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# "FORMULATION AND EVALUATION OF TERBINAFINE & MOMETASONE FUROATE TOPICAL GEL"

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**ABSTRACT:**

The aim of the present research work is to prepare and evaluate topical gel of Terbinafine and Mometasone Furoate using different agent for the treatment of Dermatophytosis (ring or tinea) supper facial fungal infection to the skin. To develop a formulation to counter Dermatophytosis by using combination of an antifungal drug Terbinafine and a corticosteriod Mometasone Furoate in a topical gel formulation to enhance patient compliances and better delivery of drug to the affected area formulated gel was evaluated with respect to different physiochemical parameters such as pH, viscosity, Spreadibility, gel strength.

The *in-vitro* drug release rate of gel was evaluated using Franz diffusion cell it was concluded that physiochemical stable and non-irritant Terbinafine and Mometasone Furoate gel was formulated and the drug release increased with increase in concentration of penetration enhancer which is suitable for topical application.

**KEYWORDS:** Terbinafine, Mometasone Furoate, FDA, DSC, DoE, Spreadibility.

**INTRODUCTION:**

Terbinafine hydrochloride (Lamisil) is a synthetic allylamine antifungal. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase (also called squalene epoxidase), an enzyme that is part of the fungal cell wall synthesis pathway. Terbinafine hydrochloride was granted FDA approval on 30 December 1992. It is chemically known as (*E*)-*N*,6,6-trimethyl-*N*-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine[1]. The chemical structure of TBH is shown in **Figure 1.**

Mometasone furoate is a corticosteroid drug that can be used for the treatment of asthma, rhinitis, and certain skin conditions. It has a glucocorticoid receptor binding affinity 22 times stronger than dexamethasone and higher than many other corticosteroids as well. Mometasone furoate is formulated as a dry powder inhaler, nasal spray, and ointment for its different indications. It is chemically known as [(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*R*)-9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16 octahydrocyclopenta[a]phenanthren-17-yl] furan-2-carboxylate[2]. The chemical structure of MF is shown in **Figure 2.**

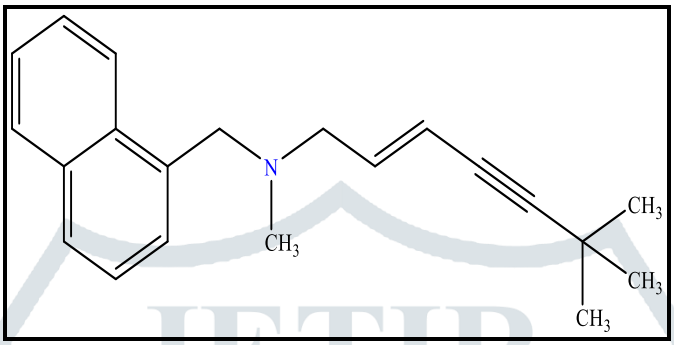


**Figure 1.** Chemical structure of TBH

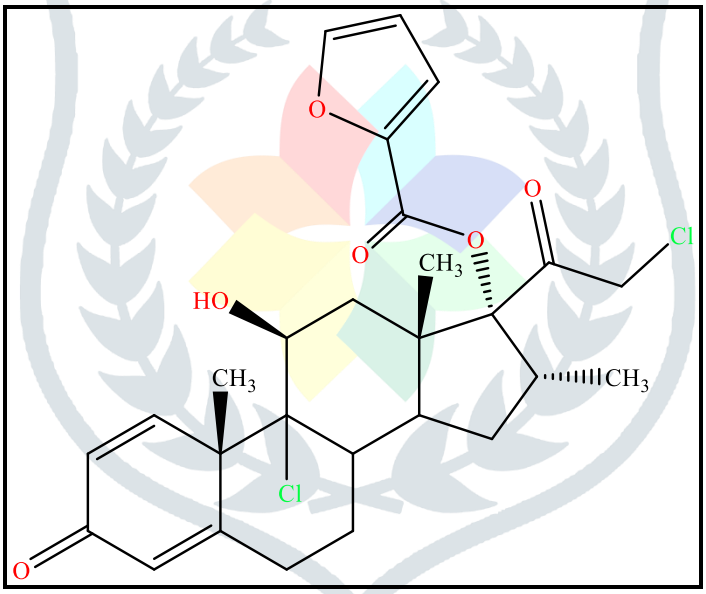


**Figure 2.** Chemical structure of MF

**MATERIALS AND METHODS:**

It contains Terbinafine hydrochloride (Dr. Reddy's, Hyderabad), Mometasone Furoate (Aurobindo Pharma, Hyderabad), Emulsifying wax - IP, Glyceryl mono stearate - IP, Propylene glycol - IP, Propyl paraben - IP (Lobachemie, Mumbai), Methyl paraben - IP, Liquid paraffin - IP, Soft paraffin - IP (Himedia, Mumbai), Hard paraffin - IP, Carbopol 940 - IP, Sodium hydroxide - IP, Simple ointment base (Merck(India) ltd, Mumbai), Carbopol 940 gel base (ILE company, Chennai), Terbinafine hydrochloride cream (Novartis Pharma, Bangalore) all showed be used to formulation of topical gel.

**FORMULATION PROCEDURE:**

1) Disperse Carbopol-940 in water using Magnetic Stirring at 1000 rpm to achieve a clear solution.
2) Add preservatives to an aqueous solution.
3) Add TBF, MF & PG to create a mixture.
4) Mix both aqueous mixtures with Carbopol-940 dispersion followed by the addition of NaOH solution.
5) Stir the entire mixture vigorously to obtain gel.

**DRUG PROFILE:**

**1) Terbinafine**

Molecular Weight: 291.4 g/mol
Molecular Formula: $C_{21}H_{25}N$
Melting point (°C): 205
logP: 6
pKa: 7.1

**2) Mometasone furoate**

Molecular Weight: 521.4 g/mol
Molecular Formula: $C_{27}H_{30}Cl_2O_6$
Melting point (°C): 215-228
logP: 4.115
pKa: 13.84

## 1. SOLID STATE CHARACTERIZATION OF DRUG [3,4,5]

### 1.1. Fourier Transfer Infrared Spectroscopy:

Both drugs were mixed with Potassium Bromide in a ratio of 9:1 which was triturated and blended evenly. The mixture was further compressed into pellets on a motorized pellet press at pressure of 15 ton. The prepared pellets were then scanned over range of 4000 - 400 $cm^{-1}$ to get the IR spectra. Functional group determination was studied visually by interpreting the peaks observed. The FT-IR experiment was conducted on FTIR- 8400S apparatus, Shimadzu, Kyoto, Japan. The FT-IR spectra show TBH & MF in **Figure 3 & 4.**

### 1.2. Differential Scanning Calorimetry:

Both drugs were hermitically sealed in perforated aluminium pan using crimper and heated at constant rate of 10°C/min over the temperature ranges of 30-300°C at 20 mL/min nitrogen purging on a Mettler Toledo DSC apparatus, Switzerland. The DSC spectra show TBH & MF in **Figure 5 & 6.**

### 1.3. Melting Point Determination:

Capillary Method was employed for Melting Point Determination. Both drugs were filled in a one end sealed capillary tube and were placed in a Liquid Paraffin bath in a Thiele's Tube. Upon visual inspection, temperature on which the solid starts turning into a liquid was noted down. The melting point data show TBH & MF in **Table 2.**

### 1.4. Solubility Analysis:

The preparation of any dosage form, it required to know the solubility of drug. The solid dosage form need particular solvent to dissolve, and produces pharmacological effect to body. Additionally, the bioavailability of drug present in solid dosage form depends upon solubility of drug. Solubility of TBF & MF both was studied in Methanol, Ethanol, DMSO, 0.1N HCl, pH 1.2 HCl buffers, pH 6.8 phosphate buffer to study the behaviour of the drugs.

Saturated solutions of both drugs with each solvent were made in 10ml glass vials and were set aside in an Orbital Shaking Incubator (Remi Instruments, Mumbai, India) at 32ºC for 24 hours at 50 rpm. The solutions were filtered using a 0.45 µm filter and diluted as required for further analysis. The solutions were analyzed by UV-2450 UV-Vis Spectrophotometer (Shimadzu, Japan) at wavelength of λ max against blank (blank contained same solvent in which drug was suspended). The solubility analysis data show TBH & MF in **Table 3 & Figure 7.**

## 2. DRUG-EXCIPIENTS INCOMPATIBILITY STUDIES [3,4]

### 2.1. Fourier Transfer Infrared Spectroscopy:

The Fourier Transform – Infrared (FT-IR) spectroscopy has numerous application in Pharmaceutical field. It is widely used in determination of identification of known and unknown compound. Apart from this it can also be used in evaluating the drug interaction. During formulation the active ingredient are used mixed with various excipients to give proper shape and appearance. Sometimes it happens after mixing the active ingredients with excipient, it produces incompatibility due to drug excipient interaction. The incompatibility of drug can alter the potency of formulation. It can also produce adverse effects to the body. Hence for pharmaceutical industries it is prime work to check the drug and excipient incompatibility.

Both drugs TBF & MF were mixed with all excipients in equal proportion forming a physical mixture were all compressed as a KBr pellet respectively for each sample at a ratio of 9:1. The prepared pellets were then scanned over range of 4000 - 400 cm-1 to get the IR spectra. Functional group determination was studied visually by interpreting the peaks observed and any changes in parent peaks were observed. The FT-IR spectra show both TBH & MF in **Figure 8.**

### 2.2. Differential Scanning Calorimetry:

Physical Mixture of drug and excipients was prepared for both drugs and sealed in a pre-washed ampoule. It was set aside in a Programmable Environmental Test Chamber, Remi Instruments Ltd. Mumbai for 28 days. Following that the sample was hermitically sealed imperforated aluminum pan and heated at constant rate of 10°C/min over the temperature ranges of 30-300°C at 20 mL/min nitrogen purging on a Mettler Toledo DSC apparatus, Switzerland. The DSC spectra show both TBH & MF in **Figure 9.**

Formulation Table for topical gel of TBF & MF composed by using Central Composite Design, all listed is trial batches.

| Formulation Code | TBF | MF | Carbopol-940 | NaOH | PG | MP | PP | Pu. Water to make Q.S |
|---|---|---|---|---|---|---|---|---|
| F1 | 1 | 0.1 | 0.5 | 0.5 | 10 | 0.2 | 0.1 | 87.6 |
| F2 | 1 | 0.1 | 2 | 0.5 | 10 | 0.2 | 0.1 | 86.1 |
| F3 | 1 | 0.1 | 0.5 | 0.5 | 20 | 0.2 | 0.1 | 77.6 |
| F4 | 1 | 0.1 | 2 | 0.5 | 20 | 0.2 | 0.1 | 76.1 |
| F5 | 1 | 0.1 | 0.19 | 0.5 | 15 | 0.2 | 0.1 | 82.9 |
| F6 | 1 | 0.1 | 2.3 | 0.5 | 15 | 0.2 | 0.1 | 79 |
| F7 | 1 | 0.1 | 1.25 | 0.5 | 7.9 | 0.2 | 0.1 | 88.9 |
| F8 | 1 | 0.1 | 1.25 | 0.5 | 22.1 | 0.2 | 0.1 | 74.7 |
| F9 | 1 | 0.1 | 1.25 | 0.5 | 15 | 0.2 | 0.1 | 81.8 |

**Table 1.** Formulation Table for topical gel of TBF & MF composed by using Central Composite Design (all ingredients in grams).

## 3. EVALUATION OF TBF & MF TOPICAL GEL:

### 3.1. Organoleptic Properties:

The organoleptic features of the samples were examined at the same temperature, lighting and packaging condition to assess variation in appearance, phase separation and color. The organoleptic properties data show TBF & MF in **Table 4.**

### 3.2. pH:

One gram of each formulation was weighed and dispersed with 10 ml distilled water. After homogenization, the pH of the sample was measured with pH meter. The pH data show TBF & MF in **Table 4.**

### 3.3. Viscosity:

The viscosity was determined by using Brookfield viscometer (Model LVDV III). The viscometer is placed on the "Standby Mode". Samples were allowed to reach room temperature and the samples were shaken vigorously. Then the samples were filled in a 600-mL, low-form Griffin beaker at least 3/4 full of slurry from the sample bottle. The spindle number 64 was selected. The spindle was inserted in to the appropriate beaker containing sample. Care was to be taken to avoid air bubbles since it may be trapped beneath the spindle. The beaker was moved in to the position beneath the viscometer and the spindle was attached so that the spindle remains submerged into the sample. The sample viscosity is measured 30° C. The reading was recorded in centipoises. The viscosity data show TBF & MF in **Table 4.**

### 3.4. Spreadibility[6,7]:

Spreadability of the formulation was determined by an apparatus, suggested by multimeter et al, which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pully at one end. A rectangular ground glass plate (20cm x 20cm) was fixed on the block. Two grams of the formulation was sandwiched between the ground fixed plates and another glass plate having the same dimensions of the fixed ground plate. The movable glass plate is provided with the hook. A 300gm weight was placed on the tip of two plates for five minutes to expel air and to provide a uniform film of the formulation between the plates. Excess of the formulation was scrapped off from the edges.

The top plate was then subject to a pull of a 30 gms, initially with the help of a string attached to the hook and moves over the pulley. The time required by the top plate to move at a distance of 10 cms was noted. A shorter time interval indicates better spreadability. The spreadibility data show TBF & MF in **Table 4.**

### 3.5. Extrudability[8]:

The apparatus used to measure is extrudability apparatus. A closed collapsible tube containing formulation was pressed firmly at the crimped end by keeping weight. When the cap was removed, formulation extruded until the pressure dissipated. Weight in grams required to extrude a 0.5 cm ribbon of the formulation in 10 seconds was determined. The experiments were repeated thrice and the average value is reported. The extrudability data show TBF & MF in **Table 4.**

### 3.6. In-Vitro Diffusion Study[9]:

The previously prepared diffusion membrane was sandwiched between the receptor and donor chamber of the Franz cell. The receptor compartment was carefully filled with phosphate buffer of pH 7.4 and the cell was placed on the magnetic plate maintained at 37°C. A small Teflon coated (3mm) magnetic bar was included in the receptor compartment such that stirring occurred throughout the duration of the experiment. After equilibrating for 30 minutes, at an appropriate time intervals a definite volume of the receptor solution was withdrawn and immediately replaced by equal volume of fresh receptor solution at the same temperature (37°C) as the receptor chamber.

The experiments were conducted under unclouded conditions for duration of 10, 20, 30, 40, 50 and 60 minutes drug content was analyzed by UV Spectrophotometer at maxima. At least 6 replicates were performed for each sample including the control. Sink condition was maintained throughout the experiment and this may be defined as ensuring that the concentration of the penetrated in the receptor does not exceed 20% of the saturated solubility of penetrate in the vehicle, in order to ensure an adequate drinking force for diffusion is maintained. The *in-vitro* diffusion study data show TBF & MF in **Table 5 & Figure 10.**

**RESULT AND DISCUSSION:**

**1. DRUG IDENTIFICATION BY SOLID STATE CHARACTERIZATION:**

**1.1. Fourier Transfer Infrared Spectroscopy:**

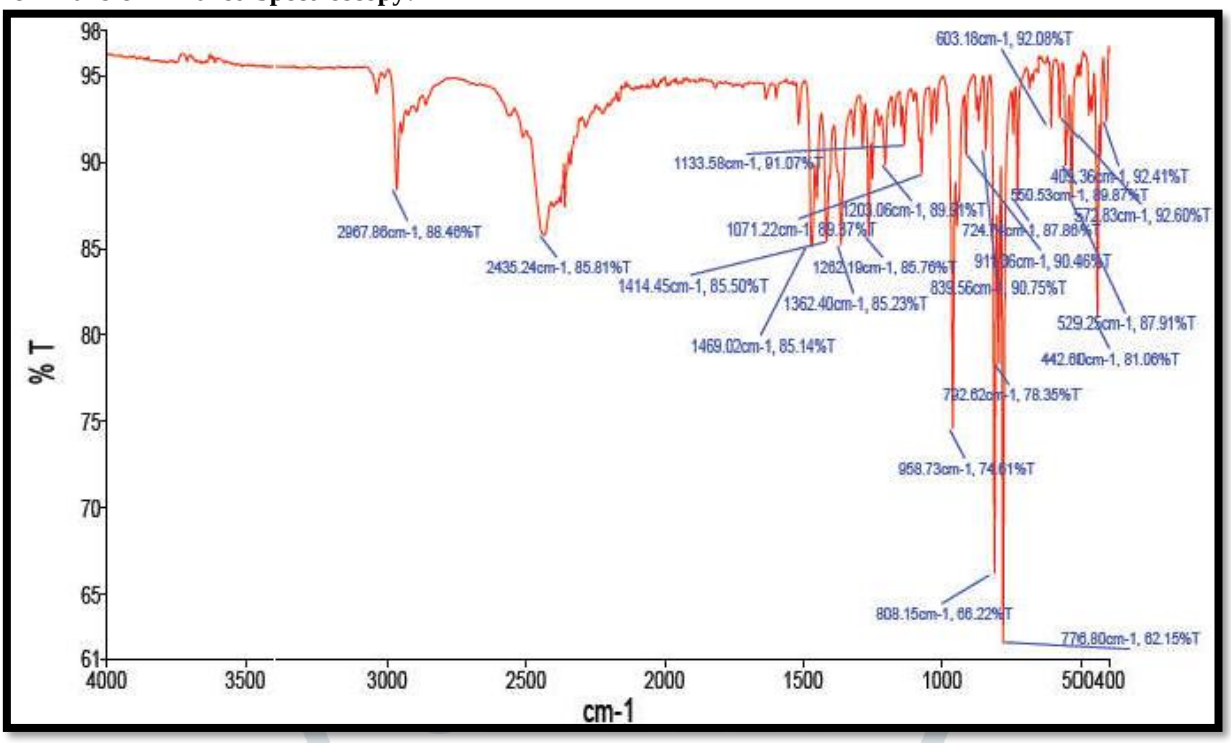


**Figure 3.** FTIR Spectra of TBF

The FTIR spectra illustrated above. FTIR for TBF showed Amine (3423), Alkanes (2967), Alkyl (2837.79), Amide (1635), Aromatic C=C (1510.41, 1455.13), C-O Alcohols, ethers, carboxylic acids (1254.81) and FTIR spectra shows MF Carbonyl (1723), keto carbonyl at position 3 (1658), O-H stretch (3500 to 3600), Amide (1635), Aromatic C=C (1323.12, 1455.13), C-O Alcohols, ethers, carboxylic acids (1254.81). Hence it was inferred that the substances were confirmed as TBF & MF respectively.

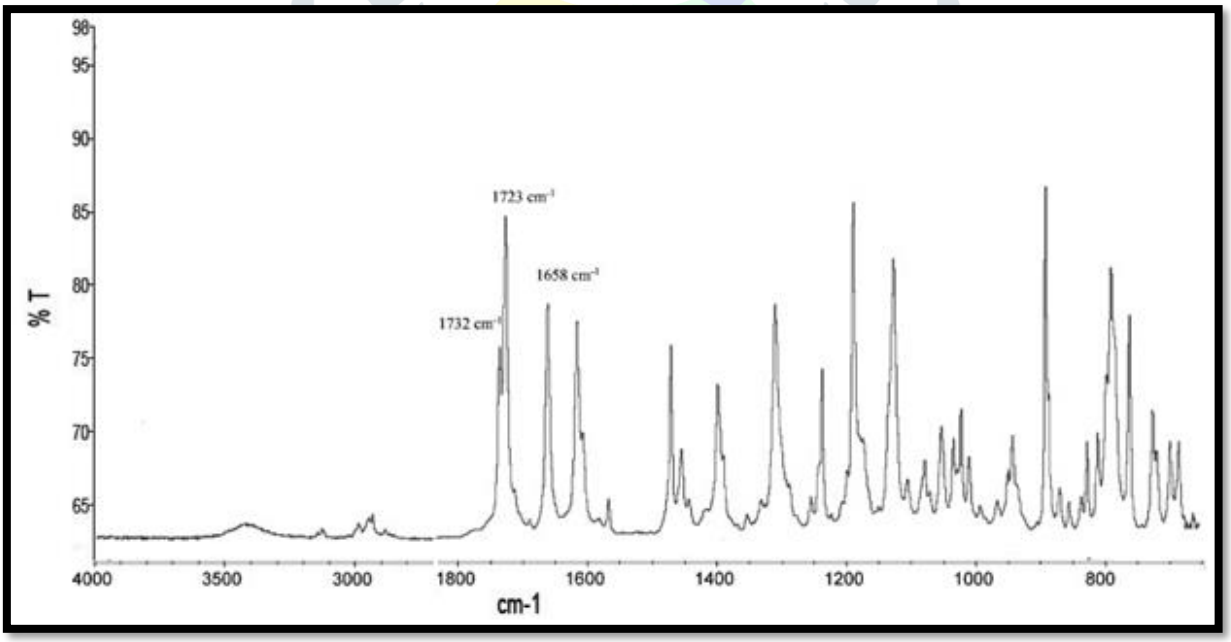


**Figure 4.** FTIR Spectra of MF

**1.2. Differential Scanning Calorimetry:**

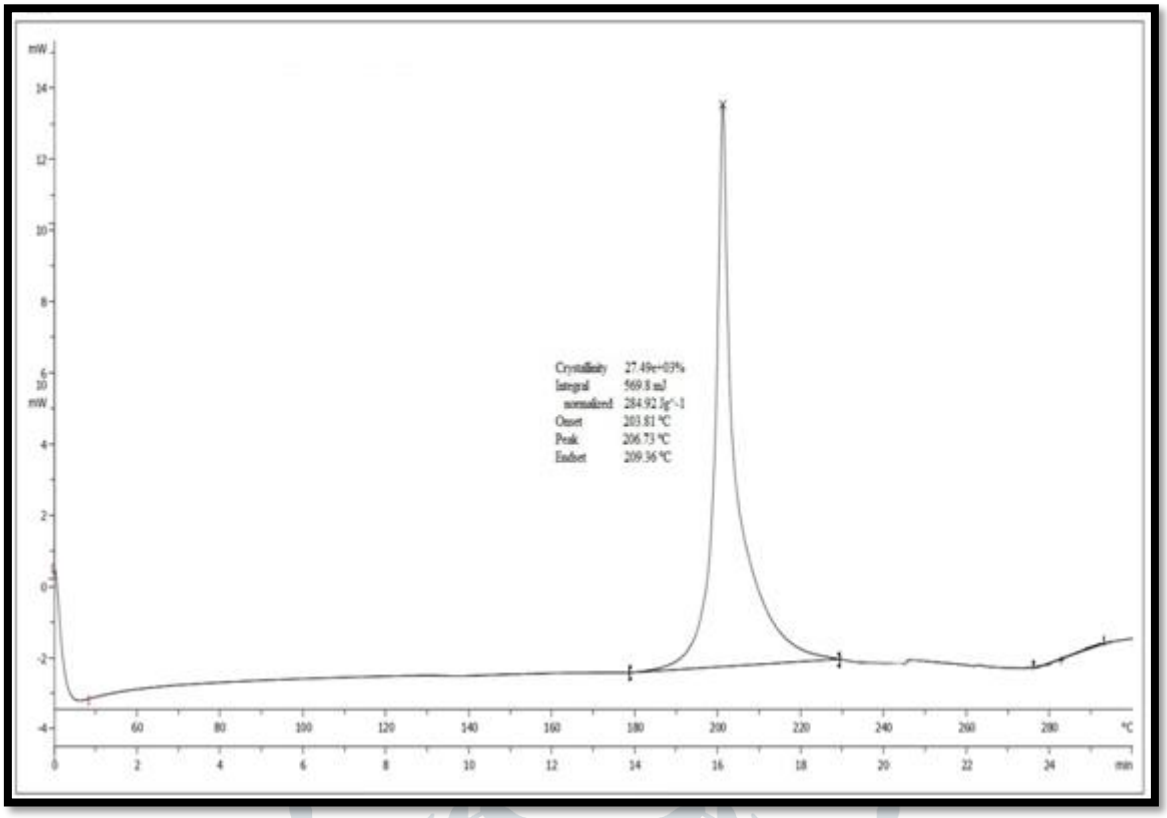


**Figure 5.** DSC TBF

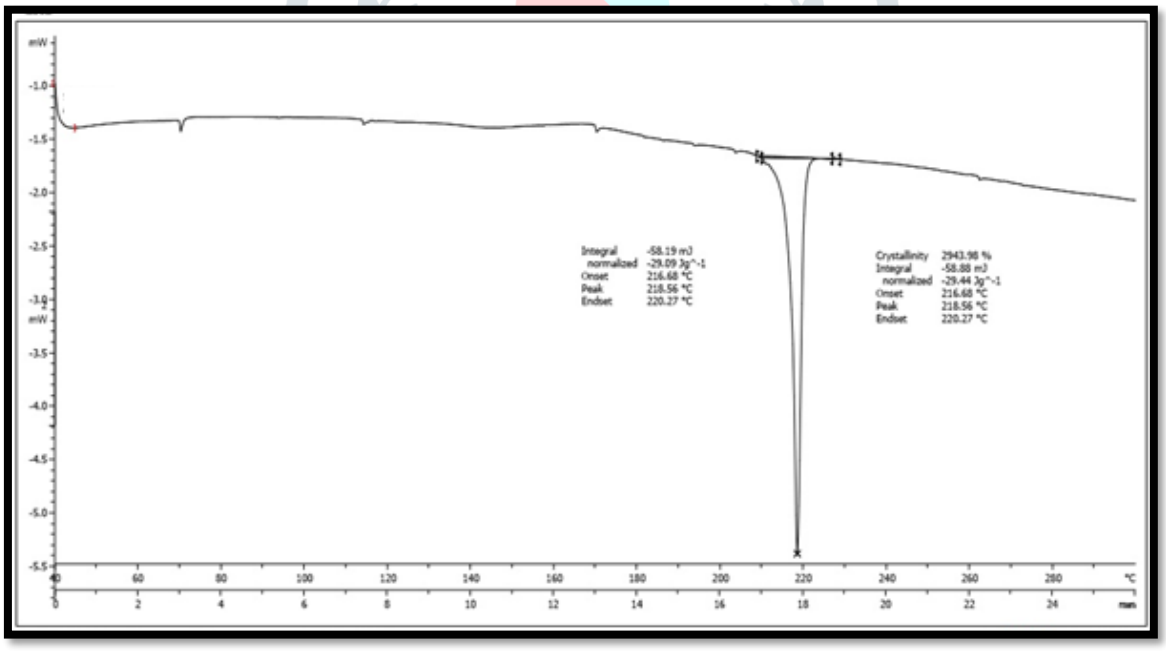


**Figure 6.** DSC MF

The DSC graphs were obtained as illustrated above. DSC for TBF showed a peak endotherm at 206.73°C and DSC for MF showed a peak endotherm at 216.60°C. The values at endotherm are congruent with the standard melting point values mentioned in the literature. Hence it was inferred that the substances were confirmed as TBF & MF respectively.

**1.3. Melting Point Determination:**

M.P determination was carried out by Thiele's Tube method and the median was recorded where the drug was completely visible to be have melted to a liquid state.

| Drug | Melting Point (°C) |
|---|---|
| TBF | 208 ±3 |
| MF | 221 ±5 |

**Table 2:** M.P. Results

**1.4. Solubility Studies:**

Solubility of TBF & MF both was studied in Methanol, Ethanol, DMSO, 0.1N HCl, pH 1.2 HCl buffers, pH 6.8 phosphate buffer to study the behaviour of the drugs. The results are illustrated.

| Solvent | Solubility (mg/ml) | |
|---|---|---|
| | TBF | MF |
| Methanol | 26 | 6 |
| Ethanol | 30 | 9 |
| DMSO | 12.5 | 12.9 |
| 0.1N HCl | 6.8 | 1.3 |
| pH 1.2 HCl buffer | 6.4 | 1.1 |
| pH 6.8 phosphate buffer | 7.8 | 1.2 |
| Water | 3 | 0.05 |

**Table 3:** Solubility Results

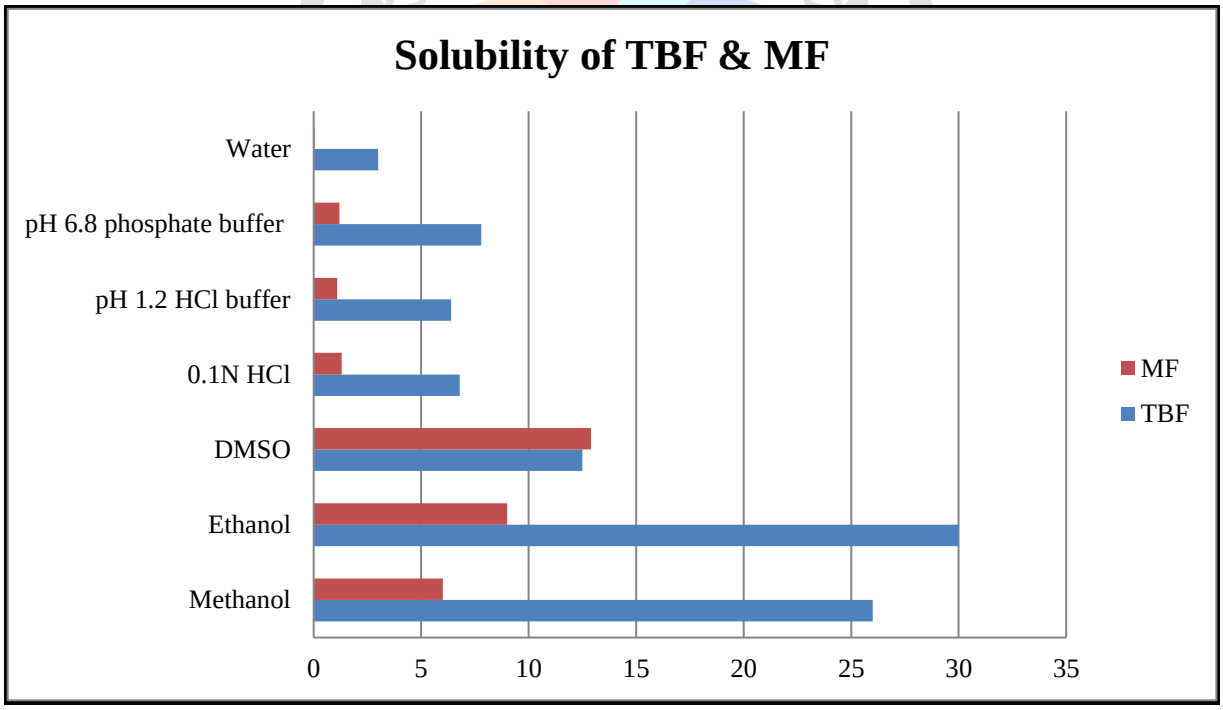


**Figure 7:** Solubility Data

Both drugs have poor water solubility, followed by poor solubility in buffers. Hence this explains the addition of PG in the preparation. Not only it aids in the formulation characteristics but it also works as a co-solvent which can enhance the solubility of these drugs. Both drugs show maximum solubility in organic solvents.

## 2. DRUG-EXCIPIENTS INCOMPATIBILITY STUDIES:

### 2.1. Fourier Transfer Infrared Spectroscopy:

The FTIR spectrum of Physical mixture containing all the excipients with the drugs is represented.

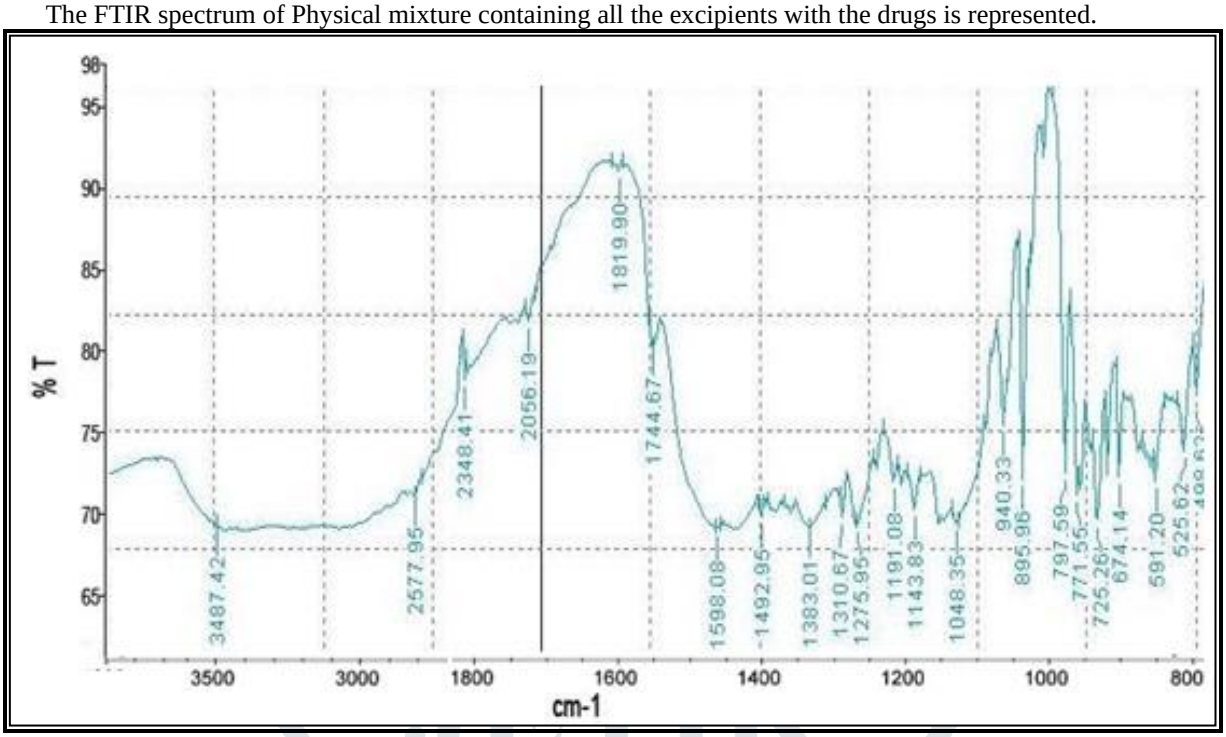


**Figure 8:** FTIR Spectra of Physical Mixture.

Mixtures viz. TBF & MF with Carbopol-940, PG, NaOH, MP, PP and Water were scanned as a mixture to analyze any possible interaction between individual excipients and the drug. TBF & MF with Carbopol-940, PG, NaOH, MP, PP and Water showed perfect retention of all the parent peaks of the drug and the excipients. It was thus confirmed that the drug shows no interaction between the listed excipients.

Only deviation was observed w.r.t PG & MP where the peaks were still obtained but the spectra was slightly evened out. It can be attributed to the fact that the excipients themselves have a very amorphous nature and minimal functional groups. Also another critique can be drawn out owning to the safe history of both the excipients and their usage as excipients in a wide diaspora. Hence it was inferred that all the excipients were found to be safe and applicable in the further study. Figure 8 demonstrates the FTIR spectra's of the same.

**2.2. Differential Scanning Calorimetry:**

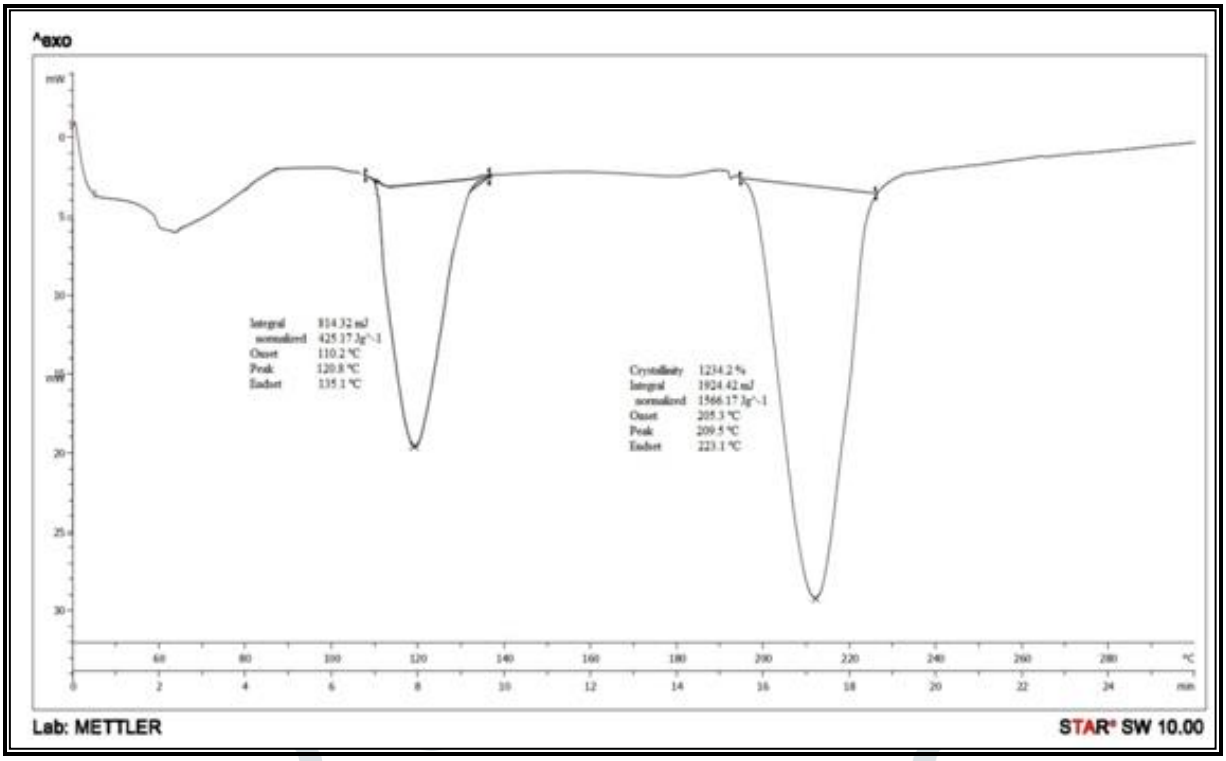


**Figure 9:** DSC graph of Physical Mixture.

A slight evened out result was obtained in a range of 40-70°C which can be attributed to a very low M.P. of PG & NaOH. Two endotherms were obtained at peak 130.8 & 208.5 respectively. Both endotherms were evened out and were broad in spectrum. The first endotherm can be explained for MP, PP & Water as their M.P. lies in the same range whereas the second endotherm exactly includes the M.P. ranges of both drugs TBF & MF respectively. As no other endotherm was observed, it can be inferred that the mixture had no Drug- Excipient incompatibility issues and the excipients can be used for the formulation.

**3. EVALUATION OF TBF & MF TOPICAL GEL**

**3.1. Appearance, pH, Viscosity, Spread ability & Extrudabiliy**

| Properties & Formulation | Appearance (Scores) | Color | pH | Viscosity (cps)at7rpmat30 °c | Spreadabilty (g.cm/s) | Extrudabiliy (g) |
|---|---|---|---|---|---|---|
| **F1** | 8 | White transparent | 7.8 | 29500 | 27 | 510 |
| **F2** | 9 | White transparent | 6.9 | 29100 | 27 | 505 |
| **F3** | 9 | White transparent | 6.5 | 25856 | 25 | 495 |
| **F4** | 9 | White transparent | 6.6 | 25350 | 24 | 500 |
| **F5** | 8 | White transparent | 6.9 | 2494 | 22 | 450 |
| **F6** | 8 | White transparent | 6.7 | 2571 | 27 | 478 |
| **F7** | 9 | White transparent | 6.8 | 2789 | 26 | 512 |
| **F8** | 9 | White transparent | 6.9 | 2634 | 24 | 548 |
| **F9** | 9 | White transparent | 7 | 2865 | 25 | 472 |
| **Tyza M** | 9 | White transparent | 7.3 | 2700 | 28 | 508 |

**Table 4:** Evaluation of Gel preparations

According to the Visual Range system, all the formulations had no phase separation and were homogeneous either virtually or completely. The colour was transparent which a very good factor is where topical gels are considered. pH lies in a neutral range and there are varying ranges of viscosity, spreadability and extrudability obtained. The same values were input in Design Expert software to obtain optimization of the formulation.

Tyza M Gel was considered to be RS and when compared with the experimental formulation more or less values fell into same ranges.

**3.2. In-Vitro Diffusion Study:**

| Time (min) | % Cumulative Drug Diffused | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| 10 | 45.4 | 38.6 | 44.6 | 37.6 | 35.2 | 39.8 | 33.8 | 38.2 | **41** |
| 20 | 61.6 | 59.8 | 66 | 63.2 | 65.8 | 67 | 64.2 | 68.2 | **73.4** |
| 30 | 72.6 | 67.8 | 69.8 | 74.4 | 71.6 | 72.4 | 67.8 | 72.2 | **79.2** |
| 40 | 79.8 | 79.8 | 83.5 | 79.8 | 74.8 | 79.2 | 77.6 | 80.2 | **84.2** |
| 50 | 80.4 | 84.2 | 85.6 | 82.6 | 77.6 | 84.2 | 84.1 | 82.6 | **88.2** |
| 60 | 86.4 | 85.8 | 89.4 | 92.3 | 87.4 | 86.2 | 86.4 | 88.8 | **91.4** |

**Table 5:** In-Vitro Diffusion Study

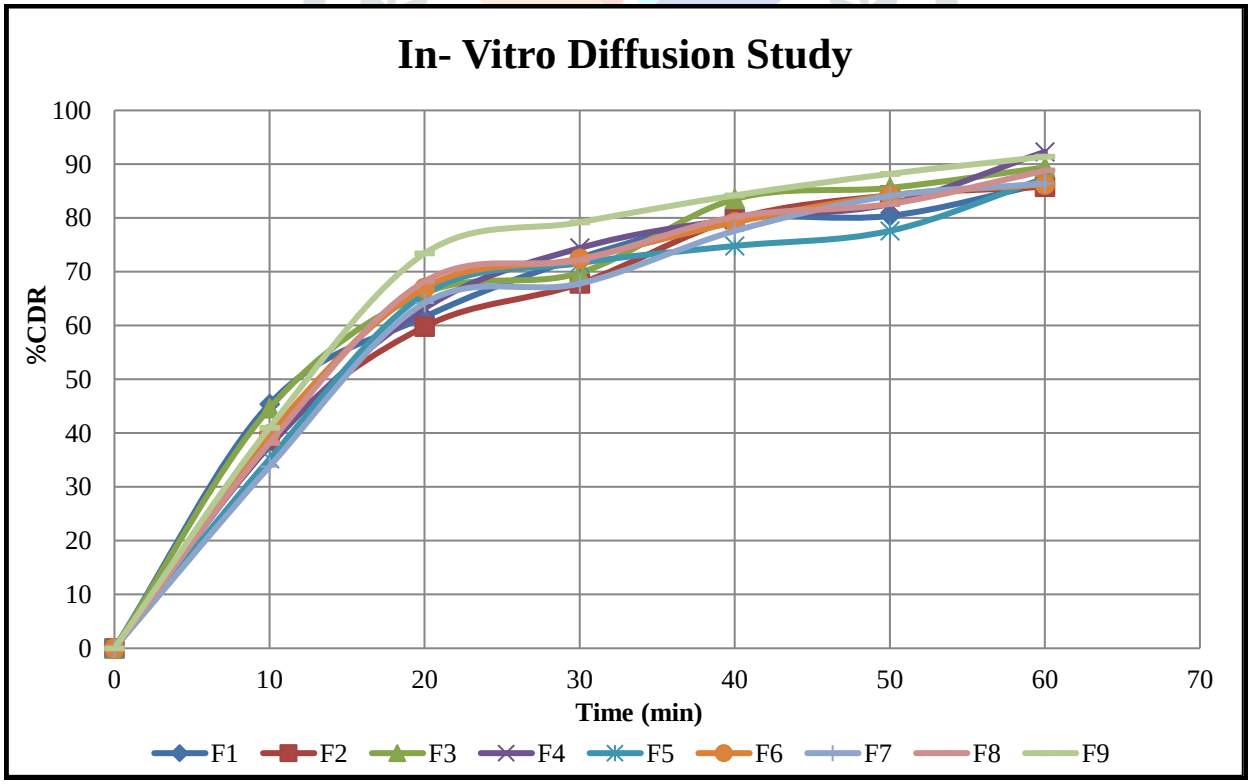


**Figure 10:** In-Vitro Diffusion Study

All the formulations showed an acceptable diffusion profile where most of the formulation have achieved maximum diffusion at 60 minutes. The data was fed into design of experiment and further optimization was performed.

**4. In-Silico Optimization using Design Expert 12.0:**

The design expert software of Stat ease 12.0 was used for statistical optimization. The model that best suits for the correlation between dependent variables and independent variables, chosen for the study was determined using the software. The best-suited model was selected on the basis of parameters of regression analysis namely p value, adjusted and predicted R2 value. The value of $p<0.05$ indicates if the model terms were significant. ANOVA was implemented at 5% level of significance

**5. Study of Effect of Formulation Variable on Drug Diffusion:**

The data of central composite design depicted a quadratic model as a best fit for response Y1 i.e. Drug Diffusion. The summary of the regression analysis and ANOVA is given in Table 6. The p value was found to be <0.05 hence the model was found to be significant. The Predicted $R^2$ of 0.0412 is not as close to the Adjusted $R^2$ of 0.7689 as one might normally expect; i.e. the difference is more than 0.2.

This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs. Ad eq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 7.391 indicates an adequate signal. This model can be used to navigate the design space. The Model F-value of 8.98 implies the model is significant. There is only a 0.59% chance that an F-value this large could occur due to noise.

| Source | Sum of Squares | Df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| **Model** | 63.58 | 5 | 12.72 | 8.98 | 0.0059 | significant |
| A-Carbopol 940 | 0.0454 | 1 | 0.0454 | 0.0321 | 0.8629 | |
| B-Propylene Glycol | 20.78 | 1 | 20.78 | 14.68 | 0.0064 | |
| AB | 3.06 | 1 | 3.06 | 2.16 | 0.1848 | |
| $A^2$ | 27.31 | 1 | 27.31 | 19.29 | 0.0032 | |
| $B^2$ | 17.39 | 1 | 17.39 | 12.29 | 0.0099 | |
| **Residual** | 9.91 | 7 | 1.42 | | | |
| Lack of Fit | 9.91 | 3 | 3.30 | | | |
| Pure Error | 0.0000 | 4 | 0.0000 | | | |
| **Cor Total** | 73.49 | 12 | | | | |

**Table 6:** Summary of Regression Analysis and ANOVA for Drug Diffusion

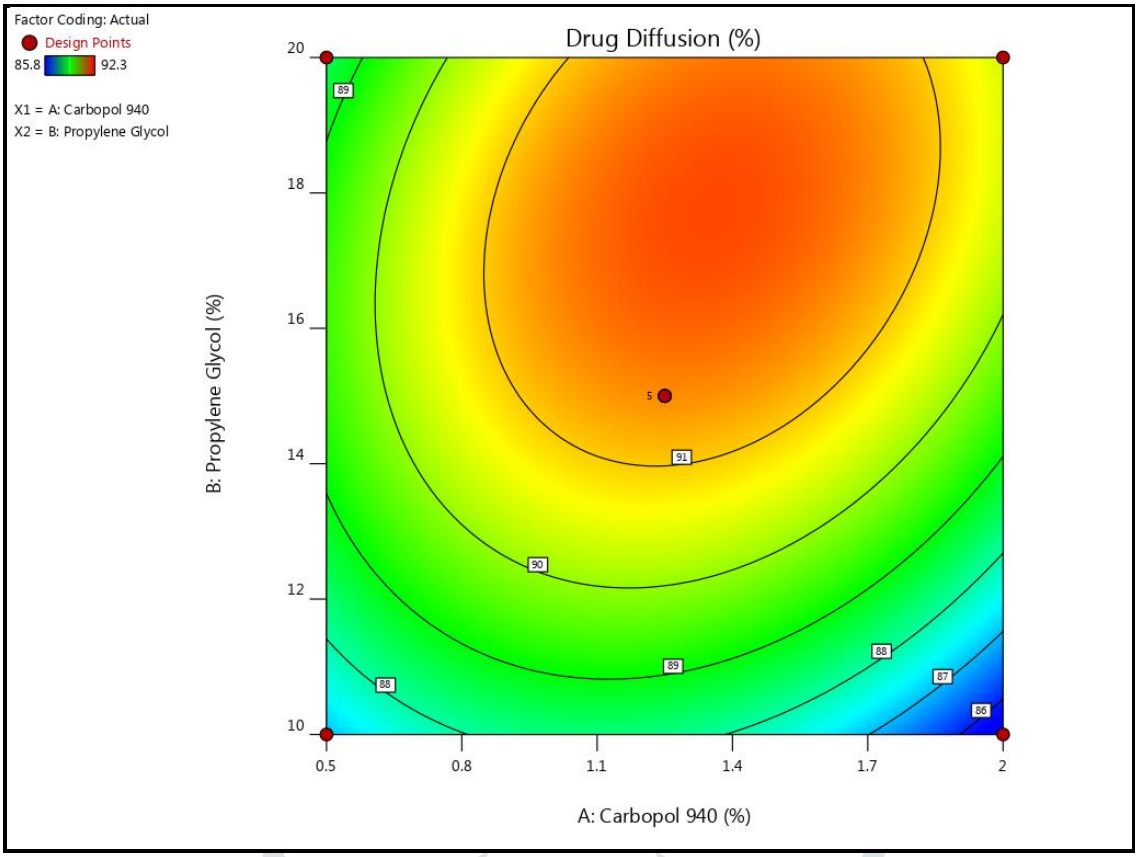


**Figure 11:** Contour Plots for Response Y1 Drug Diffusion

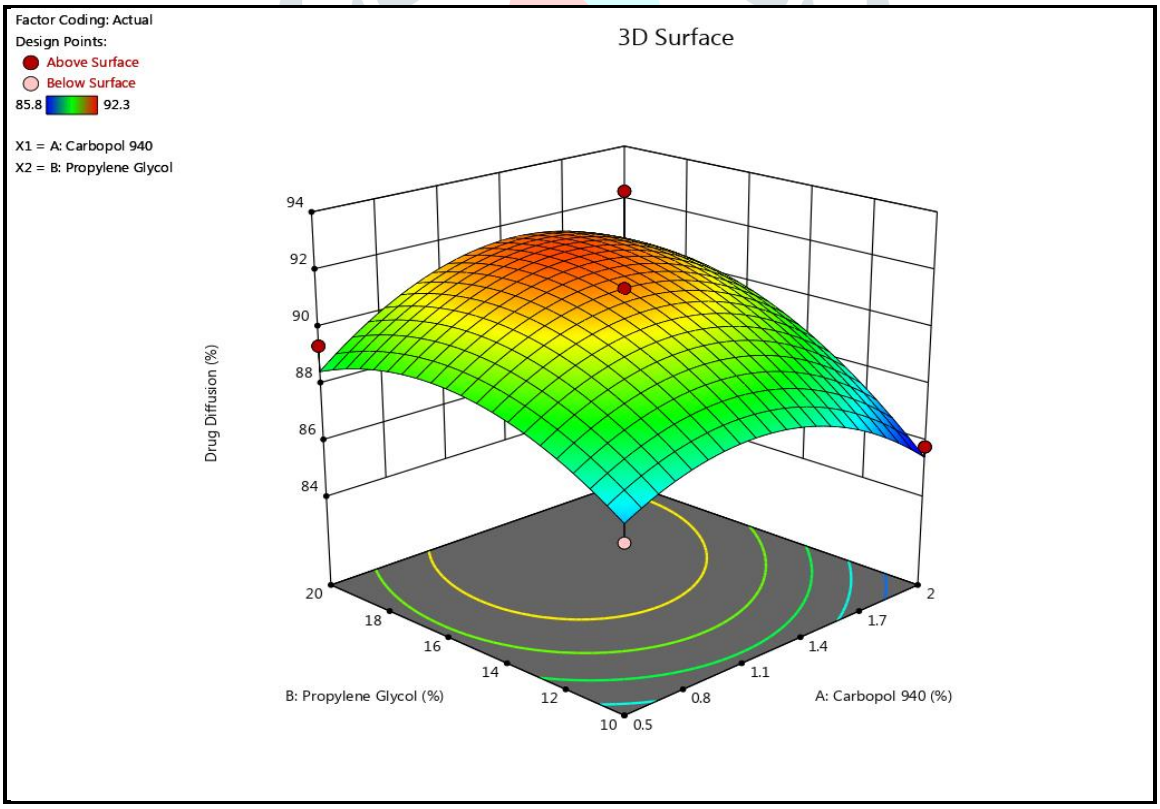


**Figure 12:** Response Surface Plot for Response Y1 Drug Diffusion

The polynomial equation generated by the software for response Y1 was found to be

| **Drug Diffusion** | = |
|---|---|
| +71.07937 | |
| +5.40605 | Carbopol 940 |
| +1.92819 | Propylene Glycol |
| +0.233333 | Carbopol 940 * Propylene Glycol |
| -3.52222 | Carbopol 940² |
| -0.063250 | Propylene Glycol² |

**Table 7:** Final Equation in Terms of Actual Factors

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space. The equation shows that a median concentration of carbopol was able to achieve accepted drug diffusion for the topical gel preparation.

**6. Study of Effect of Formulation Variable on Spreadability:**

The data of central composite design depicted a linear model as a best fit for response Y2 i.e. Spreadability. The summary of the regression analysis and ANOVA is given in Table 20.The p value was found to be <0.05 hence the model was found to be significant. A negative Predicted $R^2$ implies that the overall mean may be a better predictor of your response than the current model. In some cases, a higher order model may also predict better. Adeq Precision measures the signal to noise ratio.

A ratio greater than 4 is desirable. Your ratio of 6.768 indicates an adequate signal. This model can be used to navigate the design space. The Model F-value of 5.37 implies the model is significant. There is only a 2.61% chance that an F-value this large could occur due to noise.

| **Source** | **Sum of Squares** | **Df** | **Mean Square** | **F-value** | **p-value** | |
|---|---|---|---|---|---|---|
| **Model** | 12.27 | 2 | 6.13 | 5.37 | 0.0261 | significant |
| A-Carbopol 940 | 4.61 | 1 | 4.61 | 4.03 | 0.0724 | |
| B-Propylene Glycol | 7.66 | 1 | 7.66 | 6.71 | 0.0270 | |
| **Residual** | 11.42 | 10 | 1.14 | | | |
| Lack of Fit | 11.42 | 6 | 1.90 | | | |
| Pure Error | 0.0000 | 4 | 0.0000 | | | |
| **Cor Total** | 23.69 | 12 | | | | |

**Table 8:** Summary of Regression Analysis and ANOVA for Spreadability

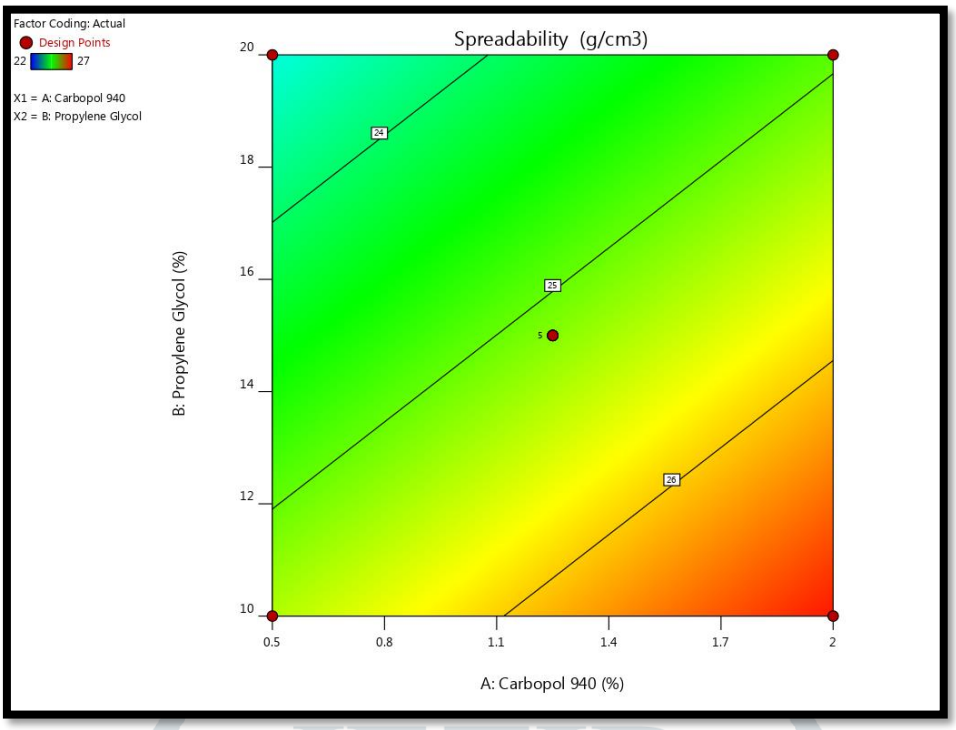


**Figure 13:** Contour Plots for Response Y2 Spreadability

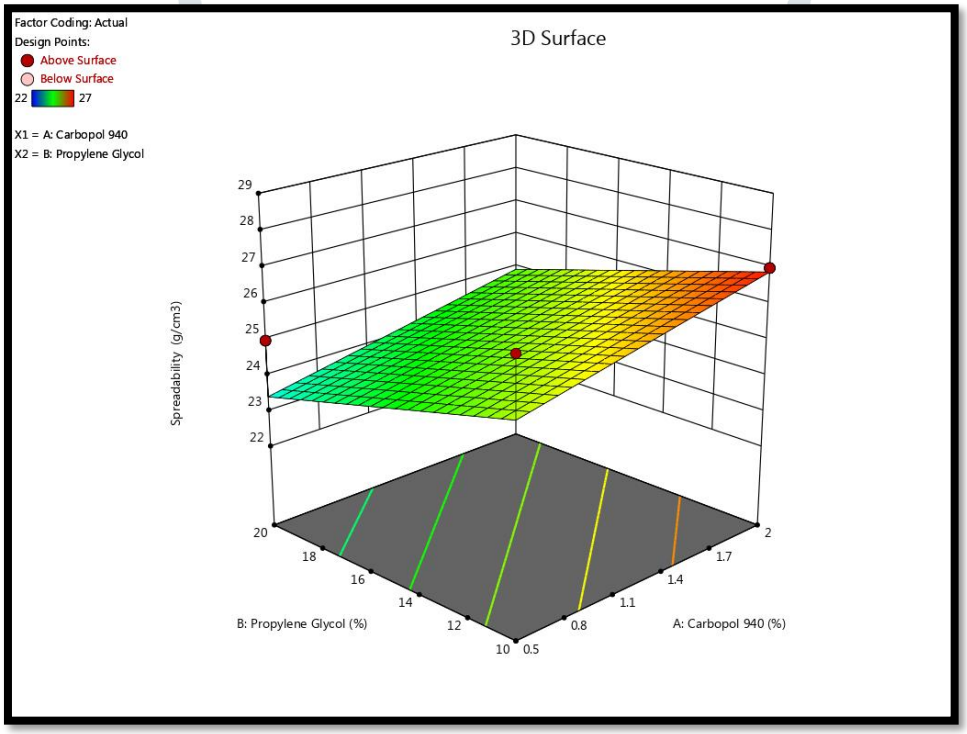


**Figure 14:** Response Surface Plot for Response Y2 Spreadability

The polynomial equation generated by the software for response Y2 was found to be.

| Spreadability | = |
|---|---|
| +26.82470 | |
| +1.01184 | Carbopol 940 |
| -0.195711 | Propylene Glycol |

**Table 9:** Final Equation in Terms of Actual Factors.

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space. The equation shows that a median concentration of Propylene Glycol was able to achieve an acceptable spreadability for topical gels.

**Confirmation**

| Solution 1 of 100 Response | Predicted Mean | Predicted Median | Std Dev | n | SE Pred | 95% PI low | 95% PI high |
|---|---|---|---|---|---|---|---|
| Drug Diffusion | 89.6935 | 89.6935 | 1.18975 | 1 | 1.3108 | 86.594 | 92.7931 |
| Spreadability | 25.0071 | 25.0071 | 1.06886 | 1 | 1.1513 | 22.4419 | 27.5724 |

**Table 10:** Confirmation

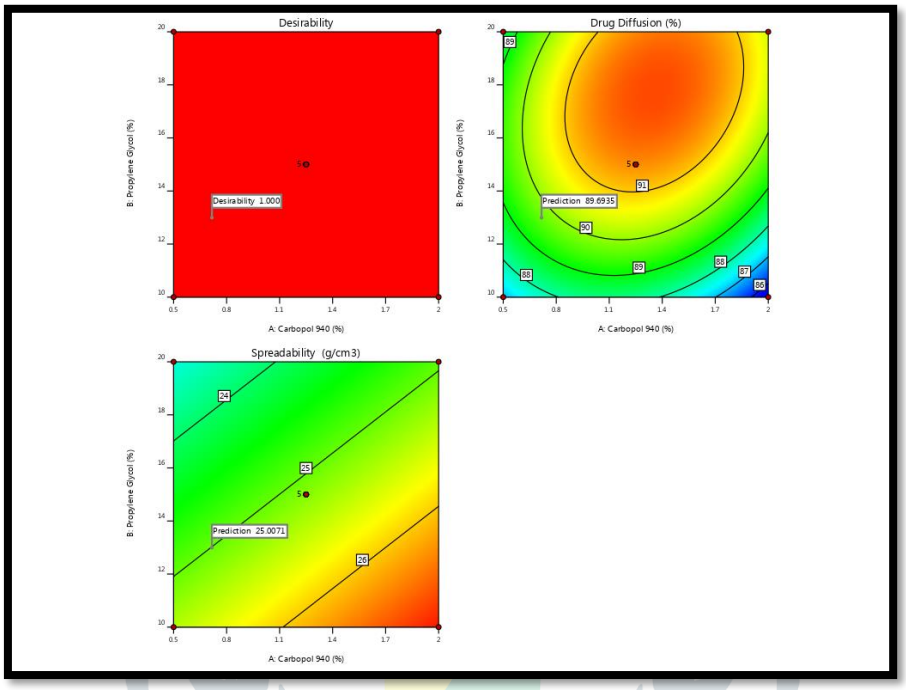


**Figure 15:** Contour Plots for Confirmation

**Formulation F9** was selected to be the optimized formulation as analysed from Response surface designs giving optimum results as expected.

**7. Comparison between In-Vitro permeation profiles of optimized gel & conventional dosage.**

| Time (min) | F9 | Tyza M Gel |
|---|---|---|
| 0 | 0 | 0 |
| 10 | 41 | 39.8 |
| 20 | 73.4 | 67.4 |
| 30 | 79.2 | 87.2 |
| 40 | 84.2 | 98.6 |
| 50 | 88.2 | 99.8 |
| 60 | 91.4 | 100.4 |

**Table 11:** Comparison between In-Vitro permeation profiles of F9 & RS

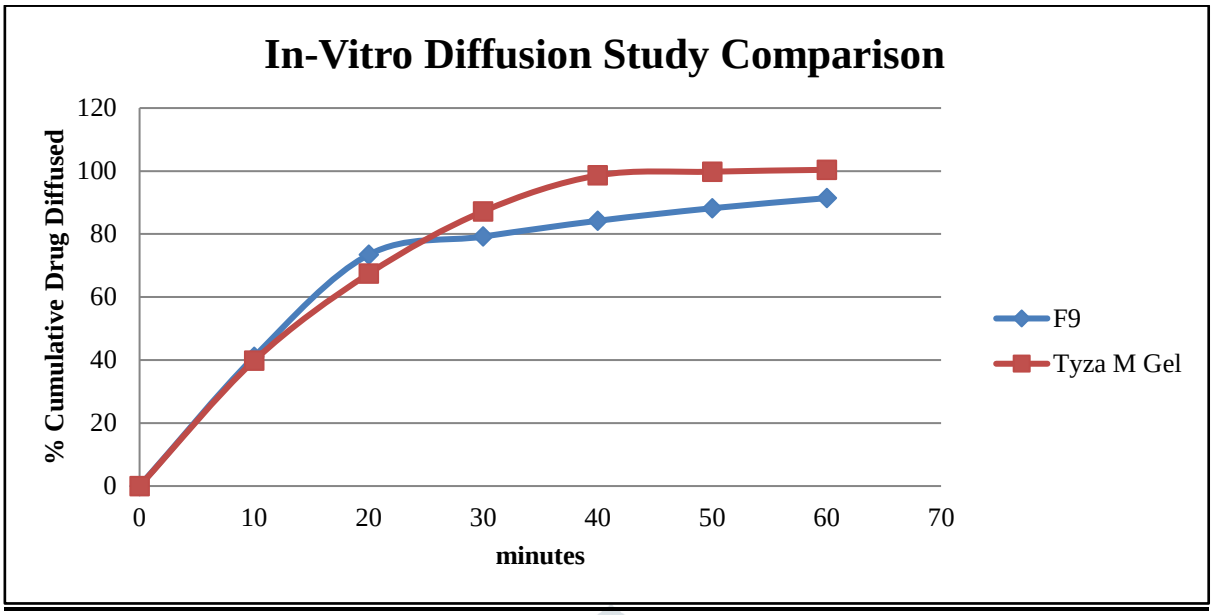


**Figure 16:** Comparison between In-Vitro permeation profiles of F9 & RS

As it is evident from the graph that both the preparations initially follow similar profile while the marketed one showing a fast diffusion at later stages. However both the profiles can be compared at ease and thus it can be declared that this work can be marked successful as it achieves near same values as the marketed preparation.

**8. Ageing Studies of F9**

| Parameter | Initial Reading | 1 Month | 2 Months | 3 Months |
|---|---|---|---|---|
| Organoleptic Properties | 9, White Transparent | 9, White Transparent | 9, White Transparent | 9, White Transparent |
| pH | 7 | 7.1 | 7.1 | 6.9 |
| Viscosity (cp) | 2865 | 2800 | 2823 | 2857 |
| Spreadibility (g/cm3) | 25 | 25 | 24 | 27 |
| Extrudability (g) | 472 | 470 | 489 | 462 |
| In-Vitro Diffusion Study (%) | 91.4 | 97.4 | 92.8 | 99.6 |

**Table 12:** Ageing Studies of F9

Considering the Results of ageing studies, it was concluded that the F9 stays stable for 3 months under accelerated stability conditions.

**CONCLUSION:**

The objective of the study was to develop a formulation to counter Dermatophytosis by using a combination of an Antifungal drug Terbinafine and a corticosteroid Mometasone Furoate in a topical gel formulation to enhance patient compliance and better delivery of drug to the affected area. The DSC graphs were obtained. DSC for TBF showed a peak endotherm at 206.73°C and DSC for MF showed a peak endotherm at 216.60°C. Solubility of TBF & MF both was studied in Methanol, Ethanol, DMSO, 0.1N HCl, pH 1.2 HCl buffers, pH 6.8 phosphate buffer to study the behaviour of the drugs. Mixtures viz. TBF & MF with Carbopol-940, PG, NaOH, MP, PP and Water were scanned as a mixture to analyze any possible interaction between individual excipients and the drug. TBF & MF with Carbopol-940, PG, NaOH, MP, PP and Water showed perfect retention of all the parent peaks of the drug and the excipients. It was thus confirmed that the drug shows no interaction between the listed excipients. Hence it was inferred that all the excipients were found to be safe and applicable in the further study. Figure 8 demonstrates the FTIR spectra's of the same. A slight evened out result was obtained in a range of 40-70°C which can be attributed to a very low M.P. of PG & NaOH.

Two endotherms were obtained at peak 130.8 & 208.5 respectively. Both endotherms were evened out and were broad in spectrum. The first endotherm can be explained for MP, PP & Water as their M.P. lies in the same range whereas the second endotherm exactly includes the M.P. ranges of both drugs TBF & MF respectively. As no other endotherm was observed, it can be inferred that the mixture had no Drug- Excipient incompatibility issues and the excipients can be used for the formulation. pH lies in a neutral range and there are varying ranges of viscosity, spreadability and extrudability obtained. The same values were input in Design Expert software to obtain optimization of the formulation. Tyza M Gel was considered to be RS and when compared with the experimental formulation more or less values fell into same ranges.

All the formulations showed an acceptable diffusion profile where most of the formulation have achieved maximum diffusion at 60 minutes. The data was fed into design of experiment and further optimization was performed. The design expert software of Stat ease 12.0 was used for statistical optimization. The model that best suits for the correlation between dependent variables and independent variables, chosen for the study was determined using the software. The best-suited model was selected on the basis of parameters of regression analysis namely p value, adjusted and predicted R2 value. The value of $p<0.05$ indicates if the

model terms were significant. ANOVA was implemented at 5% level of significance **Formulation F9** was selected to be the optimized formulation as analysed from Response surface designs giving optimum results as expected. Zeta Potential was obtained to be 8.13 mV which is a positive value. This value signifies the affinity of the gel towards the skin and thus will not occur any impediments in the drug diffusion. Both F9 & Marketed preparation was assayed by HPLC to calculate the drug content. According to calculations specified by the drug content of TBF & MF were found to be 99.8, 98.7 & 100.2, 99.5 percent for F9 & RS respectively. Thus it was confirmed that the formulation not only diffuses in an acceptable manner but also has acceptable drug content. As it is evident from the graph that both the preparations initially follow similar profile while the marketed one showing a fast diffusion at later stages. However both the profiles can be compared at ease and thus it can be declared that this work can be marked successful as it achieves near same values as the marketed preparation. Considering the Results of ageing studies, it was concluded that the F9 stays stable for 3 months under accelerated stability conditions.

**ABBRIVATION:**

1. **TBH :** Terbinafine Hydrochloride
2. **MF :** Mometasone Furoate
3. **FDA :** Food and Drug Administration
4. **DSC :** Differential Scanning Calorimetry
5. **DoE :** Design of experiments
6. **FT-IR :** Fourier Transform Infrared Spectroscopy
7. **UV/VIS** - Ultra Violet/Visible Spectroscopy
8. **NaOH :** Sodium Hydroxide
9. **mL/min :** Milliliters per minute
10. **DMSO :** Dimethyl sulfoxide
11. **HCl :** Hydrochloric acid
12. **MP :** Methyl Paraben
13. **PP :** Propyl Paraben
14. **PG :** Propylene Glycol
15. **M.P :** Melting Point

**REFERENCE:**


1. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 1549008, Terbinafine; [cited 2021 Jan. 26]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Terbinafine
2. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 441336, Mometasone furoate; [cited 2021 Jan. 26]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Mometasone-furoate
3. Storey RA, Ymén I, editors. Solid state characterization of pharmaceuticals. John Wiley & Sons; 2011 Mar 31.
4. Pavia DL, Lampman GM, Kriz GS, Vyan JA. Introduction to spectroscopy. Cengage Learning; 2008 Mar 12.
5. Higuchi T, Connors KA. Phase solubility techniques. Advances in Analytical Chemistry and Instrumentation. 1965; 4: 117–212
6. Garg A. Spreading of semisolid formulation. Pharm Tech. 2002 Sep 84-105
7. Margaret N, Meultimer, Charles Riffikin, Murry. E, Glickman and Giliman J. Am. Pharm. Asso. Sci 1946. 45. 212.
8. Venkatatamana Malipeddi, Kamal Dua, Udai vir singh sara, Abhinav agarwal Comparitive evaultion of transdermal formulations of norfloxacin with silver sulfadiazine cream USP for burn wound healing property. J.of Burns and Wounds. June 7, 2006.
9. Akomeah, FK, Martin,. Brown A.B. J. of Pharm. Sci. 2007 Apr; 96(4): 826- 827.