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Research Article

EUDRAGIT S-100 MICROSPONGES BASED GEL OF BUTENAFINE HYDROCHLORIDE FOR CANDIDIASIS: DESIGN, OPTIMIZATION, *IN VITRO* AND *IN VIVO* INVESTIGATION

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ABSTRACT

Objective: This research focused on formulating a controlled-release microsponge gel incorporating butenafine hydrochloride (BFH), designed to enhance drug retention time and reduce the risk of skin irritation.

Methods: BFH-loaded microsponges were prepared using the quasi-emulsion solvent diffusion technique. Optimization of formulation parameters, including Eudragit S-100 and dichloromethane, was performed using a 3^2-factorial design. The microsponges were evaluated for production yield, entrapment efficiency (EE), and cumulative drug release (CDR) using Fourier transform infrared spectroscopy, X-ray diffraction, differential scanning calorimetry, and scanning electron microscopy techniques. The optimized microsponge formulation was incorporated into a Carbopol 934 gel. The resulting microsponge gel was assessed for extrudability, spreadability, drug content, *in vitro* drug release, rheological properties, and *in vitro* antifungal activity against *Candida albicans*.

Results: The optimized microsponge formulation exhibited a particle size of 48.92±2.49 µm, an EE of 89.42±1.55%, and a CDR of 81.67±2.41%. The microsponge gel demonstrated a controlled drug release and was non-irritant to rat skin. The controlled release of BFH from the microsponge gel resulted in prolonged drug retention with reduced permeation activity.

Conclusion: The study revealed that the BFH microsponge gel offers enhanced topical retention and prolonged drug release. In addition, it showed superior antifungal activity compared to marketed preparations while significantly reducing skin irritation.

Keywords: Butenafine hydrochloride, Microsponge, Quasi-emulsion solvent diffusion, Topical gel, Microsponge loaded gel.

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INTRODUCTION

Microsponges are leading the advancement of innovative drug delivery technologies. Microsponge drug delivery technology offers immense potential for achieving controlled and site-specific drug delivery, making it a focal point of interest for researchers in the field [1]. Conventional drug delivery systems often result in non-specific and off-targeted effects throughout the body rather than targeting specific sites. This results in different adverse drug reactions caused by unpredictable patterns of drug release [2]. Microsponges-based drug delivery systems address these problems associated with conventional delivery by providing targeted and controlled release of the drug as per the requirements of therapy. Hence, it offers several constructive advantages compared to others, such as improved effectiveness and higher cost efficiency for the therapy [3]. Microsponge technology is an advanced method designed for the controlled release of active ingredients, offering multiple other benefits, including enhanced stability, minimum side effects, enhanced formulation characteristics, and enhanced patient acceptability [4]. Further, this technique is non-irritant, non-toxic, non-mutagenic, and non-allergenic [5].

Butenafine hydrochloride (BFH) is a benzylamine derivative and is a next-generation antimycotic agent with potent fungicidal properties. Its mechanism of action involves the inhibition of sterol biosynthesis by specifically blocking the squalene epoxidation step in fungal cells. Butenafine has poor water solubility but dissolves well in organic solvents such as methanol, ethanol, dichloromethane (DCM), and chloroform. With a molecular weight under 400 Da, it holds strong potential for incorporation into micro sponge-based formulations. At present, no sustained-release topical formulation of butenafine is commercially available, and no research studies on such formulations have been reported in the scientific literature [6].

Butenafine has a log partition coefficient of 4.65 in an n-octanol-water system, highlighting its high lipophilicity. As a result, it has poor water solubility and limited oral absorption. Despite this, it has been effectively used to treat candidiasis and onychomycosis with minimal toxicity, demonstrating a good therapeutic index. However, the penetration of butenafine from currently available cream formulations remains quite low. To improve local retention and enhance overall effectiveness, incorporating butenafine into a micro sponge-based gel could overcome the limitations of traditional delivery methods [7].

BFH-loaded microsponges are small, porous carriers that hold the drug. They solve problems found in other microcarriers, such as having a low amount of the drug, being unstable, immediate drug release, frequent application needs, and potential drug accumulation at the application site, which can lead to undesirable effects [8]. These microsponges contain many pores, which help trap active ingredients. They can be made into gels. Because of their porous design, they have a large surface area, allowing them to hold more of the drug. This structure helps improve how the drug is delivered through the skin. Microsponges also provide a controlled release of the drug and help create local effects [8].

This study aimed to formulate butenafine-loaded microsponges integrated into a Carbopol-based gel to achieve sustained drug release and improved skin permeation. The formulated system is expected to improve drug retention within the skin layers, potentially eradicating fungal infections in the dermal region and thereby reducing the cyclic recurrence of such infections.

MATERIALS AND METHODS

Materials

BFH was purchased from BLD Pharmtech India Private Limited, Hyderabad, and Telangana, India. Eudragit S100, RS 100, L 100, RL 100, and di-n-butyl phthalate were purchased from Merck Private Limited, Mumbai. Ethylcellulose, Carbopol 934, Polyvinyl alcohol (PVA), ethanol, polyethylene glycol, Triethanolamine, DCM, and methylparaben were procured from HiMedia, Mumbai, India.

Methods

Preliminary screening of formulation parameters and development of BFH microsponge

In initial trials of BFH-loaded microsponges, various parameters such as polymer concentration, PVA concentration, and stirring speed were evaluated. The effect of these parameters was assessed on yield, particle size, and entrapment efficiency (EE). A quasi-emulsion solvent diffusion technique was utilized for the development of BFH microsponges. The batch quantity of BFH and polymers (Table 1) was dissolved in a mixture of DCM and ethanol (5:15 mL), and this was considered an internal phase. PVA at 0.5% was dissolved in distilled water under continuous stirring to get the external phase. The internal phase was slowly added to the external phase at stirring speeds of 500, 1000, and 1500 rpm, followed by homogenization using a high-pressure homogenizer at 500 bars for three cycles. The organic solvent was evaporated from the emulsion by magnetic stirring at room temperature for 3 h. The collection of microsponges was performed using centrifugation at 10,000 rpm for 13 min, and the remaining organic solvent in the external aqueous phase was removed. Finally, the microsponges were air-dried for 12 h [9].

Design of experiments (DOE)

Microsponges were developed and optimized by the DOE approach using a 3^2 factorial design. Eudragit S100 (A) and PVA (B) were considered independent variables, whereas EE, cumulative drug release (CDR), and particle size were considered dependent variables. The effect of independent variables on dependent variables was determined by plotting counterplots and surface plots.

Preparation of microsponges

The novel quasi-emulsion method was employed to manufacture microsponges. In the internal phase, Eudragit S 100 (at concentrations of 0.75, 1, and 1.25 g) was dissolved in a mixture of DCM and ethanol (5:15 mL). The batch quantity of BFH was dissolved in polymeric solution using ultrasonication (Labman Scientific Instrument) at 35°C for 10 min. The internal phase was slowly added to the external phase containing 100 mL of PVA (in various concentrations of 0.25, 0.5, and 0.75 g) prepared in water and 1% dibutyl phthalate as a plasticizer. After stirring at 1000 rpm for 20 min, the mixture was further homogenized using a high-pressure homogenizer (GEA Niro Soavi-Panda plus, Italy) at 500 bars for three cycles. The organic solvent was evaporated from the emulsion by magnetic stirring at room temperature for 3 h. The collection of microsponges was performed using centrifugation at 10,000 rpm for 13 min, and the remaining organic solvent in the external aqueous phase was removed. The collected microsponges were air-dried for 12 h [9,10]. The formulation of microsponges is depicted in Table 1.

Solubility study

Solubility analysis was performed by dissolving an excess amount of BFH in aqueous polymer solution. The solution was stirred for 12 h. The resulting solutions were filtered through a 0.45 µm membrane filter to remove any undissolved particles. The samples were analyzed for BFH content using a UV spectrophotometer at 278 nm (Nano3060 UV Bio, Thermo Fisher Scientific, USA) [11].

Drug content determination

Accurately weighed, 100 mg of BFH-loaded microsponges were added to 100 mL of phosphate buffer (pH 6.8) and stirred continuously for 12 h to ensure complete drug release. Once equilibrium was reached, the samples were filtered through a 0.45 µm membrane filter. The drug concentration in the filtrate was then determined using a UV spectrophotometer (Nano3060 UV Bio, Thermo Fisher Scientific, USA) at 278 nm, with a blank solution serving as the reference. The drug content for all batches was evaluated using the following equation [12].

$$Drug\ Content\ (\%) = \frac{Actual\ content\ in\ microsponges}{Weighed\ quantity\ of\ microsponges} \times 100 \quad (1)$$

Fourier transform infrared spectroscopy (FTIR) analysis

The drug and excipient compatibility were studied using the FTIR (Shimadzu 8400S, Japan) technique, in which blank KBr was utilized as a reference. The samples were scanned through 4000–400 cm^{-1} wavelength, and based on IR peaks, comparative analysis was performed [13].

Particle size analysis

The average particle size of the microsponges was determined using the dynamic light scattering technique with a Mastersizer (Malvern Instruments, Worcestershire, UK) following a tenfold dilution in distilled water at 25°C. This analysis helped determine the uniformity and distribution of particle sizes of the formulation [13].

EE

Accurately weighed, 100 mg BFH microsponges were dissolved in 100 ml of pH 6.8 phosphate buffer under continuous stirring for 12 h to ensure complete drug release. The resulting solution was filtered through a 0.45 µm membrane filter and analyzed at 278 nm using UV spectroscopy(Nano3060 UV Bio, Thermo Fisher Scientific, USA). The EE was calculated using the below formula [12,14].

$$Entrapment\ Efficiency\ (\%) = \frac{Practical\ drug\ content}{Theoretical\ drug\ content} \times 100 \quad (2)$$

Table 1: Formulation of microsponges

Formulation	BFH (g)	Es 100 (g)	DCM: Ethanol (mL)	PVA (%W/V)	Dibutyl phthalate (%)	Water up to (mL)
F1	1	1.25	20	0.5	1	100
F2	1	1.25	20	0.25	1	100
F3	1	1.25	20	0.75	1	100
F4	1	1	20	0.5	1	100
F5	1	1	20	0.25	1	100
F6	1	1	20	0.75	1	100
F7	1	0.75	20	0.5	1	100
F8	1	0.75	20	0.25	1	100
F9	1	0.75	20	0.75	1	100

BFH: Butenafine hydrochloride, DCM: Dichloromethane, PVA: Polyvinyl alcohol

Production yield
The yield was calculated using the below formula

$$\text{Production Yield}\ (\%) = \frac{\text{Wt of Microsponges}}{\text{Theoretical Mass of Microsponges}\ (\text{drug} + \text{Polymer})} \times 100 \quad (3)$$

X-ray diffraction (XRD)
The crystalline structure of BFH and BFH-loaded microsponges was analyzed using XRD [Miniflex II X-ray diffractometer (Rigaku)]. The XRD patterns were determined using an X-ray diffractometer operated at 30 kV voltage and 30 mA current. The scanning was done over a 2θ range of 5°–50°, allowing the detection of crystalline peaks and any possible changes in the drug's crystalline structure upon incorporation into the microsponges [15].

Differential scanning calorimetry (DSC)
The thermal behavior of BFH and BFH-loaded microsponges was analyzed using a DSC instrument (Mettler-Toledo DSC 1 Star System, Mettler-Toledo International Inc. USA). Samples (5 mg) were kept in aluminum pans and sealed thematically. Heating was done at 10°C/min between 30°C and 240°C temperature range in the presence of nitrogen at 50 mL/min flow rate. This thermal analysis was used to investigate the melting behavior and interactions between BFH and excipients in microsponges [16].

Scanning electron microscopy (SEM)
The surface properties of the BFH-loaded microsponges were analyzed by the SEM (JSM-6390LV, JEOL Ltd., Japan) technique. The samples were placed on the metal surface grids. SEM was utilized to examine the structural characteristics and surface texture of the microsponges [16].

Drug release
The USP dissolution apparatus (Type I) (Electrolab India Private Limited, Mumbai) with a modified basket with a 5 µm stainless steel mesh was used to assess the BFH-loaded microsponges' *in vitro* drug release profile. The temperature was maintained at 37±0.5°C during the experiment, and a sample eq. to 100 mg of BFH was put in the basket and rotated at 100 rpm. The dissolution was performed in 900 mL of phosphate buffer (pH 6.8. Aliquots of the dissolution medium were taken out and replaced with new buffers at pre-arranged intervals. A UV-visible spectrophotometer set to 278 nm was used to evaluate the samples and measure the amount of drug released at each time point. The CDR was calculated based on the absorbance measurements [17].

Formulation of gel
Carbopol 934 was added slowly, and distilled water, under continuous stirring, was kept for hydration for 24 h. The developed microsponges were dispersed in ethanol and added to the polymeric phase of Carbopol under stirring to ensure uniform dispersion. The pH was adjusted to neutral using the dropwise addition of Triethanolamine [18]. The formula composition is presented in Table 2.

pH
pH of the final formulation was determined using a digital pH meter (LT-11, LABTRONICS, India). The weight quantities of 5 g of each gel formulation were transferred to 10 mL of the beakers and measured using a pH meter [19].

Table 2: Formulation of gel

S. No.	Ingredients% w/w	G1	G2	G3
1	Drug (g)	0.1%	0.1%	0.1%
2	Carbopol 934 (g)	1.5	2	1
3	Propylene glycol (mL)	2	2	2
4	Ethanol (mL)	5	5	10
5	Tween 20 (mL)	1	1.25	1.5
6	Methyl Paraben	0.03	0.03	0.03
7	Glycerin (mL)	10	10	10
8	Triethanolamine (mL)	Q. S.	Q. S.	Q. S.
9	Water (mL)	Q. S.	Q. S.	Q. S.

Viscosity
The viscosity was determined using a Brookfield viscometer (Brookfield DV-E 205, Brookfield Engineering Laboratories, Inc. USA) with spindle no. S7 at a speed of 50 rpm and a temperature of 37±0.5°C [19].

Spreadability
The gel was applied between two horizontal glass slides (7.5 × 2.5 cm) to conduct spreadability tests of microsponges loaded gel formulations. To evenly distribute the gel between the two slides, a 100 g weight was placed on top of them. The excess gel was scraped out once the weight was removed. In triplicate, the experiment was conducted [19].

$$\text{Spreadability} = \frac{\text{Weight kept on the upper slide} \times \text{length of glass slide time taken in seconds}}{\text{Time taken in Seconds}} \quad (4)$$

Extrudability
The gel was filled properly in clear, collapsible aluminum tubes. The extrudability of gel was estimated as weights in grams required to extrude out through the tip of the tube with criteria that at least 0.5 cm ribbon of micro sponge gel in 10 s [19].

Drug content
Using a mechanical stirrer, a weighed amount of microsponge gel was dissolved in 100 mL of phosphate buffer solution (pH 6.8) and agitated for 2 h to solubilize the drug properly. After the drug solution was filtered through 0.45 µm filter paper, it was spectrophotometrically measured at 278 nm using an appropriate dilution and a blank phosphate buffer pH 6.8 [18,19].

Percentage of drug release and kinetics
The *in vitro* skin permeation study was conducted using Franz diffusion cells with an effective diffusion area of 2 cm^2. Before the experiment, the dialysis membrane was pre-soaked for 12 h and then placed between the donor and receptor compartments. A microsponge-based gel containing BFH was placed in the donor compartment, whereas the receptor compartment was filled with a phosphate buffer (pH 6.8), maintained at 37±1°C, and stirred at 600 rpm. At regular intervals over 12 h, 10 ml samples were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The collected samples were analyzed using a UV spectrophotometer at 278 nm, and the concentration of BFH released over time was determined using a calibration curve, with the data plotted against time [19]. Drug release data was subjected to a kinetic study to get the order of release and release mechanism [20].

***Ex-vivo* drug deposition study**
The *ex vivo* diffusion study was conducted using excised Wistar rat skin. The abdominal skin was carefully shaved and positioned on the Franz diffusion cell, with the epidermal side facing the donor compartment and the dermal side in contact with the receptor solution. The receptor compartment was filled with 20 mL of phosphate buffer (pH 6.8) and continuously stirred. The test sample was applied to the donor compartment, and the system was allowed to run for 8 h. After the study period, the diffusion cell was dismantled, and the skin was carefully removed. Any residual drug on the skin surface was washed off with distilled water.

To analyze drug penetration, the skin was cut into small pieces and homogenized with 10 mL of ethanol using a tissue homogenizer. The homogenized mixture was then subjected to ultrasonication for 10 min to ensure complete drug extraction. Following this, the ethanolic extract was centrifuged at 5000 rpm for 10 min, and the supernatant was collected and evaporated. The sample was filtered through a 0.2 µm membrane filter and analyzed using a UV spectrophotometer. The

drug content detected in the stratum corneum indicated the extent of drug deposition within the skin. All measurements were performed in triplicate. The study was conducted following the guidelines approved by the Animal Ethics Committee [20,21].

In vitro antifungal study

The *in vitro* antifungal activity was evaluated using Sabouraud's dextrose agar disc diffusion method with the "cup-plate technique" in a pre-sterilized Petri dish. The formulations of gel without drug BFH (1 mg/mL), Drug BFH, BFH loaded microsponge gel, and marketed formulation (Fintop) (1 mg/mL) were prepared in 8 mm cups and then added to wells that had already been seeded with the *Candida albicans*. After allowing the fluid to diffuse for 2 h, the plates were incubated at 27°C for 48 h. The inhibition zones around each cup were then measured and compared with the standard. The findings of three replicate measurements were reported, along with their means [21].

Primary skin irritation study

Twelve male Wister rats 180 g served as the subjects for the initial skin irritation investigations for the BFH, BFH-loaded microsponge gel, and marketed formulation. All animal experiments were approved by the department animal ethics committee (IACS/DPS/SU/1401). This is a commonly used method for hair removal in animal studies as it is simple, quick, and minimizes skin irritation. A razor is used to remove each rat's back hair leaving the skin exposed for treatment, followed by marking a 4 cm^2 region. Three experimental groups of three rats each were used to experiment. In the experiment, Group I was used as the control, whereas Group II received BFH treatment, Group III received BFH-loaded microsponge gel treatment, and Group IV received Fintop (Marketed Formulation). Each group was administered 10 mg of sample daily except for the control as determined by the Draize patch test. Before dose application, the skin was washed, and any subsequent reactions, including erythema and edema, were evaluated on days 1, 3, and 5. The criteria for the Draize test and the skin irritation score scale are provided in Table 3.

The following equations were used to determine the primary irritation index (PII). The results from three replicate measurements were reported, along with their averages. PII¼ Average scores for the variables, including skin type at the time of reading, and average scores for erythema grade, edema grade, and the number of animals on days 1, 3, and 7 (Scale Score).

PII ¼ average scores X variable factors

Whereas average scores = Σ Erythema grade* + Σ Edema grade*/ Number of animals * at 1, 3, 5, and 7 days and variable factor = types of skin × time of reading [21].

Stability study

The BFH-loaded microsponge gel was formulated and packed in 5 g aluminum collapsible tubes and subjected to stability testing for 6 months at 30°C and 40°C/75% RH. Samples were periodically removed and analyzed for physical characteristics, pH, drug content, and drug release [22].

Statistical analysis

The mean standard deviation is used to express all data. The statistical analysis was completed, and $p<0.05$ is considered statistically significant.

RESULTS AND DISCUSSION

Solubility study

Solubility is the ability of a drug to be dissolved in an aqueous medium. Solubility plays a critical role in drug effectiveness as the insoluble drug substance cannot be absorbed [23]. In this study, the solubility of a specific drug was evaluated in the presence of various polymers to determine their impact on the drug's dissolution characteristics. Among the polymers tested, Eudragit S 100 exhibited superior solubility in water compared to other polymers Fig. 1. The results indicate that Eudragit S 100 has a significantly higher solubility, suggesting that it could be particularly effective in improving the rate of dissolution. This higher solubility of Eudragit S 100 may be attributed to its unique physicochemical properties, which influence its interaction with water and the drug. The findings suggest that Eudragit S 100 could be a preferable choice for formulations requiring improved solubility of the drug.

FTIR

FTIR analysis of drug BFH, its formulation, BFH loaded microsponge, revealed significant characteristic peaks, specifically for C-H stretching at 2962.76 cm^{-1}, C-N stretching at 1269.20 cm^{-1}, and C=C stretching vibrations at 1514.17 cm^{-1} (Fig. 2a and b, Table 4). The presence of these peaks in both the drug and the BFH-loaded microsponge formulation suggests that there was no chemical change in the drug throughout the formulation process. This is a critical finding, as it indicates that the active pharmaceutical ingredient did not undergo any chemical degradation or transformation, which is essential for maintaining its efficacy. Furthermore, the observation of these peaks remains unchanged, pointing to excellent compatibility between the drug and excipients used in the microsponges formulation, implying that there were no adverse interactions that could affect the performance of the drug. The study concluded excellent compatibility between BFH and Eudragit S-100 maintaining excellent integrity of the drug throughout the manufacturing process. This compatibility is crucial for ensuring the drug can be effectively delivered in its intended form, maintaining its therapeutic properties while potentially enhancing stability and controlled release characteristics in the final formulation.

Preliminary batch

The results of the initial trial of BFH microsponges are presented in Table 5. Batch B-2, which contained Eudragit S100, demonstrated a good yield percentage and mean particle size. However, the use of Eudragit

Table 3: Skin irritation score scale

Grading	Description of irritant response
0	No Reaction
+	Weakly positive reaction (usually characterized by mild erythema across most of the treatment sites)
++	Moderate positive reaction (usually distinct erythema, possibly spreading beyond the treatment site)
+++	Strongly positive reaction (strong, often spreading erythema with edema)

Table 4: IR spectra of drug BFH

Material	Functional Group	Standard IR ranges (cm^{-1})	Observed IR ranges (cm^{-1})
BFH	C=C Stretching	1500–1650	1514.17
	C-N Stretching	1200–1350	1269.20
	C-H Stretching	2900–2964	2962.76

BFH: Butenafine hydrochloride, IR: Infrared

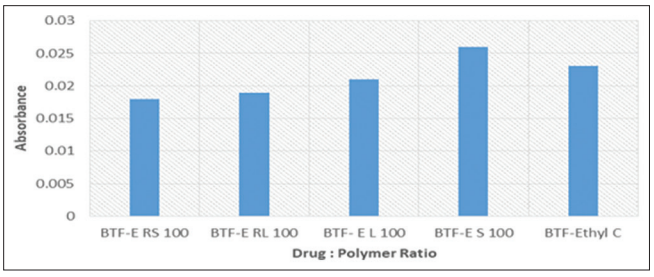

Fig. 1: Solubility of butenafine hydrochloride

ERS-100 in batch B3 resulted in uneven or larger particle sizes. Hence, a speed of 1000 rpm was selected for the subsequent preliminary trial batch. The findings from the initial study demonstrated that both Eudragit S100 and PVA were essential to attain the targeted particle size and EE. Therefore, further trials were carried out using different combinations of Eudragit S100 and PVA to evaluate their effects and determine the optimal concentrations required to achieve the desired release profile.

Design experiment

3^2 factorial design was used for evaluation. In this experimental design, a particle size of <50 µm and at least 80% CDR was considered optimized. Among batches F1 to F9, batch F2 showed the lowest particle size, 48.92±2.49 µm and 81.67±2.41% drug releases (Table 6), so it is considered an optimized formulation. F2 formulation was further added to the gelling system consisting of Carbopol 934.

Impact on EE

Drug: Polymer ratio has an impact on the EE of the drug, as shown in Fig. 3. The higher drug EE observed at elevated drug-to-polymer (D: P) ratios ($p<0.05$) can be attributed to the increased drug availability per unit of the polymer, allowing for greater drug incorporation within the polymer matrix. Similarly, the emulsifier also proportionally showed an effect on EE, as shown in Fig. 3. PVA was used as an emulsifier, which is a non-ionic emulsifier and helps to reduce the particle size enhancement in EE.

Effect on CDR

As shown in Fig. 4, an increase in the drug-to-polymer ratio provides more polymer for drug encapsulation ($p<0.05$) within the microsponge. This results in a thicker polymer matrix wall, which extends the diffusion pathway and ultimately leads to a reduction in drug release ($p<0.05$). Fig. 4 also demonstrates that higher concentrations of PVA

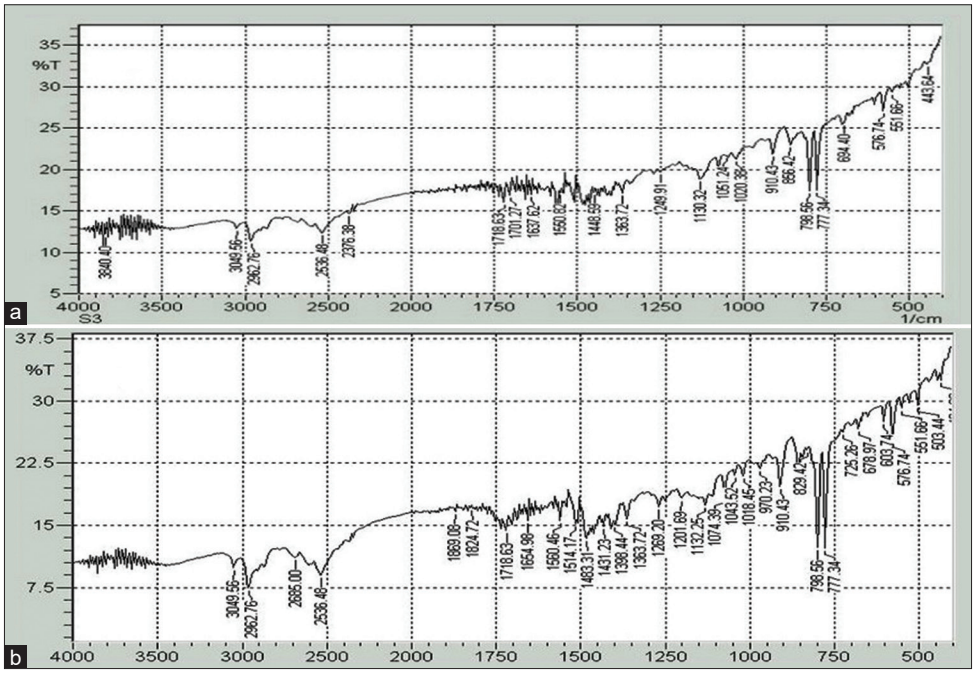

Fig. 2: Fourier transform infrared spectra of (a) Drug butenafine hydrochloride (BFH), (b) Drug BFH loaded microsponge

Table 5: PreliminaryBatcheswiththeirstirringspeed, entrapment efficiency, production yield, and particle size

Formulation code	Concentration polymer	PVA	Speed (rpm)	Production yield %	Entrapment efficiency (%)	Particle (µm)
B1	1% E S 100	0.5	500	75.54±1.25	79.48±1.61	62.56±1.37
B2	1% E S 100	0.5	1000	78.63±1.72	82.18±1.57	58.61±1.34
B3	1% E RS 100	0.5	500	64.27±1.58	68.31±1.29	74.15±2.58
B4	1% E RS 100	0.5	1000	72.31±2.34	74.65±1.71	69.43±1.02
B5	1% E S 100	0.5	1500	88.32±1.64	64.51±1.62	48.16±1.26

(All values are mean±SD; n=3)

Table 6: Formulation with their entrapment efficiency, production yield, particle size, and cumulative drug release (% CDR)

Formulation code	Entrapment Efficiency (%)	Production yield (%)	Particle size (µm)	CDR (%)
F1	88.41±1.24	79.38±1.27	52.16±1.26	78.11±2.18
F2	89.42±1.55	75.52±2.10	48.92±2.49	81.67±2.41
F3	85.25±1.07	73.41±1.49	67.27±1.59	77.43±1.37
F4	81.64±1.34	71.53±2.16	54.04±0.86	74 0.28±1.07
F5	80.36±1.25	62.26±2.27	34.59±2.56	76.32±1.54
F6	83.34±1.62	65.52±1.22	60.24±1.51	72.23±1.02
F7	74.14±1.09	70.63±2.35	46.74±1.86	68.45±2.24
F8	82.86±1.19	72.26±1.28	40.46±1.38	70.71±1.47
F9	84.14±1.07	61.31±1.48	58.80±1.53	65.28±1.53

(All values are mean±SD; n=3)

lead to a decrease in drug release. This effect is attributed to the polymer matrix's swelling behavior. Drug release occurs only after complete polymer swelling, and the swelling time is directly proportional to the stabilizer concentration [24]. Consequently, increased PVA levels prolong the swelling process, resulting in a slower drug release rate.

Effect on particle size

Fig. 5 illustrates that increasing the concentration of PVA results in a decrease in particle size. However, further increasing the PVA emulsifier concentration above 0.5% ($p<0.05$) leads to increased viscosity, which results in larger emulsion droplets and, ultimately, larger microsponge sizes.

Data, optimization

The response equations obtained were analyzed using factorial models considering Eudragit S100 (A) and PVA (B) as independent variables. The influence of these variables on the dependent responses is depicted in surface plots and contour plots (Figs. 3-5). The optimized formulation (F2) exhibited a minimal particle size of 48.92±2.49 µm, a high EE of 89.42±1.55%, and a CDR of 81.67±2.41%, with a desirability value of 0.781.

Drug content

The determination of drug content in BHM reveals critical insights into the efficacy and reliability of the optimized formulation. The reported drug content of 90.64±1.21% indicates that the formulation has a high level of drug encapsulation with a low degree of variability, suggesting consistent quality across batches.

DSC

The thermal characteristics of BFH and BFH-loaded microsponges are illustrated in Fig. 6a and b. The thermograms revealed a sharp endothermic peak at 217.83°C, which corresponds to the MP of BFH, indicating pure and crystalline form.

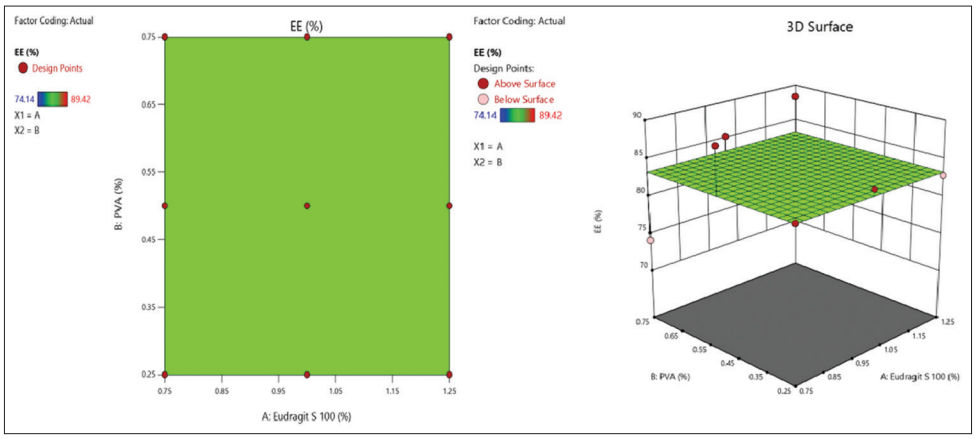

Fig. 3: Counter plot and surface plot of entrapment efficiency

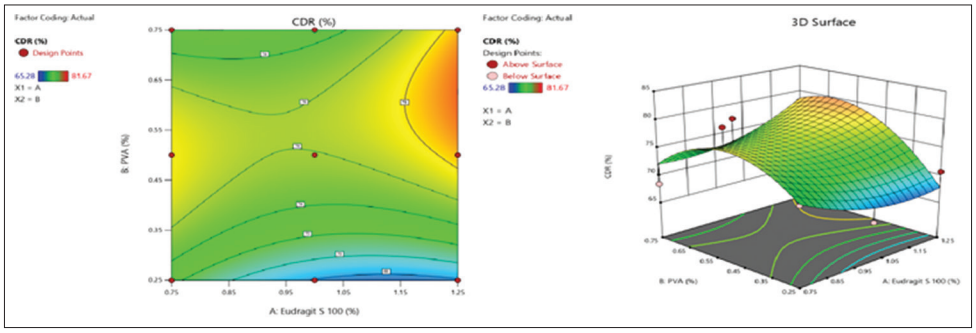

Fig. 4: Counter plot and surface plot of % cumulative drug release

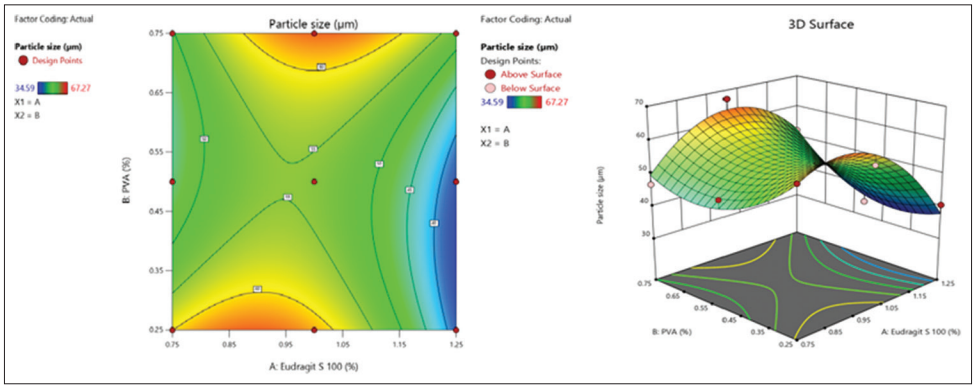

Fig. 5: Counter plot and surface plot of particle size

The optimized batch F2 showed no characteristic peak of BFH, suggesting that BFH is encapsulated within the microsponges. In addition, the disappearance of the melting endotherm of BFH in BFH-loaded microsponges supports the conclusion that BFH has transformed from a crystalline state to an amorphous form. The DSC spectra of pure BFH exhibit an endothermic peak at its melting point of 217.83°C with crystalline characteristics. However, in microsponges, the endothermic peak was shifted to 199.84°C. This shift suggests a possible interaction between the drug and the excipients, leading to changes in the drug's crystalline structure or its conversion to an amorphous state, thereby affecting its thermal properties.

XRD

XRD pattern of the pure drug BFH shows spectra 5.626°, 10.942°, 16.187°, 17.263°, 19.957°, 20.372°, 21.638°, 22.337°, 23.50°, 25.599°, 27.125° and 29.387°. Diffraction peaks between 5° and 50° and 2θ angles indicate high-intensity crystallinity. The XRD analysis demonstrates that pure BFH Fig. 7a is highly crystalline, and the microsponges formulation BFH loaded microsponges Fig. 7b modifies its physical properties by transitioning the drug to a less crystalline or amorphous state.

Through P-XRD analysis, it was found that BFH in microsponges was not in crystalline form. The decreased crystalline nature observed in the

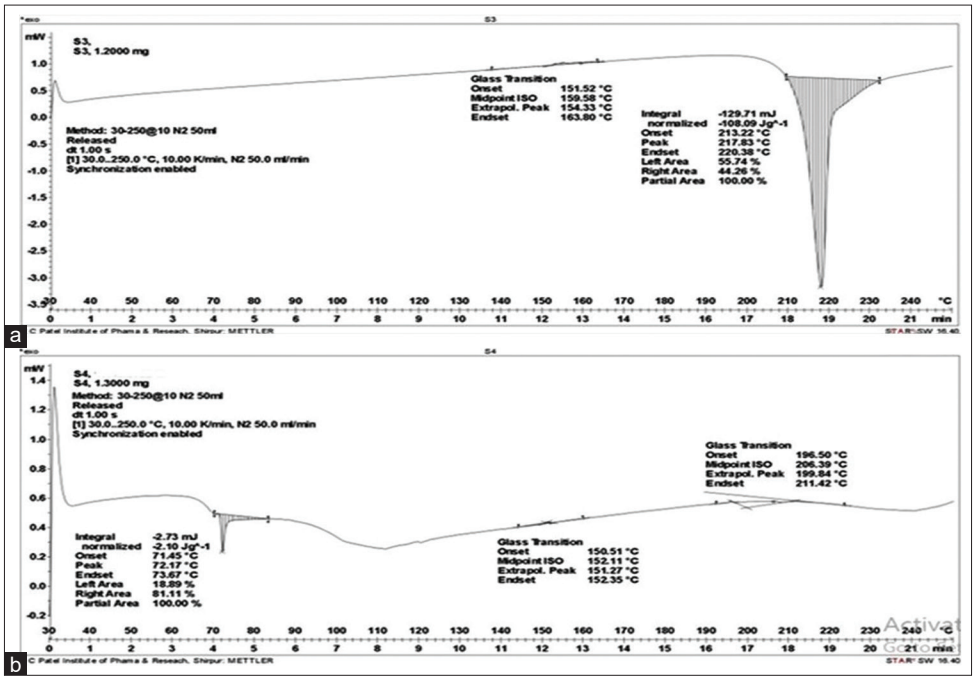

Fig. 6: Differential scanning calorimetry of (a) butenafine hydrochloride (BFH), (b) BFH-loaded microsponge

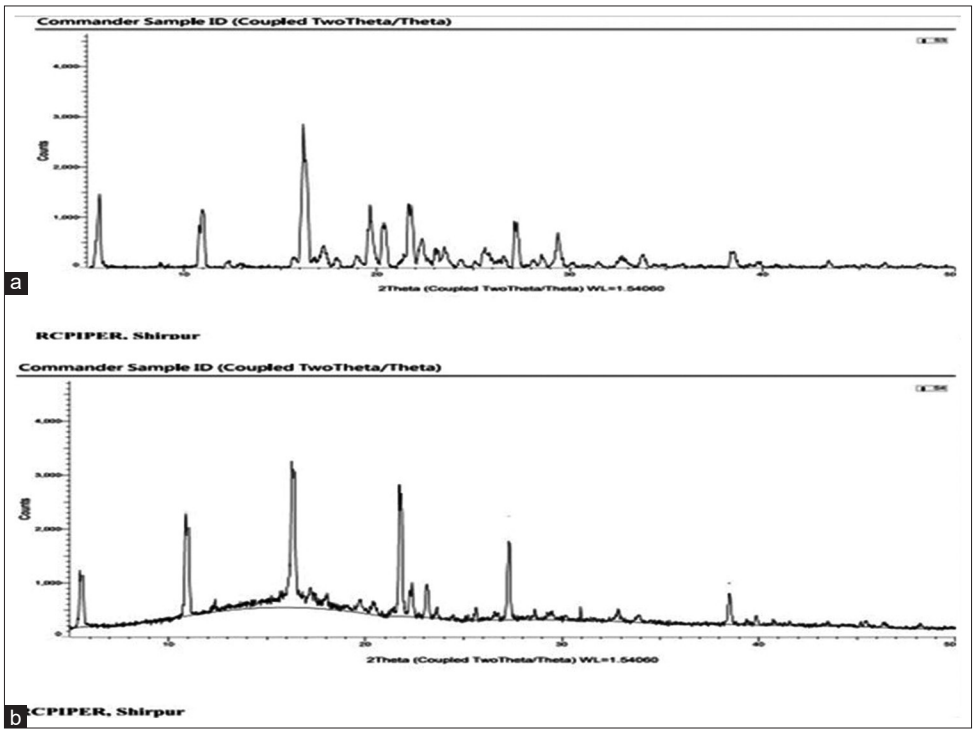

Fig. 7: X-ray diffraction of (a) Pure butenafine hydrochloride (BFH), (b) BFH-loaded microsponge

microsponges formulation indicates a transformation from crystalline form to amorphous form. This change is significant as it may enhance the solubility of the drug, which are critical factors for its therapeutic effectiveness. This transformation is beneficial for improving the drug's performance and suggests that the microsponges system is a promising approach for optimizing drug delivery.

SEM

The morphology and surface topography of the formulated microsponges were analyzed using SEM, as shown in Fig. 8. The SEM images confirmed that the microsponges were spherical, smooth, and porous. The surface topography analysis further revealed the presence of tiny pores within the microsponges, likely formed due to the diffusion of volatile solvents. The SEM micrographs of BFH-loaded microsponges demonstrated that the microsponges were predominantly spherical and exhibited a porous structure.

Evaluation results of gel

pH

The pH of the gels was found in between 6.7 and 6.8, as shown in Table 7. This range is acceptable for preventing the risk of skin irritation upon application.

Viscosity

Viscosity studies for the microsponge formulations were conducted to evaluate their rheological properties, and all observations are presented in Table 7. Among formulations tested, optimized BFH microsponges loaded gel (MG3) exhibited a viscosity that meets the desired specifications for effective application. This optimal viscosity is critical, as it ensures the gel is neither too thick nor too thin, allowing for easy spreadability while maintaining stability. The appropriate viscosity enhances the gel's ability to adhere to the skin, facilitating the controlled release of the active ingredient and improving patient compliance. Overall, the findings indicated that MG3 possesses the necessary viscosity characteristics to function effectively as a topical delivery system for BFH.

Spreadability

The spreadability values suggest that the gel can be easily applied with minimal shear force required [25]. Specifically, the spreadability of the MG3 was measured at 13.34 g·cm/s (Table 7), which indicates favorable spreadability characteristics. It indicated that the gel can be uniformly distributed over the skin, enhancing its effectiveness and improving patient comfort during application. The low shear requirement also suggests that the gel maintains its integrity while being spread, ensuring that the active ingredients are delivered effectively.

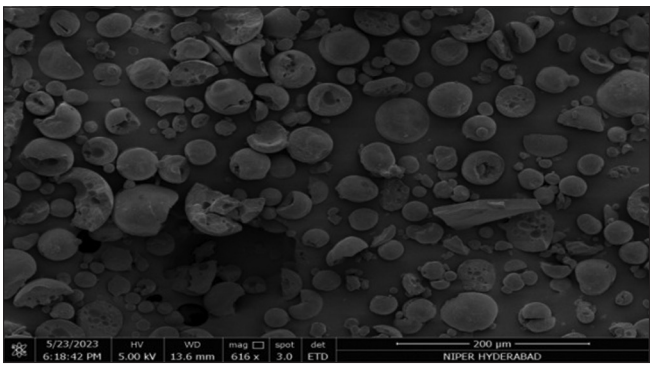

Fig. 8: Surface morphology of butenafine hydrochloride-loaded microsponges by scanning electron microscopy

Drug content

The measured drug content ranged from 90.42 to 92.56 mg per microsponges (Table 7), indicating a consistent and uniform distribution of the drug within the microsponges. These results suggest that the encapsulation process effectively incorporated the drug into the microsponges, ensuring that the active ingredient is well-distributed. This uniformity is crucial for achieving optimal therapeutic effects, as it allows for controlled release and enhanced stability of the drug, ultimately improving its efficacy in targeted applications [26]. The findings support the potential of microsponges as a delivery system for BFH, highlighting their role in achieving sustained release and better bioavailability.

Diffusion study

The diffusion study results of MG3 and BFH-marketed cream (Fintop) are illustrated in Fig. 9. The results indicate that the Fintop achieved a drug release of 96.08% within 10 h, whereas the MG3 released 82.46% of the drug over 12 h, with the potential to extend drug release up to 24 h.

Formulation MG3 demonstrates release kinetics, as shown in Table 8, following Higuchi's diffusion model. This suggests that the rate-limiting step in the drug release process is the diffusion of the dissolved drug through the Carbopol 934 gel network into the external medium. This mechanism accounts for the extended drug release. The results from fitting the mathematical model revealed that the Higuchi model is the best fit in both cases, confirming the diffusion mechanism of drug release.

Drug deposition study

The optimized MG3 drug release pattern was compared to the Fintop, revealing significant differences. At the end of the study, the amount of BFH-marketed gel Fintop drug remaining on the skin surface for MG3 was 0.52±0.13 mg, whereas for the Fintop, it was 1.08±0.04 mg. The lower amount of drug remaining on the skin surface of MG3 compared to Fintop suggests the MG3 drug release is more efficient and sustained. This can be explained by the presence of microsponge in the MG3 formulation, which serves as a drug reservoir. These microsponges can encapsulate the drug and release it in a controlled manner, offering a prolonged release over time; as a result, the drug is slowly delivered to the skin, ensuring that the therapeutic concentration is maintained over an extended period, as indicated by the sustained drug efficacy for up to 24 h. The drug retention in the skin from MG3 was twice as high as that from Fintop. This indicates that the MG3 effectively enhanced the drug's residence time and retention time in the skin. Microsponges are known for their ability to store active ingredients and slowly release them when needed, preventing rapid drug loss and maintaining a therapeutic level for a longer duration. This controlled release mechanism is crucial for achieving prolonged therapeutic effects as it allows the drug to continuously interact with the skin without the need for frequent reapplication. As a result, the therapeutic drug concentration was sustained for up to 24 h. Furthermore, the BFH microsponges-loaded gel enhanced the overall drug efficacy.

Table 7: Evaluation parameters of gel

Formulation	pH	Viscosity (CP)	Spreadability (g/cm^2)	Drug content (mg)	Extrudability (g/cm^2)	% drug release at 12 h
MG1	6.7±0.06	3280.21±112.54	12.20±1.08	90.42±1.08	0.87	70.14±2.36
MG2	6.6±0.08	1565.76±132.26	13.06±1.24	91.26±1.25	1.04	71.53±1.84
MG3	6.81±0.01	2568.54±118.42	13.34±1.02	92.56±1.36	0.98	82.46±1.72
Fintop	6.80±0.08	-	-	-		93.08±1.57

(All values are mean±SD; n=3)

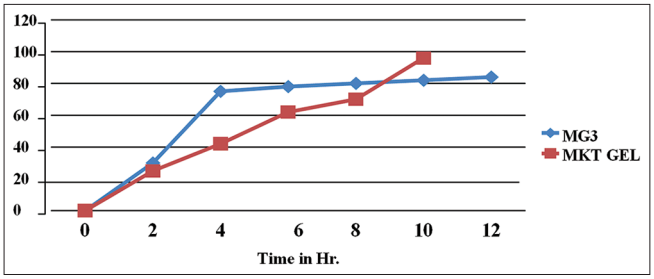

Fig. 9: The *in vitro* release profiles of MG3 and Fintop

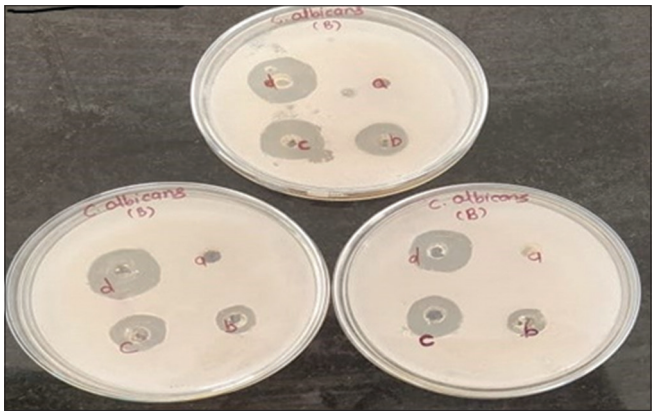

Fig. 10: Zone of inhibition

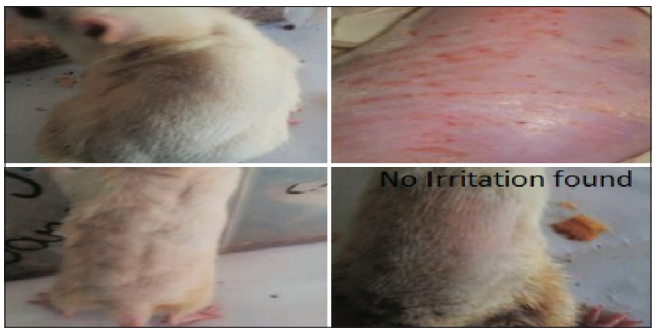

Fig. 11: Skin irritation study of MG3 microsponge gel

In vitro antifungal study

Fig. 10 illustrates that the results for the zone of inhibition of the drug, gel without the drug, MG3, and the Fintop formulation are presented in Table 9.

The placebo gel showed no zone of inhibition. In contrast, MG3 exhibits a zone of inhibition measuring 15.06 mm, whereas the Fintop shows a larger zone of 17.09 mm after 24 h. The smaller zone of inhibition observed with the microsponge gel may be due to its controlled antifungal activity, which causes a gradual release of BFH. This suggests that the prepared MG3 is more effective than the Fintop.

Stability study

Stability studies of the MG3 formulation, as shown in Table 10, revealed no significant changes in physical appearance or drug content, indicating the formulation's stability.

Skin irritation study

Fig. 11 demonstrates that the gel formulation did not cause skin irritation, making it suitable for patient use. The skin irritation test showed no signs of erythema, edema, or redness, confirming that MG3 was non-irritating [27]. These findings support the acceptability of the gel for topical application. In addition, the *in vivo* skin irritation study included images of the dorsal region of Wistar rats after application.

Table 8: Release kinetic of BFH microsponge-based gel

Series	Formulation code	Kinetic order		
		Zero order (r2)	First order (r2)	Higuchi (r2)
Series 1	MG1	0.699	0.23	0.923
Series 2	MG2	0.726	0.127	0.945
Series 3	MG3	0.738	0.32	0.948
Series 4	Fintop	0.691	0.911	0.922

Table 9: *In vitro* antifungal activity

Code	Candida albicans	ZOI at 12 h (mm)	ZOI at 24 h (mm)
a	Gel without drug	-	-
b	Drug	5 mm	5 mm
c	MG3	12.03±0.2 mm	15.06±0.1 mm
d	Mkt formulation (Fintop)	14.03±0.1 mm	17.09±0.2 mm

Table 10: Stability analysis of BFH microsponge-based gel

S. No.	Properties	Observation
1	pH	6.81
2	pH (After 6 month)	6.81
3	% Drug content at 30±2°C 60% RH	90.45±0.8
4	% Drug content at 40±2°C 75% RH	90.08±1.30
5	Drug release	82.46%
6	Drug release (after 6 months)	82.24%

CONCLUSION

The development of a BFH-loaded microsponge formulation demonstrated its potential as an effective carrier for topical drug delivery. The formulation parameters, including the drug-to-polymer ratio and PVA concentration, significantly influenced particle size, drug EE, and release kinetics. The porous structure of the microsponges facilitated controlled drug release, enhancing therapeutic efficacy. The optimized microsponges formulation, incorporated into a Carbopol-based gel, exhibited superior skin deposition and non-irritant properties compared to the conventional BFH gel. *In vivo* studies further confirmed its efficacy in treating candidiasis. These findings suggest that BFH-loaded microsponge gel holds promise as an advanced topical formulation and warrants further clinical evaluation for the treatment of candidiasis.

AUTHOR'S CONTRIBUTIONS

Sailesh Wadher designed the experimental framework and data analysis and finalized the manuscript. Ashwini Potulwar conducted experimental work, managed the data collection and statistical analysis, and was involved in the preparation of figures and tables. Sanjay Pekamwar Assisted in the experimental design and provided expertise in the application of microsponge technology. Shradha Tiwari Contributed to the literature review and provided critical insights into the theoretical aspects of the microsponge drug delivery system.

CONFLICTS OF INTERESTS

All authors have none to declare.

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Nil.

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