Research Article

Design, Optimization and Evaluation of Microemulgel Containing Antifungal Drugs

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ABSTRACT

Microemulgel has lately emerged as one of the pharmaceutical industry's most intriguing topical medicines. It is easier to administer microemulgel than standard formulations, and the medicine stays in the skin for a longer period, allowing for more effective absorption and absorption into the bloodstream. Benzoic and salicylic acid microemulgels for the treatment of fungal infections were designed, optimised, and evaluated in this work. Carbopol 934 and HPMC k15m were used as gelling agents, oil as a preservative, and emulsifying agent as a penetration enhancer in the research to create benzoic and salicylic acid microemulgels. Using ATR-FTIR spectroscopy, the produced microemulgel formulations were evaluated for drug excipient interaction interactions and exhibited satisfactory syneresis, spreadability, and drug content. For the F4 formulation, *in vitro* drug diffusion experiments demonstrated a maximum release of 95.37 percent. Drugs and excipients are well-integrated and physically stable in the tailored microemulgel formulation thanks to the microemulgel's appropriate characteristics. Therapeutically effective, it may help increase patient compliance.

Keywords: Microemulsion, Microemulgel, Topical drug delivery, Benzoic and Salicylic acid.

INTRODUCTION

Microemulgel is a formulation created by mixing microemulsion and gel. With the benefits of microemulgel, a dual control release system (gel and microemulsion) might be achieved, resulting in increased pharmacological activity at the site of action and fewer adverse effects. Oil is likely to have certain pharmacological properties, and one surfactant and cosurfactant from every category will be evaluated based on drug solubility tests in it, overcoming the problem of drug solubility.[1] The microemulgel formulation increases API skin deposition, presumably increasing therapeutic action. Microemulgels offer a wide surface area for medication absorption, and the oil component promotes drug permeability, increasing bioavailability. Salicylic acid is a white powder with a fine consistency. It is applied to the skin externally. It can be used to treat athlete's foot, scalp ringworm, and the removal of warts, corns, and calluses. Salicylic acid is also found in products designed to treat acne, dandruff, seborrhea, and insect bites.[2]

As an antimicrobial preservative, benzoic acid is widely used in cosmetics, foods, and pharmaceuticals. Benzoic acid has also been used as an antifungal agent in topical therapeutic preparations for a long time. The goal of this research is to create, develop, and test antifungal Microemulgels.[3]

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MATERIALS AND METHODS

Benzoic acid, Salicylic acid was obtained as a gift sample from Indochem Health Specialities Pvt. Ltd. Tween 80 was a gift sample from SD fine chemicals, Chennai. Glycerin and propylene glycol was purchased from

madras scientific supplies, Salem. Carbopal934, HPMC K15m and triethanolamine were purchased from mercury's scientific chemicals industries, Salem.

UV spectral analysis

The UV–Vis spectra (UV–Vis) were acquired in the 200–400 nm range using a Shimadzu spectrophotometer; ethanol was used for this analysis. The result is shown in the Figure 1, 2.

ATR-FTIR Spectra analysis

The spectrum was captured at wavelengths ranging from 4000 to 400cm^{-1}. After loading a homogeneous mixture of the drugs, and physical mixture into the sample holder, an IR spectrum was acquired using an ATR-FTIR spectrophotometer. The result is shown in the Figure 3, 4, 5, 6.

Microemulsion Preparation[4]

A specific amount of the drug was accurately weighed and dissolved in oil using a magnetic stirrer. The surfactant and the water were mixed. This solution was added to an oily drug solution drop by drop and mechanically stirred to produce an emulsion. Co-surfactant was added to the emulsion one drop at a time. The formation of a transparent solution indicated the development of a microemulsion.

Gel Phase Formulation[5]

For the gel phase, carbopol 934, HPMC k15m were chosen. Before use, the polymers were dispersed separately in warm water and soaked for 24 hr.

Microemulsion-Based Gel Development (MBG)[6]

Carbopol 934 and HPMC K15M polymers were utilised as gelling agents in the formulation of a micro emulsion-based gel. The polymer at a time was soaked in water for 24 hr. They were combined to make the gel phase.

UV-Visible Spectrophotometer

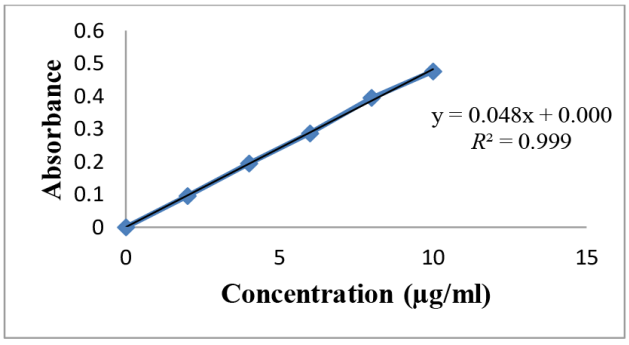

Figure 1: Standard Calibration Graph of Benzoic acid at 230nm.

The produced microemulsion was then combined with the gel phase to form a microemulsion-based gel, which was then smoothed and elegant. The Formulation of Microemulgel shown in the Table 1.

Evaluation of Microemulgel[7-10]

Syneresis

The percent syneresis of the formulation was discovered to be very low or high. This demonstrated whether the

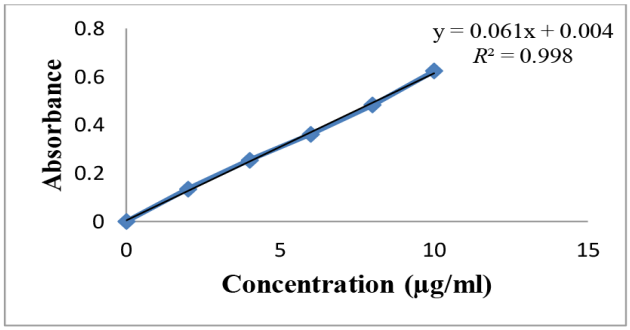

Figure 2: Standard Calibration Graph of Salicylic acid at 230nm.

ATR-FTIR Study

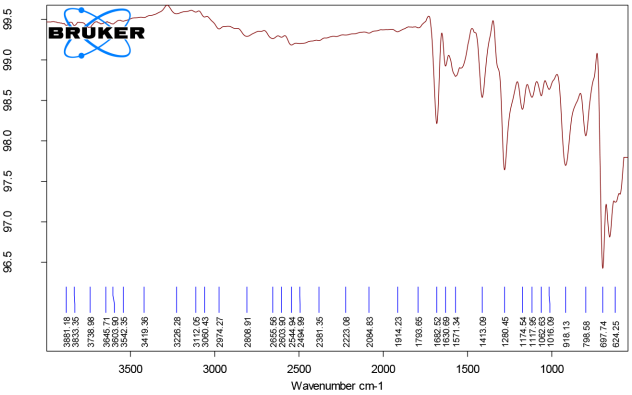

Figure 3: ATR- FTIR Spectroscopic Studies for pure Benzoic acid.

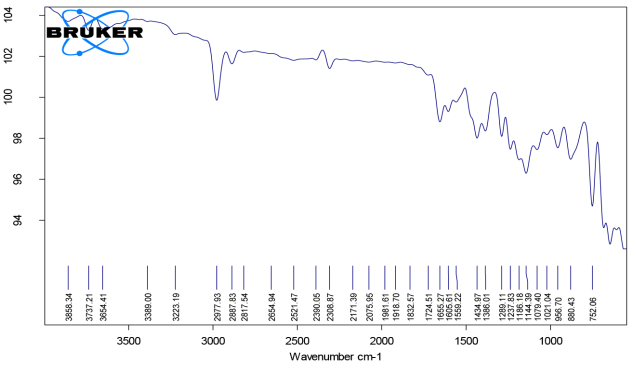

Figure 4: ATR- FTIR Spectroscopic Studies for pure salicylic acid.

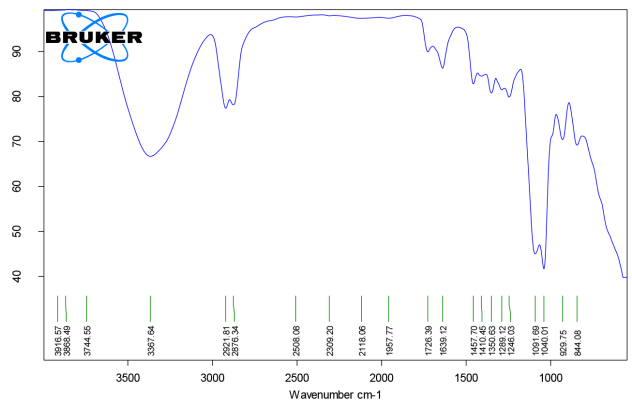

Figure 5: ATR- FTIR Spectroscopic Studies for a physical mixture.

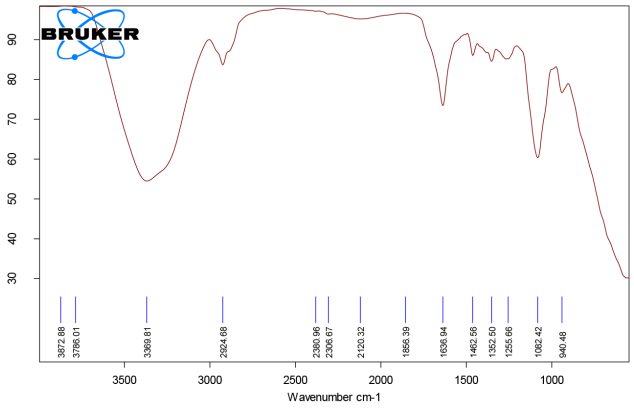

Figure 6: ATR- FTIR Spectroscopic Studies for optimized microemulgel F4.

Table 1: Formulation of microemulgel.

Sl. No	Ingredients (%w/w)	F1	F2	F3	F4	F5	F6
1.	Benzoic acid + Salicylic acid	0.1	0.1	0.1	0.1	0.1	0.1
2.	Glycerin	4.5	4.5	4.5	4.5	4.5	4.5
3.	Tween 80	1.25	1.25	1.25	1.25	1.25	1.2
4.	Propylene glycol	1.25	1.25	1.25	1.25	1.25	1.25
5.	Carbopal	0.4	0.6	0.4	0.6	0.4	0.6
6.	HPMC	04	0.4	0.6	0.6	0.8	0.8
7.	Triethanolamine	Adjust pH 5 to 7					
8	H_2O	q.s					

Evaluation of Microemulsion Based Gel

Syneresis Evaluation

Table 2: Syneresis Evaluation for microemulgel.

Formulation	% Syneresis
F1	4.93
F2	2.47
F3	1.79
F4	1.54
F5	1.72
F6	3.90

formulation was stable at room temperature or not. The result is shown in the Table 2.

Spreadability Test

The uniformity, ease, and application of transdermal formulations are all inspected using spreadability as a criterion. The spreading coefficient is how it's expressed (S). A modified apparatus was used to calculate the spreading coefficient. The apparatus consisted of two glass slides, one fixed to a wooden board and the other movable and attached to a thread that passed through a pulley and carried weight. 1gm of microemulgel was placed between two glass slides. A 100g weight was allowed to lie on the upper slide for 1 to 2 min to evacuate entrapped air between slides and generate a homogeneous coating of the formulation. After removing the weight, the top slide was subjected to a pull obtained by attaching a known weight over the pulley. Spreadability was defined as the time it took a moving slide to move a set distance (cm) in seconds. The spreadability was estimated using the equation below. The result is shown in the Table 3.

Spreadability

Table 3: Spreadability determination for microemulgel.

Formulation Batch	Spreadability(gm.cm/s)
F1	18.17
F2	19.36
F3	19.74
F4	20.71
F5	18.14
F6	19.48

$$\text{Spreadability} = \frac{M \times L}{T}$$

Where,

M =the amount of weight required to move the slide (gm).

L=the distance covered by the glass slide (cm).

T=L is the time required by the slide to travel a given distance (sec).

Drug content

To analyse the uniform distribution of the medicine in the formulation, the drug content must be determined. It ensures that variance between batches is maintained

Table 4: Drug content determination of Microemulgel.

Formulation Batch	Drug content (%)
F1	88.05
F2	89.02
F3	92.01
F4	95.08
F5	87.04
F6	81.05

to a minimum. The amounts of benzoic and salicylic acids in microemulgel were measured. The result is shown in the Table 4.

In-Vitro Diffusion Study[11-13]

Egg Membrane

To extract all of the contents of a raw egg, a tiny hole was cut in the bottom. After that, the eggshell was immersed in 0.1 N HCl for 2 hr. After the eggshell was dissolved, the membrane was collected. The fresh egg membrane was then rinsed in distilled water before being treated with phosphate buffer pH 6.8. This was a factor in the study. A freshly detached egg membrane is utilised each time the investigation is undertaken.

Franz Diffusion Study

The Franz diffusion cell is used to determine drug release *in vitro*. The Microemulgel is ready to diffuse from the egg membrane after *in vitro* release from the prepared formulation using a double-end open cylinder. The releasing media was a phosphate buffer solution with a pH of 6.8, and cellulose acetate paper was soaked in it for two hours. A separate open-end glass tube was weighed with 2.5 gm of the formulated Microemulgel (equivalent to 200 mg benzoic acid and salicylic acid). The glass tube was then suspended in a 250 mL phosphate buffer solution with a pH of 6.8 that was kept at 370.5°C. At 15, 30, 60 min to 8 hr, the paddles were rotated at 300 rpm and aliquots of 1ml were withdrawn. Equal volumes of phosphate buffer solution were used to replace aliquots. Based on the concentrations obtained for the various microemulgels over time as a function of the loading doses, the cumulative percentage drug release was calculated (equivalent weight of benzoic acid and salicylic acid in 1 g samples of the microemulgel). The result is shown in the Table 5 and Figure 7.

Stability Study

The time from the date of production and packaging of the formulation until its chemical or biological activity

Table 5: *In-vitro* Drug Diffusion Study for all BA and SA microemulgel formulations (F1-F6).

Sl.no	Time (min)	Cumulative percentage of drug release (%)					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	15	6.47	6.52	8.21	9.32	4.75	5.21
3	30	12.44	14.85	18.27	16.74	7.32	10.24
4	60	20.19	23.21	25.02	26.53	12.04	16.85
5	120	30.02	30.54	33.50	36.32	20.45	21.45
6	180	36.24	42.35	43.88	45.22	30.14	29.54
7	240	46.72	50.24	52.97	54.43	41.14	36.78
8	300	51.24	59.34	68.53	63.79	49.58	46.98
9	360	65.75	67.31	84.15	70.71	58.25	59.58
10	420	74.23	79.07	89.46	90.74	73.05	75.32
11	480	88.14	89.41	92.25	95.37	87.23	81.44

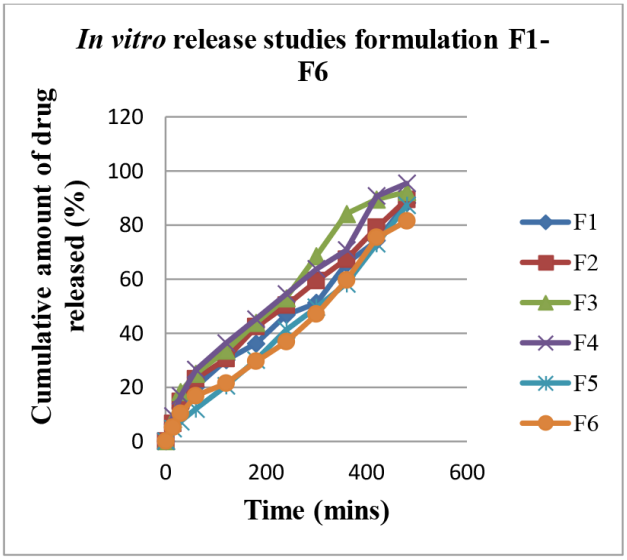

Figure 7: *In vitro* release studies microemulgel formulation F1-F6.

is not less than a particular level of labelled potency and its physical qualities have not altered considerably or adversely is referred to as drug stability. There are certain exceptions, but the lowest permissible potency level is 90% of the advertised potency. The International Conference on Harmonization's (ICH) "stability testing of new drug substance and products" (QIA) guideline sets the stability test requirements for drug registration applications in the European Union, Japan, and the United States. The optimized batch's stability was tested according to ICH guidelines. At 30°C±2°C/ 65%RH ±5%RH, a long-term stability study. A month of accelerated gel stability was carried out at 40°C±2°C/ 75%RH±5%RH was conducted for 1, 2, and 3 months by using Humidity Chamber. The Accelerated stability

Table 6: Stability studies of Optimized Microemulgel formulation.

Parameters	Initial	After one month		After two months		After three months	
		(40°C ±2°/ 75%RH±5%) Accelerated stability study	Room Temperature stability study	(40°C ±2°/75%RH±5%) Accelerated stability study	Room Temperature stability study	(40°C ±2°/ 75%RH±5%) Accelerated stability study	Room Temperature stability study
Appearance	Off white colour	Off white colour	Off white colour	Off white Colour	Off white colour	Off white Colour	Off white Colour
Spreadability (gm.cm/s)	20.71±1.34	19.55±1.2	20.71±1.34	18.14±1.12	20.68±1.10	17.55±1.12	20.15±1.24
Viscosity (cps)	16000±1.50	15000±1.80	16000±1.5	14000±1.77	15800±1.40	13000±1.97	15700±1.23
In vitro drug release (min)	95.06±0.37	94.08±0.41	95.0±0.37	93.09±0.31	94.94±0.10	92.02±0.71	94.89±0.10

optimized formulation was taken for three months of 40°C±2°C/ 75%RH±5%RH for accelerated and 25°C±2°C/ 60%RH±5RH. The result is shown in the Table 6.

RESULTS

DISCUSSION[5,14]

The current study was conducted to create a microemulsion gel formulation of benzoic acid and salicylic acid to improve drug absorption and bioavailability. The important factor is a large amount of drug-loaded in microemulgel, as well as studying the preformulation and evaluation factors, were investigated for this technique, and the findings are detailed below.

UV-Visible Spectrophotometer

The different concentrations (2, 4, 6, 8 and 10 g/ml) of benzoic acid and salicylic acid were prepared with ethanol and analysed through UV at 230nm and 210nm using corresponding media as a blank and good linearity with an R^2 value of 0.999 for Benzoic acid, an R^2 value of 0.998 for Salicylic acid, which suggests that it obeys the Beer-Lamberts law.

ATR-FTIR Study

The drug interaction studies were analysed by ATR-FTIR based on the functional category these excipients were mixed in different ratios with benzoic acid and salicylic acid. This indicates that the medicine is compatible with the other ingredients in the formulation.

Evaluation of Microemulsion-based Gel

Syneresis Evaluation

The percentage of syneresis for prepared microemulgel formulations F1 to F6 was found to be 1.54 % to 4.93 %. This F4 formulation has low syneresis of 1.54 % which shows better when compared to other formulations.

Spreadability

The spreadability of the prepared microemulgel formulation of F1 to F6 was found to be between 18 and 21gm.cm/s, indicating that it spreads well. From this formulation F4 20.71 gm.cm/s is better than compared to other formulations.

Drug Content

The drug content of prepared microemulgel formulations of F1 to F6 has 85 to 96 %. This F4 formulation of 95.08 % shows high drug content than other formulations.

In-vitro Diffusion Study

In vitro drug release study of the prepared microemulgel was carried out using Franz Diffusion method were conducted for 8hrs. *In vitro* release studies, formulation F1 – 88.14%, F2 – 89.41%, F3 – 92.25%, F4 – 95.37%, F5 – 87.23% and F6 – 81.44%, In that F4 microemulgel the highest drug release rate of 95.37%, indicating that it was an optimized formulation.

Stability Study

The stability studies for the optimized F4 microemulgel formulation were conducted for three months. The study results indicated negligible level of changes were observed in appearance, viscosity, spreadability, and *in vitro* drug release indicating that stability problems during storage at accelerated temperature and (40°C 2°/ 75%RH 5%) and the room temperature were observed. The appearance of microemugel is off-white, viscosity was found in the range of 15000±1.80cps to 13000±1.97cps, and spreadability was found to be 19.14±1.82cm to 17.55±1.12cm, *in vitro* drug release was found to be 94.08±0.41 to 92.02±0.71 are within the pharmacopeial limits.

CONCLUSION

The goal of this research is to design, develop, and evaluate antifungal Microemulgels. This occurred as an attempt was made to create microemulgel to improve drug bioavailability. The goal of this study was to create a microemulgel formulation of BA and SA for topical microemulgel bioavailability enhancement. As a result of these findings, it is possible to conclude that the Benzoic acid and Salicylic acid Microemulgel formulation, particularly the F4, exhibited improved release behaviour, resulting in an effective modified route of administration. It improved the formulation's stability, elegance, and effectiveness.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **ATR-FTIR:** Attenated Total Reflectance- Fourier Transform Infrared; **Gm:** Gram; **HCl:** Hydrochloric acid; **HPMC:** Hydroxy Propyl Methyl Cellulose.

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