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FORMULATION AND EVALUATION OF TOPICAL MICROEMULGEL CONTAINING TERBINAFINE HYDROCHLORIDE

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ABSTRACT

The aim of the present investigation is to develop and evaluate Terbinafine hydrochloride microemulgel. Terbinafine hydrochloride is FDA approved antifungal drug for treatment of topical fungal infection. It is a BCS class II drug; has poor bioavailability. Now, microemulgel has developed as one of the most interesting topical preparation in the field of pharmaceutical sciences. Microemulgel as a delivery system is advantageous to use such as ease of administration, increased residence time at applied site, steady drug release with improved bioavailability, better thermodynamic stability and high transdermal permeability over simple conventional formulations. The microemulgel of Terbinafine hydrochloride were prepared, using carbopol 940 and HPMC as a gelling agent, oleic acid as oil, parabens as preservative, tween 20 as emulgent and penetration enhancer. The prepared microemulgel formulation was inspected visually for appearance, spreadability, homogeneity, viscosity, pH, % drug content and In vitro diffusion studies. Results obtained has proved that development of terbinafine hydrochloride containing microemulgel will be more effective however its clinical efficacy must be understood using clinical trials.

Keywords: Microemulgel, Terbinafine hydrochloride, Carbopol 934, HPMC, penetration enhancer

INTRODUCTION:

Skin is the important part of human body which protects and differentiates in-vivo biology from external environment. However skin is more prone to microbial infection. Treatment of such topicalinfection done using topical drug delivery system that give local action and avoids first pass metabolism, GI degradation and irritation associated with oral administration.

Microemulgel is a dual drug delivery systemwhich is prepared by converting liquid microemulsion to semisolid gel. It isconsidered as one of the promising novel drug delivery system due to its dual mechanism via emulsion and gel. Moreover, it was proved that by combining emulsion with gel, its stability increased. The reason behind choosing microemulsion system was its excellent capacity to solubilize and also its capability to permeate into the skin;while gel can sustain drug release providing long drug residence time.

Microemulgel drug delivery system is best option for skin related diseases with improved efficacy using small quantity of drug. Terbinafinehydrochloride is an FDA approved antifungal drug and is widely used topically and orally. Many conventional formulations of terbinafine are available in market which has been associated with serious life threatening events such as hepatic failure, severe cutaneous reaction and severe neutropenia when given orally. Microemulgel can overcome these problems of traditional topical delivery systems by keeping the drug in solubilized form and the formation of small sized droplets provides large interfacial area for drug absorption.

MATERIALS AND METHODS:

A) Materials:

Terbinafinehydrochloride 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.

B) Methods:

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 100ml 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.

2. Drug exicipient compatability studies:

The FTIR study performed to detect any suspiciousinteractions 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.

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 preparedin two step: 1) Formation of micro-emulsion and 2) Conversion of micro-emulsion to emulgel.

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, isotropicmicro-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**.

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

4. Evaluation of Microemulgel:

i. Physical characteristics:

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

ii. 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.

iii. 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.

vi. Spreadability:

The spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of micro-emulgel. About 2 gm of formulationis placed in between 2glass 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:

$$S = \frac{ML}{T}$$

Where, S=Spreadability

M=Weight applied on upper slide

L = Length of glass slides

T=Time taken to spread upon application of mass.

v. 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 indonor 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 buffer7.4 to maintain sink condition. Sample withdrawn were analyzed at 223nm on UV.

vi. 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.

RESULT AND DISCUSSION:

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 Figure 1**.

2. **FTIR Studies of Drug and Excipients (Table 3, Figure 2, 3)**
3. From the above FTIR **(Table 4)** 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.
4. **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 **(Table 5)**.

5. **Viscosity and spreadability (Table 6)**
6. **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 **(Table 7, Figure 7)**.

7. **Stability Study:**

Results obtained after stability testing of optimized batch F7 can state that the formulation is stable at accelerated temperature 40 ± 2°C and 75 ± 5% humidity condition **(Table 8)**.

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

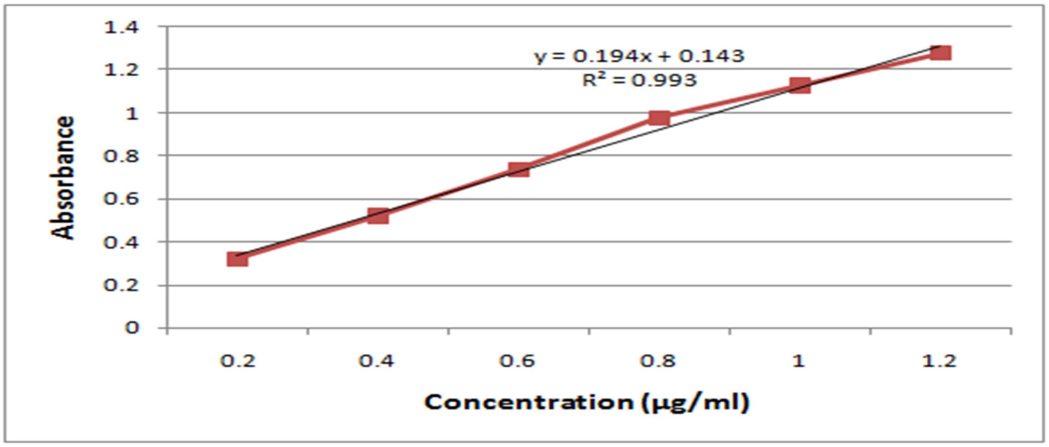

Figure 1: Calibration Curve of Terbinafine at 223 nm wavelength

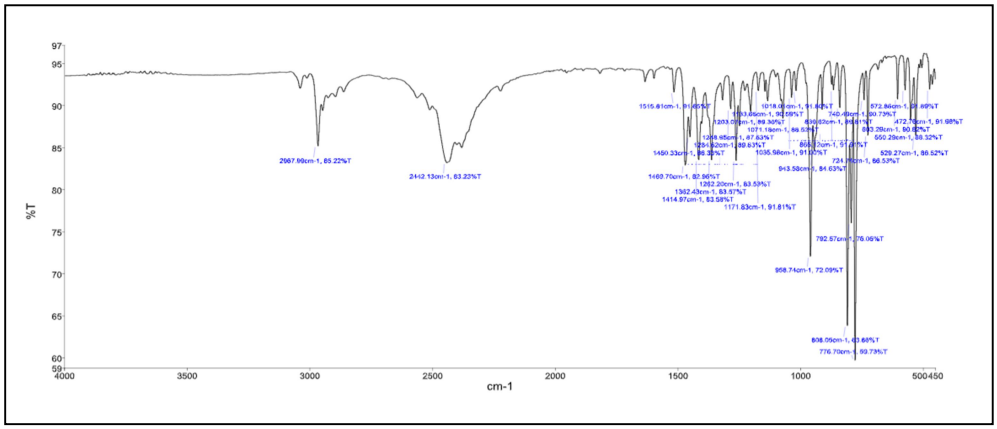

Figure 2: FTIR graph of Terbinafine

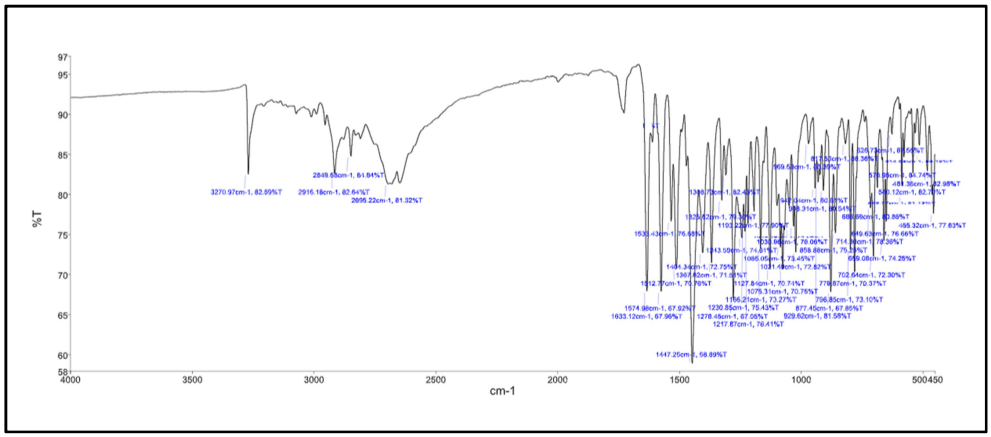

Figure 3: FTIR graph of Drug + Excipients

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

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

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

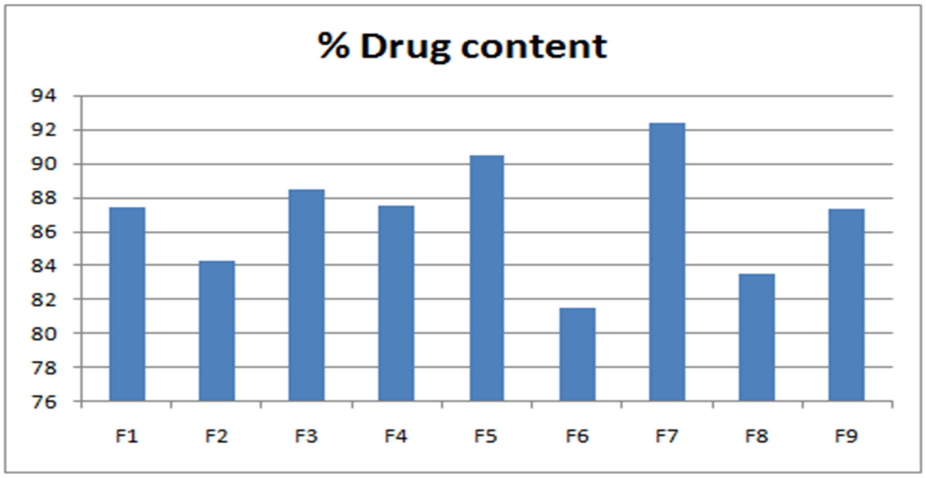

Figure 4: Graph of % drug content

Table 6: Viscosity and spreadability of all batches F1-F9

Formulationcode	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

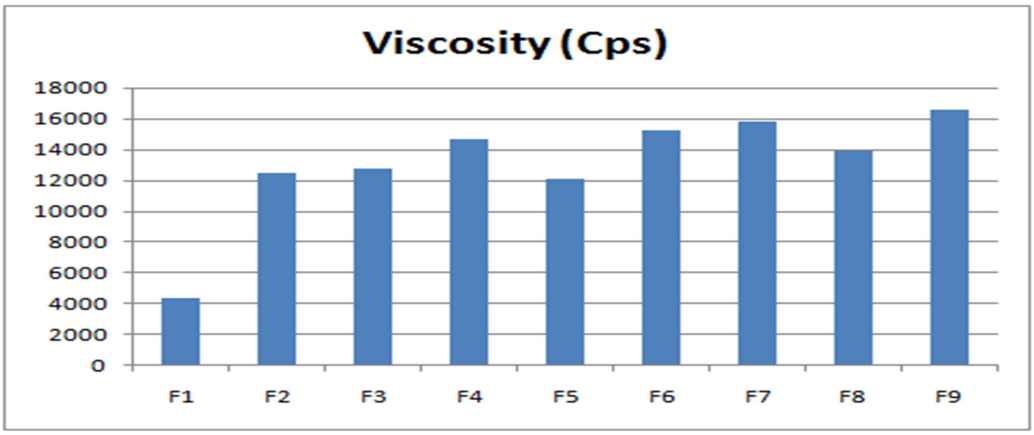

Figure 5: Graph of viscocity

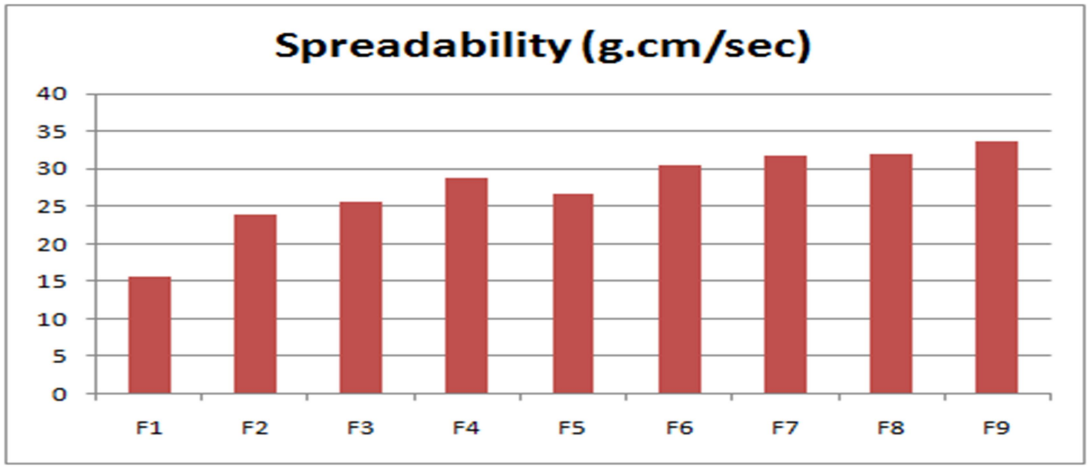

Figure 6: Graph of spreadability

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

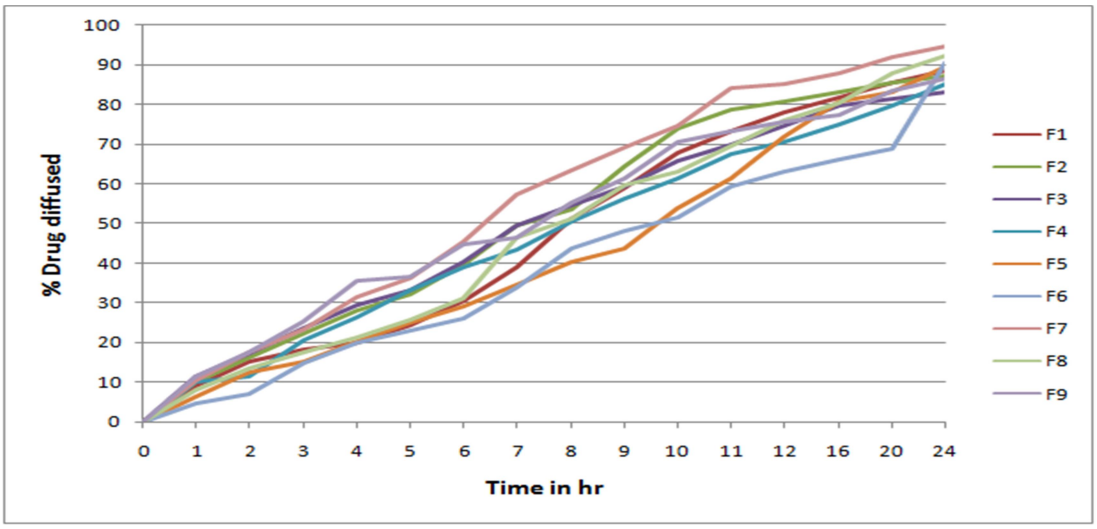

Figure 7: % Drug diffusion of all batches

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

CONCLUSION:

The research conducted showed the better suitability of poorly bioavailable drugterbinafine hydrochloride towards micro-emulgel formulation. Results showed maximum drugrelease within 24 hr (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 innature that is hard to penetrate via skin which is hydrated. Although formulation of micro-emulgel can enhance drug efficacy, future studies are required to determine its clinical efficacy.

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