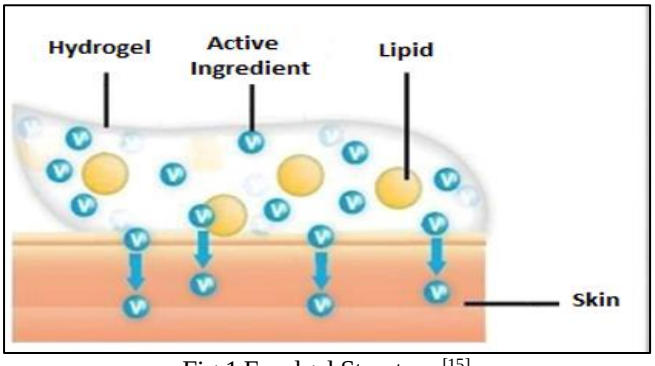

Fig 1 Emulgel Structure [15]

➢ *Advantages of Emulgel:*

- Avoids the body's first-pass metabolism, reducing systemic side effects.
- Enhances patient comfort and adherence.
- Suitable for self-administration.
- Delivers medication directly to the target area.
- Allows for easy discontinuation of the medication if needed.
- Simple to apply on hairy skin.
- Low production cost and easy to prepare.
- Serves as an alternative to oral medications [16]

➢ *Constituents of Emulgel Formulation*

- **Vehicle:** Acts as a carrier to deliver the drug to the target site and produce a pharmacological effect.

✓ Aqueous Materials: These make up the emulsion's water-based phase. Commonly used agents include water and alcohols.
✓ Oils: These constitute the oil phase. In emulsions meant for external application, mineral oils, either on their own or combined with soft or hard paraffins, are frequently used.

- **Emulsifier:** Emulsifying agents are utilized to facilitate the formation of emulsions during manufacturing and to maintain stability throughout the product's shelf life. Examples include sorbitan monolaurate (Span 20) and polysorbate (Tween 20).
- **Preservatives:** Prevent microbial growth and extend shelf life. E.g. Propyl paraben, methyl paraben.
- **Humectants:** Used to prevent moisture loss from the formulation. Examples include glycerin and propylene glycol.
- **Gelling Agents:** These agents increase the consistency of a dosage form and can also function as thickening agents. Example: Carbopol 934.
- **Penetration Enhancers:** Compounds that interact with skin components to temporarily increase skin permeability. Examples include eucalyptus oil and clove oil.
- **Mechanism of Penetration Enhancers:** These enhancers should not cause loss of bodily fluids, electrolytes, or other internal substances. After removal, the skin should rapidly regain its barrier function. Common penetration enhancers in emulgel formulations include oleic acid, clove oil, and menthol. [17]

II. MATERIALS AND METHODOLOGY

A. *Materials*

Tolnaftate was provided as a gift sample by Sujalam Chemicals (A-43, M.I.D.C, Kurkumbh, Pune, India). Carbopol 940 was received as a gift sample from Research Chem Lab Fine Industries, Mumbai, India. All other ingredients used were of analytical grade.

B. Methodology

➢ *Calibration Curve for Tolnaftate*

A stock solution of the standard drug was prepared in ethanol at a concentration of 1 mg/mL. From this stock solution, dilutions of 10 µg/mL, 20 µg/mL, 30 µg/mL, 40 µg/mL, and 50 µg/mL were made using ethanol. The maximum absorption wavelength (λmax) of tolnaftate was identified by scanning these dilutions between 200 nm and 400 nm with a UV-Visible spectrophotometer. [18]

C. Method of Preparation

➢ *Preparation of Tolnaftate Emulgel*

- *Step 1: Gel Base Preparation*

Dissolve carbopol in warm water under constant stirring until fully mixed. Adjust the pH by adding triethanolamine (TEA) gradually to achieve the desired consistency.

- *Step 2: Aqueous Phase Preparation*

Dissolve Tween 20 in purified water and heat to 70°C. Separately, mix propyl paraben and methyl paraben with propylene glycol to use as preservatives. Dissolve tolnaftate in ethanol, then add both the preservative mixture and the tolnaftate solution to the warmed aqueous phase.

- *Step 3: Oil Phase Preparation*

In a separate container, dissolve Span 20 in light liquid paraffin and heat the mixture to 70°C.

- *Step 4: Emulsification Process*

Gradually combine the heated oil phase with the aqueous phase, stirring continuously until the mixture cools down, forming a stable oil-in-water emulsion.

- *Step 5: Emulgel Formation*

Blend the prepared emulsion into the carbopol gel base with constant stirring. Add clove oil as a penetration enhancer and continue mixing until a uniform emulgel is obtained. Finally, transfer the emulgel into jars and secure with tight lids for storage. **[19]**

➢ *Formula for Preparation of Emulgel*

Table 1 Formula for Preparation of Emulgel

Ingredients %w/w	**F1**	**F2**	**F3**	**F4**	**F5**
Tolnaftate	1	1	1	1	1
Carbopol 934	1	1	1	1	1
Triethanolamine	1.2	1.2	1.2	1.2	1.2
Tween 20	1.5	1.5	1.5	1.5	1.5
Light liquid Paraffin	8	8	8	8	8
Span20	3	3	3	3	3
Ethanol	5	5	5	5	5
Propylene Glycol	5	5	5	5	5
Methyl Paraben	0.5	0.5	0.5	0.5	0.5
Propyl Paraben	0.3	0.3	0.3	0.3	0.3
Clove oil	-	5	3	2	1
Purified water	100	100	100	100	100

➢ *Evaluation Parameters:*

- **Physical Examination:** The emulgel formulations were visually examined to assess color, homogeneity, consistency, spreadability, and any signs of phase separation. [20]
- **Determination of pH:** A 1 gm sample of the emulgel was dissolved in 100 mL of distilled water and left to stand for two hours. The pH of the resulting solution was then measured using a pH meter to determine the formulation's pH. [21]
- **Spreadability:** To assess the spread ability of the emulgel formulations, two glass slides were used. A small amount of emulgel was placed on one slide, and the second slide was positioned on top, forming a thin layer of gel between them. The slides were pressed together to eliminate any air bubbles, and excess gel along the edges was wiped away. The slides were then positioned in a stand, with the lower slide held securely and the upper slide free to move. A 20-gram weight was attached to the upper slide, and the time taken for it to slide completely off the lower slide was recorded as the spread ability measurement.

Spreadability (S) is calculated using the formula:

$$S=M \times L/T$$

Where:

- **S** = Spreadability
- **M** = Weight applied to the upper slide (in grams)
- **L** = Distance moved by the upper slide (in centimetres)
- **T** = Time taken for the upper slide to slide off the lower slide (in seconds)

This formula allows for the quantification of the spreadability of the emulgel formulations based on the applied weight, distance moved, and time recorded. [22]

- **Extrudability:** The extrudability test was carried out using a Pfizer hardness tester. Initially, 15 grams of gel were placed in a collapsible aluminum tube, which was then secured in place. A pressure of 1 kg/cm² was applied for 30 seconds. After the pressure was released, the amount of gel that had been extruded from the tube was

weighed. This procedure was repeated at three different locations on the tube, and the entire test was conducted three times to ensure consistency and accuracy in the results.

Extrudability is calculated by using the following formula:

Extrudability = weight applied to extrude emulgel from tube (in gm) / Area (in sq.cm)

This formula provides a measure of how easily the emulgel can be extruded from the tube, considering the weight applied and the cross-sectional area of the tube. **[23]**

- **Washability Assessment:** The formulations were applied to the skin, and the ease and extent of washing them off with water were evaluated manually. This involved observing how easily the formulation could be removed and assessing any residual product left on the skin after washing. [24]
- **Viscosity:** The viscosity of the formulated emulgel was determined using a Brookfield viscometer with spindle number 52. The measurement was conducted at a speed of 100 RPM and at a temperature of 25°C. [25]
- **Swelling Index:** To measure the swelling index of the prepared topical emulgel, follow these steps:

✓ Take 1 gram of the emulgel and place it on a piece of porous aluminum foil.
✓ Immerse the foil with the gel into a 50 mL beaker containing 10 mL of 0.1 N NaOH solution.
✓ Remove the samples from the beaker at predetermined time intervals.
✓ Allow the samples to rest in a dry area for a short period.
✓ Weigh the samples again to determine the change in weight.

This process will allow for the calculation of the swelling index based on the weight changes observed over time.

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

Where, (SW) % = Equilibrium % swelling,

Wo = Original weight of emulgel at zero time after time t,

Wt. = Weight of swollen emulgel [26]

- **Drug Content Determination:** To determine the drug content in the emulgel, follow these steps:

✓ Dissolve 1 gram of the emulgel in a phosphate citrate buffer to ensure proper solubilization.
✓ Filter the resulting solution to obtain a clear liquid, removing any undissolved particles.
✓ Measure the absorbance of the clear solution using a UV-visible spectrophotometer at the appropriate wavelength for the drug.
✓ Utilize the measured absorbance along with a pre-established calibration curve to calculate the drug content in the emulgel.

This method allows for the quantification of the active ingredient in the emulgel formulation based on its absorbance in the UV-visible range. [27]

- **Skin Irritation Test:** Apply the emulgel to the properly shaved skin of eight rats. Monitor the application site for any adverse effects, such as changes in color or skin morphology, over a period of up to 24 hours. If no signs of irritation are observed, the test is deemed successful. However, if more than two rats exhibit any signs of skin irritation, the study must be repeated to ensure the safety and compatibility of the formulation. [28]
- **In vitro Drug release Study:** in-vitro release profiles of different formulations, an experiment was conducted using Franz Diffusion Cells with synthetic membranes. These membranes have a porous structure made from a hydrophobic material, which makes them similar to human skin in a simplified way. While these membranes are more permeable to drugs than human skin, the data they provide is useful for comparing the relative permeability of different formulations. Pieces of synthetic membrane were soaked in a potassium dihydrogen phosphate buffer (pH 7.4) for 24 hours before being used in the Franz-type diffusion cell. About 200 mg of each sample was placed on the donor side, fully covering the membrane. The entire setup was placed in a water bath at 32°C and continuously stirred. Care was taken to remove any air bubbles from beneath the membrane and from the receiving solution. At specific time intervals (0, 5, 10, 20, 30, 60, 90, 120, 150, and 180 minutes), 2 ml samples were taken from the receiver compartment and replaced with an equal volume of fresh buffer solution. These samples were then analyzed for Tolnaftate content using a spectrophotometer at a wavelength of 260 nm. [29]
- **Stability Study:** The Tolnaftate emulgel formulations were stored in collapsible tubes, kept away from light, at temperatures: 25±2°C, 40±2°C, and 4±2°C for three months. After this period, the samples were tested for their physical appearance, pH, spreadability, rheological Studies, drug release, and skin irritation test. [30]
- **Antifungal Activity:** In-vitro Antifungal Activity of Tolnaftate Emulgel Formulations was carried out against Candida albicans using Sabouraud agar medium and the agar-cup method. First, they prepared a suspension of C. albicans in Sabouraud dextrose broth and poured it into sterile Petri dishes, allowing it to solidify. Then, they used a borer to create 1 cm diameter wells in the solidified agar. They filled these wells with different formulations: a 1% emulgel without a penetration enhancer, an emulgel with essential oil (EO), and a marketed formulation. The plates were then incubated at 37°C for 24 hours. After incubation, they measured the diameter of the zones of inhibition to assess antifungal activity. The entire procedure was performed under aseptic conditions. [31]

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III. RESULTS AND DISCUSSION

The Objective of this study was to create and evaluate a topical drug delivery system for Tolnaftate, a drug that's difficult to dissolve in water. We decided to use a method called emulgel, which combines emulsions with gels. This method helps improve the solubility of hydrophobic drugs and enhances their ability to penetrate the skin. Emulgels also release the drug slowly over time, thanks to the polymers in the formulation. The study focused on the physical and chemical properties of the Tolnaftate emulgel.

➢ *Standard Calibration Curve of Tolnaftate Drug:*

Table 2 Concentration and Absorbance value of Tolnaftate Drug

Concentration (µg/mL)	Absorbance
10	0.569
20	0.958
30	1.335
40	1.984
50	2.467

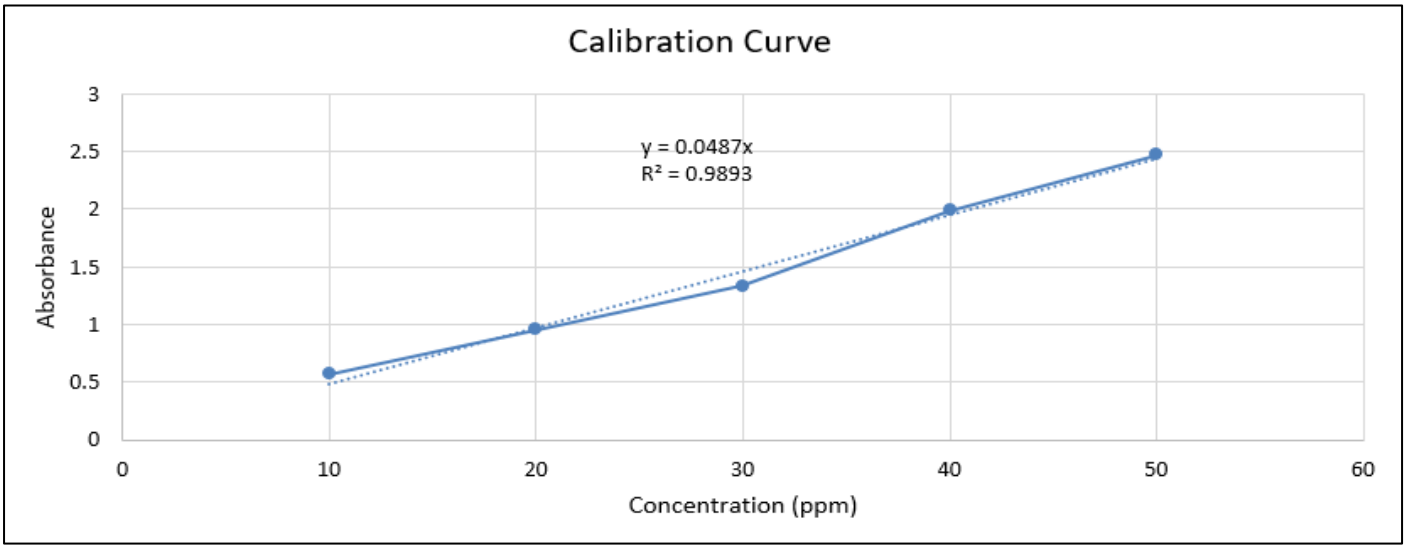

Fig 2 Calibration Curves of Tolnaftate

- **Physical Examination:** The prepared Tolnaftate Emulgel formulations were white viscous creamy Preparation with a smooth and homogeneous Appearance. The pH values of all prepared formulation Ranged from 5.4 to 5.8, which are acceptable to avoid the risk of irritation upon application to the skin, there is no phase Separation observed in Formulations. Results have been discussed in following Table. 3

Table 3 Physical Properties of Tolnaftate emulgel

Parameters	F1	F2	F3	F4	F5
Color	Milky white	Milky white	Milky white	Milky white	Milky white
Clarity	Clear	Clear	Clear	Clear	Clear
Grittiness	Non-gritty	Non-gritty	Non-gritty	Non-gritty	Non-gritty
Consistency	Smooth	Smooth	Smooth	Smooth	Smooth
Homogeneity	Excellent	Excellent	Excellent	Excellent	Excellent
Phase Separation	None	None	None	none	none

- **Determination of pH:** The pH values of all the prepared formulations were Ranging from 5.7 to 6.3, which is good because it helps prevent skin irritation.

Table 4 pH value of Tolnaftate Emulgel Formulations

Sr.No.	Formulation	pH
1	F1	6.0
2	F2	5.7
3	F3	6.3
4	F4	5.9
5	F5	6.2

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- **Spreadability Test:** The value of Spreadability indicate that the emulgel is Easily spreadable by small amount of shear. The spredability shown in Table 5.

Table 5 Spreadability Study of Tolnaftate Emulgel Formulations

Sr. No.	Formulation	Spreadability (g.cm/s)
1	F1	14.36
2	F2	22.13
3	F3	40.21
4	F4	15.67
5	F5	28.19

- **Extrudability:** The Extrudability of prepared Emulgel formulations are Excellent.
- **Washability:** The Washability of Prepared Emulgel Formulations are easily Washable.
- **Rheological studies:** The viscosity of different emulgel formulation was determined using a brook field viscometer (Brookfield DV-E viscometer). And reported in table. 6

Table 6 Rheological Study of Tolnaftate Emulgel Formulations

Sr. No.	Formulation	Viscosity (Cps)
1	F1	12,654
2	F2	12,582
3	F3	12,350
4	F4	13,260
5	F5	12,875

- **Swelling Index:** Tolnaftate Emulgels showed swelling index ranging from 13.54 to 29.65%, which was found to be satisfactory. The results of the swelling index are reported in Table.7.

Table 7 Swelling Index Study of Tolnaftate Emulgel Formulations

Sr.no.	Formulation	Swelling Index%
1	F1	29.65
2	F2	28.32
3	F3	13.54
4	F4	18.47
5	F5	22.85

- **Drug Content Determination:** The drug content of all the formulated Act gels was in the range of 86.12–95.62%, and formulation (F-2) showed the highest drug Content among the other Four Formulations. The results of the drug content are shown in Table. 8

Table 8 Percent drug analysis of Tolnaftate emulgel formulations

Sr.no.	Formulation	Drug content%
1	F1	92.3%
2	F2	95.62%
3	F3	86.12%
4	F4	89.36%
5	F5	90.25%

- **Skin Irritation Test:** No allergic symptoms like Inflammation, Redness, Irritation appeared on rats up to 24hrs.
- **In vitro Drug Release Study:** The in vitro release profiles of Tolnaftate from its different emulgel formulations are shown in the figure.3 It is clear that all the emulgel formulations release the drug effectively. The formulations can be ranked in descending order based on the amount of drug released after 21 hours, which were 89.12%, 97.45%, 76.28%, 79.02%, 72.98% (Table. 9)

Table 9 In Vitro Drug Release Study of Tolnaftate Emulgel Formulations

Time(min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	7.76	20.69	12.92	15.99	10.32
10	14.52	30.74	18.31	24.87	17.38
20	22.93	38.97	24.82	30.65	26.38

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30	32.54	42.39	32.68	35.75	35.42
60	38.29	58.26	41.93	43.66	41.38
90	45.23	62.87	52.06	52.34	49.42
120	55.87	70.75	62.51	60.98	57.61
150	62.49	78.34	68.96	62.42	70.46
180	89.12	97.45	76.28	79.02	72.98

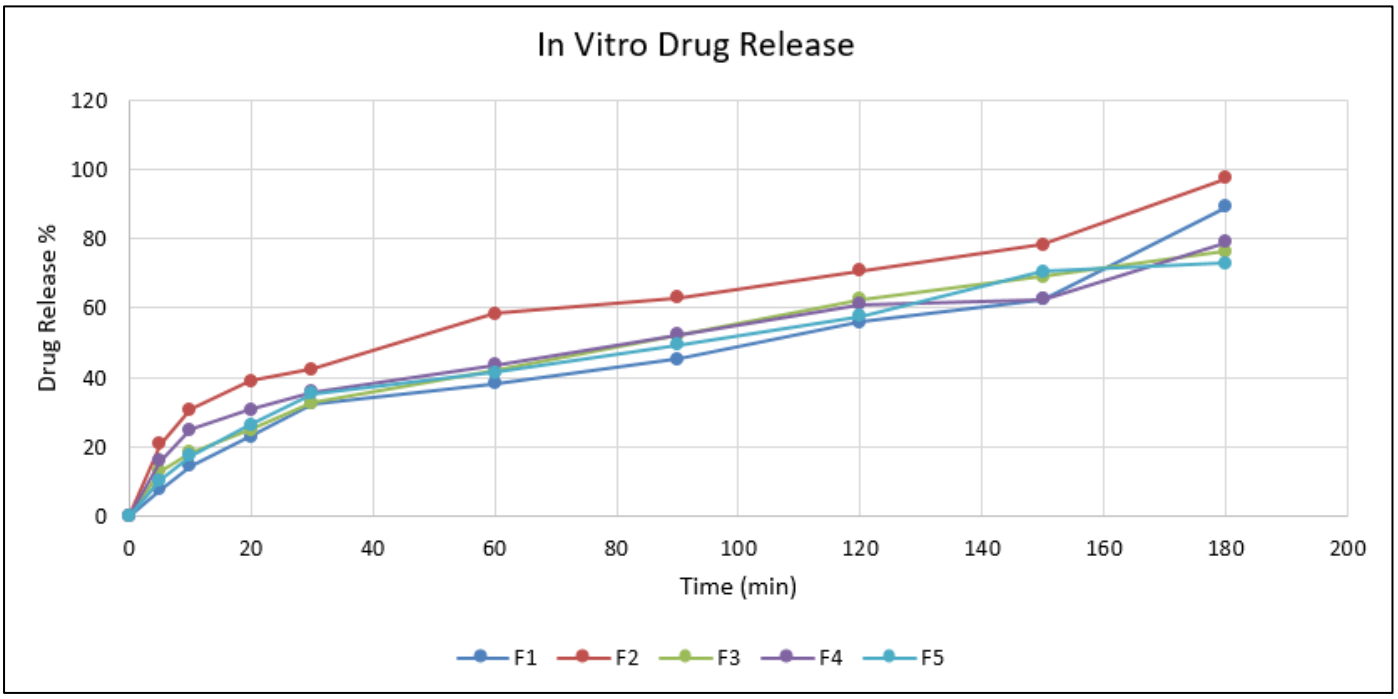

Fig 3 In Vitro Drug Release Study of Emulgel Formulation

- **Stability Studies:** All the formulations of Tolnaftate emulgel were found to be stable after 3 months at room temperature. No change was recorded in parameters like Physical appearance, Color, pH, and drug content. Results were reported in Table. 10

Table 10 Stability Study of Tolnaftate Emulgel Formulations

Sr. No.	Test	After 3 months
1	Physical appearance	Semisolid
2	Color	Milky white
3	pH	5.7
4	Drug content	95.62%

- **Antifungal Activity:** As the drug solution yielded a median concentration of 100 ppm for exhibiting the zone of inhibition for the Antifungal activity, emulgel equivalent to 100 ppm of TNF was selected for the study. It was observed that 100 ppm of the pure TNF produced a zone of inhibition of around 1.5 cm, whereas the emulgel formulated using 5 % Clove oil (F7) produced a zone of inhibition of about 2.5 cm. Moreover, the zone of inhibition produced by F7-batch of emulgel was comparable with that of the marketed Tolnaftate cream (Tinaderm) as depicted in Table. More importantly, the emulgel formulated with 5% Clove oil showed twice the zone of inhibition as compared to the drug solution. This may be attributed to incorporation of Clove oil in the emulgels which has facilitated the penetration across the diffusion membranes as well as through the fungal cell wall translating into efficient antifungal activity.

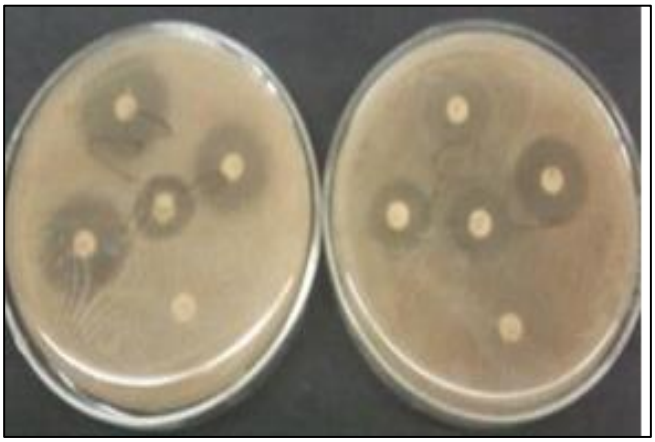

Fig 4 Zone of Inhibition Study

Table 11 Zone of Inhibition Study of Tolnaftate Emulgel Formulations

Dilutions	Concentration (ppm)	Zone of Inhibition (cm)
Pure drug	100	1.7
Emulgel without penetration enhancer	100	1.86
Emulgel with CO	100	2.8
Marketed cream	100	2.46
Blank control	0	No zone

IV. CONCLUSION

The aim of this study was to improve the penetration of the drug into skin. In the future, topical drug delivery system will be widely used to enhance patient compliance. In this study, a topical emulgel containing tolnaftate was prepared using natural penetration enhancer clove oil, polymer carbopol 934, liquid paraffin as emolient and emulsifiers span 20 and tween 20, with propylene glycol as a humectant. The formulation was evaluated for physical appearance, pH, spreadability, and rheological properties, Drug content, Skin irritation test, In vitro Release Study all of which were found to be within acceptable limits. The study successfully formulated tolnaftate in an emulgel using clove oil as penetration Enhancer. In the future, we will conduct in-vitro diffusion studies and other evaluations based on these formulation parameters. Testing in Relevant animal models will provide more insights into the effectiveness of this drug delivery system, highlighting the need for further research.

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