# Formulation and Evaluation of Topical Microemulgel Containing Terbinafine Hydrochloride

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*Authors' contributions*

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

The purpose of this study is to create and test a Terbinafine hydrochloride microemulgel. Terbinafine hydrochloride is an FDA-approved antifungal medication used to treat fungal infections on the skin. It's a BCS class II medication with little bioavailability. In the realm of pharmaceutical sciences, microemulgel has evolved into one of the most intriguing topical preparations. Microemulgel as a delivery technique has several advantages over simple traditional formulations, including simplicity of administration, increased residence duration at the application site, consistent drug release with improved bioavailability, superior thermodynamic stability, and excellent transdermal permeability. Terbinafine hydrochloride microemulgels were made with carbopol 940 and HPMC as gelling agents, oleic acid as an oil, parabens as a preservative, and tween 20 as an emulgent and penetration enhancer. The appearance, spreadability, homogeneity, viscosity, pH, percent drug content, and in vitro diffusion studies of the generated microemulgel formulation were all visually checked. The findings show that developing a terbinafine-containing microemulgel is more effective, but clinical efficacy must be determined through clinical trials.

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## 1. INTRODUCTION

The skin is an important element of the human body that protects and distinguishes in-vivo biology from the outside world. Skin, on the other hand, is more susceptible to microbial infection. The treatment of such a topical infection is done with a topical medication delivery system that has local effect and avoids the first-pass metabolism, GI degradation, and discomfort that oral administration entails [1-3]. Microemulgel is a dual drug delivery device made by turning a liquid microemulsion into a semisolid gel. Due to its dual mechanism of emulsion and gel, it is regarded as one of the most promising new drug delivery systems. Furthermore, it was demonstrated that mixing emulsion with gel boosted the stability of the emulsion. The microemulsion technology was chosen because of its great solubility and ability to permeate into the skin, whereas gel can sustain drug release and provide a lengthy drug residence time [4-7]. The greatest option for skin-related disorders is the microemulgel drug delivery technology, which has better efficacy while utilising a minimal amount of medicine. Terbinafine hydrochloride is an antifungal medicine that has been licenced by the FDA and is commonly used topically and orally. Many standard Terbinafine formulations are available on the market, and when taken orally, they have been linked to major life-threatening outcomes such as hepatic failure, severe cutaneous response, and severe neutropenia. By maintaining the medication in a solubilized condition and forming small sized droplets, Microemulgel can overcome the difficulties of standard topical delivery systems by providing a broad interfacial area for drug absorption [8-10].

## 2. MATERIALS AND METHODS

### 2.1 Materials

Terbinafine hydrochloride obtained as a gift sample from FDC Pvt. Ltd. Goa, India. The other chemicals, reagents and solvents used like propylene glycol, oleic acid, carbapol, methanol, tween 20, methyl paraben, propyl paraben, triethanolamine are of analytical grade quality.

### 2.2 Methods

#### 2.2.1 Development of standard calibration curve

Accurately weighed 50 mg of Terbinafine hydrochloride was dissolved in 50 ml of methanol and from this 1 ml is diluted using phosphate buffer pH 7.4 in 100 ml volumetric flask to get the stock solution of 10 µg/ml concentration. From the stock solution 2, 4, 6, 8, 10 and 12 ml were withdrawn and further diluted to phosphate buffer pH 7.4 in 100 ml volumetric flasks to obtain a concentration range of 0.2-1.2µg/ml. The absorbance of the solutions was measured at 223 nm by using a UV-spectrophotometer. A graph of Concentration vs. Absorbance was plotted [11,12].

#### 2.2.2 Drug exicipient compatability studies

The FTIR study performed to detect any suspicious interactions which affect stability, efficacy of drug and excipients chosen for the preparation of microemulgel, over the range of 4000-400 $cm^{-1}$ in the Perkin Elmer FTIR spectrometer [11,12].

#### 2.2.3 Formulation method of Terbinafine hydrochloride micro-emulgel

The preparation of microemulgel was carried out containing Terbinafine hydrochloride (API), oleic acid (oil), Tween 20 (surfactant), propylene glycol (co-surfactant), carbopol and HPMC (gelling agent), methyl / propyl paraben (preservative), methanol (solvent). The micro-emulgel formulations were prepared in two step: 1) Formation of micro-emulsion and 2) Conversion of micro-emulsion to emulgel [13-25].

Micro-emulsions were formulated by dissolving drug into oil phase subsequently addition of water takes place with drop wise addition of surfactant mixture on a continuous magnetic stirrer. The clear, isotropic micro-emulsion obtained then mixed with pre-swelled gelling polymer and preservatives using a homogenizer to form micro-emulgel. Quantities of ingredients taken are mentioned in Table 1.

## 3. EVALUATION OF MICROEMULGEL [19-30]

### 3.1 Physical Characteristics

Microemulgel were evaluated for their visual appearance, consistency, grittiness and phase separation with naked eyes.

### 3.2 pH

1% aqueous solution of the prepared micro-emulgel was made by dissolving 1gm of

formulation in 100 ml distilled water and; kept it a side for 2 hr. After stabilization pH of the formulation is measured using digital pH meter in triplicate manner at room temperature.

## 3.3 Determination of Viscosity

To determine viscosity 20 gm of micro-emulgel was filled in a 25 ml beaker and the beaker is subjected to Brookfield viscometer assembled with spindle number S6.

## 3.4 Spreadability

The spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of micro-emulgel. About 2 gm of formulation is placed in between 2 glass slides (sandwich) and 1 kg weight is placed on the upper slides for 5 minutes to expel air and to provide a uniform film of the micro-emulgel between the slides. By putting a weight of 1kg, the time (in seconds) required by the top slide to cover a distance of 7.5 cm with the help of string attached to the hook is noted. A shorter interval indicates better spreadability, which is calculated by the formula:

$$S = M.L/T$$

Where, S = Spreadability
M = Weight applied on upper slide
L = Length of glass slides
T = Time taken to spread upon application of mass.

## 3.5 *In vitro* Drug Diffusion Study

The in vitro drug diffusion study was carried out using diffusion cell method. In this method, 1gm of micro-emulgel is placed in donor compartment which is allowed to penetrate diffusing membrane which separate receptor compartment containing phosphate buffer. The whole assembly is maintained at 37°C and stirred with the help of a magnetic stirrer. Samples from receptor compartment were withdrawn at different time intervals and replaced with fresh buffer 7.4 to maintain sink condition. Sample withdrawn were analyzed at 223 nm on UV.

## 3.6 Stability Study

All the formulations are subjected to short term accelerated stability study as per ICH guidelines at in an airtight container with proper sealing and conditions maintained at 40±2°C, 75±5% RH. The formulation was withdrawn and evaluated for physico-chemical parameters after particular period of interval.

## 4. RESULTS AND DISCUSSION

### 4.1 Standard Calibration Curve of Drug in UV Spectrophotometer

The UV absorbance of Terbinafine standard solutions in the range of 0.2-1.2 µg/ml of drug in buffer pH 7.4 calculated at λ max 223 nm. The linearity was plotted for absorbance (A) against concentration (C) with $R^2$ value 0.993 and with the slope equation y=0.194x + 0.143. The absorbance values and standard curve were shown in Table 2 and Fig. 1.

### 4.2 FTIR Studies of Drug and Excipients

From the above FTIR interpretations, it can be seen that; there were no significant change in functional group of drug by the excipients, it can be concluded that drug and excipients chosen are compatible to each other.

**Table 1. Formulation table**

| Ingredients (mg/ml) | Formulation batch | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Terbinafine hydrochloride | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Tween 20 | 3 | 3.5 | 4 | 4.5 | 4.7 | 4.9 | 5 | 5.5 | 6 |
| Propylene glycol | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Oleic acid | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| Carbopol 934 | 1.5 | 1.7 | 1.9 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 |
| HPMC | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 |
| Triethanolamine | 0.2 | 0.2 | 0.2 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 |
| Methyl paraben | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| Propyl paraben | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Purified water | QS | QS | QS | QS | QS | QS | QS | QS | QS |

**Table 2. Absorbance values of Terbinafine on UV**

| Sr. No. | Concentration (µg/ml) | Absorbance at 223 nm |
|---------|----------------------|----------------------|
| 1. | 0.2 | 0.322 |
| 2. | 0.4 | 0.521 |
| 3. | 0.6 | 0.735 |
| 4. | 0.8 | 0.975 |
| 5. | 1 | 1.125 |
| 6. | 1.2 | 1.275 |
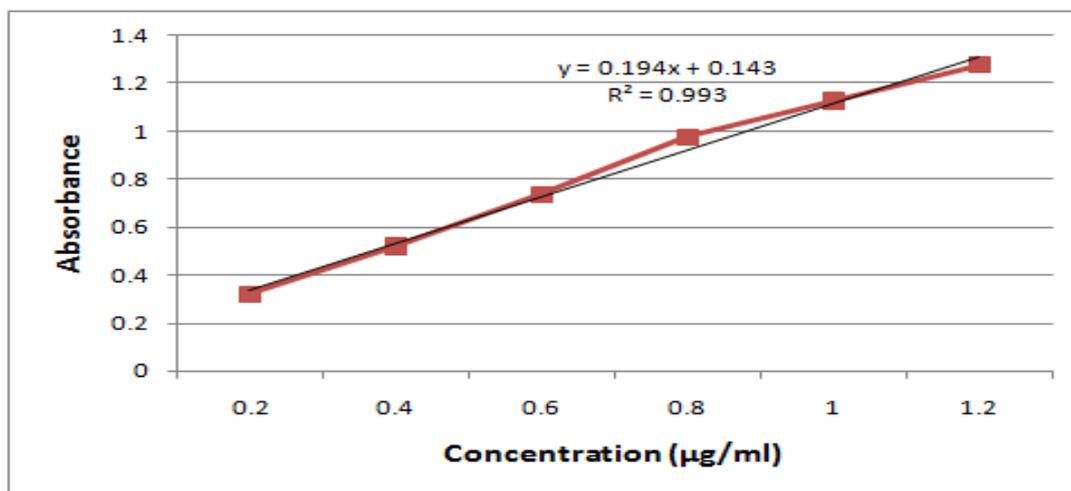


**Fig. 1. Calibration Curve of Terbinafine at 223 nm wavelength**
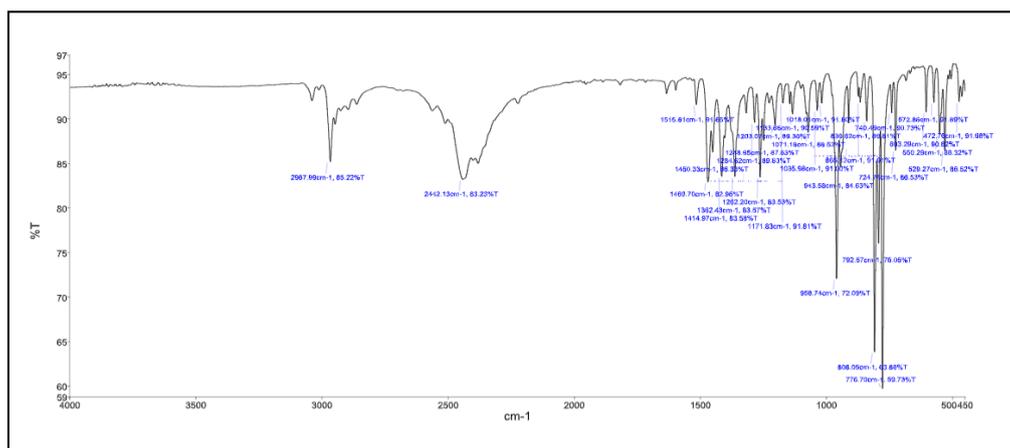


**Fig. 2. FTIR graph of Terbinafine**

**Table 3. Interpretations of FTIR of Drug**

| Functional group | Standard frequency | Peaks observed |
|------------------|-------------------|----------------|
| C=C bending | 1700-1500 | 1668.52 |
| C-O stretching | 1250-1050 | 1160.21 |
| C-N Stretch | 1020-1230 | 1225.55 |
| C-H bending | 860-680 | 856.22 |
| N-H stretching | 3500-3300 | 3339.92 |
| Alkyl C=C Stretch | 2100-2260 | 2155.87 |
| Carboxylic Acid (O-H) | 2500-3000 | 2921.72 |

**Fig. 3. FTIR graph of Drug + Excipients**

**Table 4. Interpretations of FTIR of Drug + Excipients**

| Functional group | Standard frequency | Peaks observed |
|---|---|---|
| N-H stretching | 3500-3300 | 3339.92 |
| C=C bending | 1700-1500 | 1327.26 |
| C-O stretching | 1250-1050 | 1235.34 |
|  |  | 1088.85 |
| C-N Stretch | 1020-1230 | 1064.03 |
| C-H bending | 860-680 | 826.63 |
|  |  | 879.51 |
| Alkyl C=C Stretch | 2100-2260 | 2189.84 |
| Carboxylic Acid (O-H) | 2500-3000 | 2917.26 |



**Fig. 4. Graph of % drug content**

**Table 5. Physical appearance, pH, drug content of all batches F1-F9**

| Formulation code | Physical appearance | pH | % Drug content |
|---|---|---|---|
| F1 | Milky white | 7.3 | 87.456 |
| F2 | Milky white | 6.9 | 84.324 |
| F3 | Milky white | 5.7 | 88.453 |
| F4 | Milky white | 7.2 | 87.492 |
| F5 | Clear transparent dispersion | 7.8 | 90.501 |
| F6 | Clear transparent dispersion | 7.1 | 81.492 |
| F7 | Clear transparent dispersion | 6.5 | 92.356 |
| F8 | Clear transparent dispersion | 6.9 | 83.502 |
| F9 | Clear transparent dispersion | 7.2 | 87.361 |

**Table 6. Viscosity and spreadability of all batches F1-F9**

| Formulation code | Viscosity (Cps) | Spreadability (g.cm/sec) |
|---|---|---|
| F1 | 4350 | 15.56 |
| F2 | 12486 | 23.98 |
| F3 | 12800 | 25.56 |
| F4 | 14700 | 28.76 |
| F5 | 12089 | 26.60 |
| F6 | 15200 | 30.51 |
| F7 | 15856 | 31.78 |
| F8 | 13900 | 31.98 |
| F9 | 16600 | 33.56 |
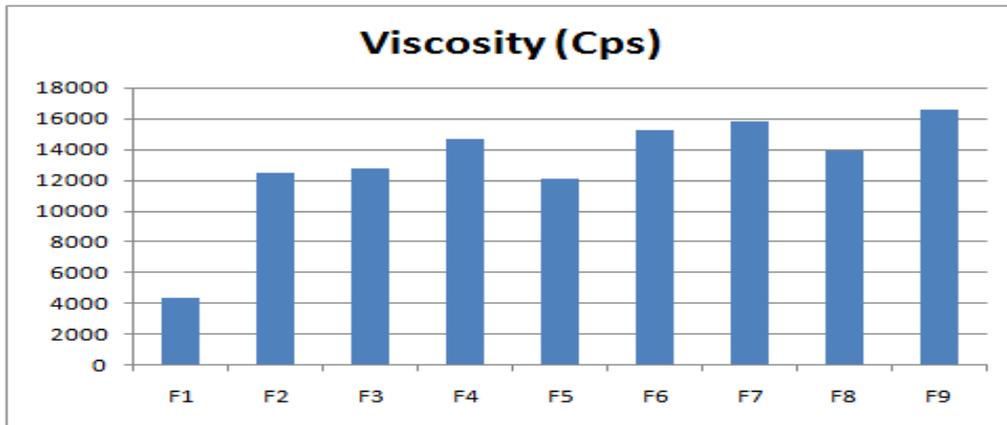


**Fig. 5. Graph of viscocity**
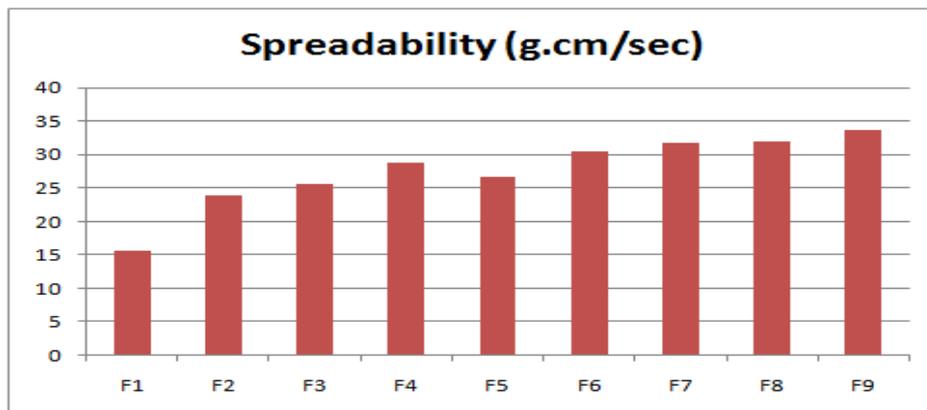


**Fig. 6. Graph of spreadability**

**Table 7. In Vitro drug diffusion study**

| Time (hr) | % Drug diffused | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 9.12 | 10.20 | 11.69 | 10.05 | 6.54 | 4.89 | 10.5 | 8.12 | 11.5 |
| 2 | 15.20 | 16.15 | 17.28 | 11.45 | 12.7 | 7.12 | 17.5 | 13.45 | 17.5 |
| 3 | 18.22 | 22.25 | 23.67 | 20.57 | 15.34 | 14.76 | 23.34 | 17.56 | 25.34 |
| 4 | 20.12 | 28.13 | 29.55 | 26.45 | 20.34 | 19.98 | 31.54 | 21.45 | 35.45 |
| 5 | 24.35 | 32.16 | 33.44 | 33.16 | 25.12 | 23.12 | 36.12 | 25.67 | 36.68 |
| 6 | 30.50 | 39.60 | 40.45 | 39.12 | 29.23 | 26.11 | 45.23 | 31.34 | 44.83 |
| 7 | 39.12 | 49.70 | 49.66 | 43.56 | 34.60 | 33.76 | 57.12 | 46.45 | 46.56 |
| 8 | 51.34 | 53.55 | 54.60 | 50.60 | 40.35 | 43.87 | 63.43 | 51.23 | 55.34 |
| 9 | 59.23 | 64.62 | 59.34 | 56.46 | 43.68 | 47.99 | 69.23 | 59.54 | 61.32 |
| 10 | 67.97 | 73.94 | 65.76 | 61.60 | 53.98 | 51.56 | 74.64 | 63.23 | 70.46 |
| 11 | 73.20 | 78.68 | 70.12 | 67.50 | 61.56 | 59.29 | 84.12 | 69.43 | 73.21 |
| 12 | 78.22 | 80.92 | 74.83 | 70.60 | 72.01 | 63.08 | 85.15 | 75.94 | 75.51 |
| 16 | 81.67 | 83.25 | 79.78 | 75.11 | 80.88 | 65.95 | 87.82 | 80.37 | 77.28 |
| 20 | 85.42 | 85.58 | 81.37 | 79.84 | 83.32 | 68.89 | 91.63 | 87.86 | 83.36 |
| 24 | 88.60 | 87.25 | 83.20 | 85.29 | 89.70 | 90.50 | 94.50 | 92.23 | 86.50 |
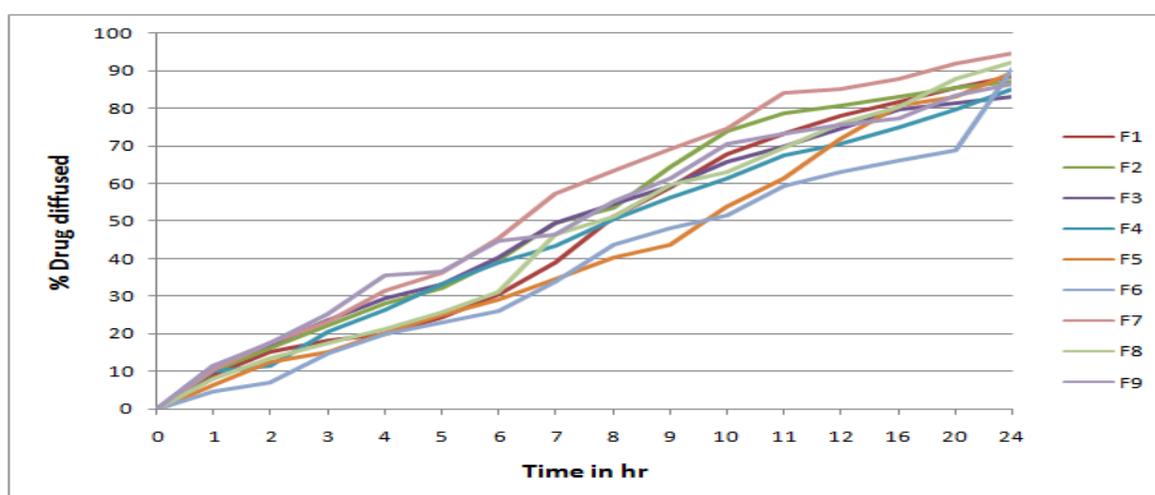


**Fig. 7. % Drug diffusion of all batches**

**Table 8. Stability study data of optimized micro-emulgel formulation F7**

| Sr. no. | Parameter | Stability after 1 month | Stability after 2 month | Stability after 3 month |
|---|---|---|---|---|
| 1 | Physical Appearance | Clear transparent homogeneous microemulgel | No change | No change |
| 2 | Drug Content (%) | 92.35% | 91.85% | 90.94% |
| 3 | In vitro drug diffusion | 94.50% | 94.12% | 93.94% |
| 4 | pH | 7.2 | No change | No change |

## 4.3 Physical Appearance, pH, Drug Content and Homogeneity

All developed micro-emulgels were found homogeneous in appearance; there is no any presence of air gap or clumps. All formulations were found to have pH in range of 5.70-7.80. Drug content of all batches was in range of 81-93 %; where the highest drug content showed by F7 formulation. Hence, F7 were considered as optimized batch.

## 4.4 Viscosity and Spreadability

Viscosity and spreadability was measured to determine ease of applicability of formulation. Results obtained showed that all batches are of desired viscosity and spreadability however F1-F5 batches are of less as compared to F6-F9 itermediate viscosity and spreadability.

## 4.5 *In Vitro* Drug Diffusion Study

% Drug diffusion was determined using diffusion cell method. Samples were withdrawn and examined for % drug diffused. Among all batches F7 batch showed steady release pattern and complete drug is released upto 24 hr hence it is considered to be optimized batch.

## 4.6 Stability Study

Results obtained after stability testing of optimized batch F7 can state that the formulation is stable at accelerated temperature and humidity condition.

## 5. CONCLUSION

The research conducted showed the better suitability of poorly bioavailable drug terbinafine hydrochloride towards micro-emulgel formulation. Results showed maximum drug release within 24 hrs (94.50%) can be achievable with micro-emulgel. The work on formulation development of terbinafine hydrochloride micro-emulgel was very much advantageous than the existing dosage forms as the drug is lipophilic in nature that is hard to penetrate via skin which is hydrated. Although formulation of micro-emulgel can penetrate drug, future studies are required to determine its clinical efficacy.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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