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Original Research Article

Formulation and Assessment of Tolnaftate Microsponges for Topical Medication Deliverance

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Abstract: ***Objective*:** This study aimed to develop and evaluate the sustained delivery of Tolnaftate using topical polymeric microsponges. ***Materials and Methods*:** Tolnaftate-loaded microsponges made of ethyl cellulose were prepared via quasi-emulsion solvent diffusion. The effects of the drug-to-polymer ratio on active drug content, particle size, and entrapment efficiency were examined. The optimized formulation was incorporated into a Carbopol gel and evaluated for drug content, pH, viscosity, and in vitro drug release. The study considered internal phase volume, stirring rate, and emulsifier concentration as variables and analyzed their impact on entrapment efficiency and particle size. ***Results*:** Increasing stirring speed reduced particle size and improved entrapment efficiency, while a higher volume of dichloromethane decreased particle size. Scanning electron microscopy revealed porous and spherical microsponges. The 1.5:1 drug-to-polymer ratio yielded the highest active drug content, optimal entrapment efficiency, and smallest particle size, making it the preferred ratio for further studies. ***Conclusions*:** The drug release from the microsponge gel was more sustained compared to both the marketed product and pure drug gel. An ex vivo drug deposition study using rat abdominal skin showed satisfactory drug deposition. These polymeric microsponges show potential as a topical drug delivery system for antifungal therapy.

Keywords: Quasi-Emulsion, Tolnaftate Microsponges, Ethyl Cellulose, Microspheres.

INTRODUCTION

Topical therapy is an attractive option for managing cutaneous infections. Its advantages include delivering the drug directly to the infection site and reducing the risk of systemic side effects. Conventional dermatological products often provide high concentrations of active ingredients but with short durations of action, leading to a cycle of short-term overmedication followed by long-term under medication. This can cause side effects such as rash, irritation, itching, redness, and allergic reactions. There is a need for a system that maximizes the duration an active ingredient remains on the skin surface or within the epidermis while minimizing its transdermal penetration [1, 2].

Microsponges are polymeric delivery systems made up of porous microspheres of an inert polymer that can entrap active ingredients and control their release rate. These sponge-like spherical particles have numerous interconnecting voids within a non-collapsible structure, providing a large porous surface area to hold the drug. The interconnected void spaces give microsponges a large surface area to hold the drug. This technology enables an even and sustained release rate, reducing irritation while maintaining efficacy. Microsponges can be prepared using two methods: a one-step process (liquid-liquid polymerization) and a two-step process (quasi-emulsion solvent diffusion). The most common and feasible method for preparing microsponges is the quasi-emulsion solvent diffusion method [3].

Tolnaftate is a synthetic thiocarbamate used as a topical antifungal agent. It is lipophilic, has poor aqueous solubility, a high molecular weight (307.41g/mol), and exhibits poor permeability, classifying it as a BCS class IV drug. Tolnaftate works by inhibiting the enzyme squalene epoxidase, leading to a deficiency of ergosterol in the fungal

membrane, which results in the accumulation of intracellular squalene and cell death. Adverse effects of Tolnaftate include burning, irritation, itching, and allergic reactions like rashes and swelling at the application site. These side effects can be mitigated through controlled release of Tolnaftate. Encapsulation of Tolnaftate reduces the cycle of short-term overmedication and thereby minimizes side effects [4-7].

The objective of this investigation was to develop and evaluate Tolnaftate microsponges using ethyl cellulose as the polymer, employing the quasi-emulsion solvent diffusion method. This approach aimed to create an effective delivery system that enhances the sustained release of Tolnaftate, optimizing its therapeutic efficacy while minimizing potential side effects.

MATERIALS AND METHODS

Tolnaftate, ethyl cellulose (20 cps), and Eudragit were provided as gift samples, while all other ingredients used in this study were of analytical grade and sourced from ResearchLab Fine Chemicals Ltd., India.

Preparation of Microsponge

Tolnaftate microsponges were fabricated via the quasi-emulsion solvent diffusion method. Here, an organic internal phase containing dichloromethane (DCM), Tolnaftate, and ethyl cellulose was slowly introduced into distilled water (external phase) containing polyvinyl alcohol (PVA) as an emulsifier. The blend underwent stirring with a digital mechanical stirrer at speeds ranging from 1000 to 1800 rpm for 60 minutes to eliminate DCM. Subsequently, the formed microsponges were filtered through Whatman filter paper, dried at 40°C, and weighed.

Initial trials were conducted to assess various polymers, including Eudragit RS 100, Eudragit RL 100, and ethyl cellulose [8]. Microsponges formulated with Eudragit were observed to be non-spherical and rigid, whereas those with ethyl cellulose exhibited optimal characteristics. Ethyl cellulose yielded spherical and rigid microsponges of the desired micrometer size, prompting its selection for further investigation. Subsequently, Tolnaftate microsponge formulations were developed using different weight ratios of drug to ethyl cellulose (2:1, 1.5:1, 1:1, 1:1.5, and 1:2).

Refining Formulation Parameters and the Variables

The study assessed the impact of varying drug-to-ethyl cellulose ratios on actual drug content (ADC), particle size, and entrapment efficiency of microsponges. Additionally, a Box-Behnken design was employed to optimize internal solvent volume (5, 10, and 15 ml), emulsifier concentration (400, 500, and 600 mg), and stirring rate (1200, 1500, and 1800 rpm) as independent variables affecting particle size, ADC. And entrapment efficiency.

Assessment of Tolnaftate Microsponges [9]

The weighed sample of Tolnaftate microsponges was dissolved in ethanol under ultrasonication for up to 1 hour. The solution was filtered, and the absorbance was measured at 283.5 nm using a UV spectrophotometer after appropriate dilution with water. The drug content and entrapment efficiency [10-12], were calculated using the following equations:

$$ADC\ (\%) = \frac{M\ acual}{M\ microsponge}\ X\ 100\%$$

$$Entrapment\ Effeciency\ (\%) = \frac{M\ actual}{M\ theoraticle}\ 100\ \%$$

$$Drug\ loading = \frac{Mass\ of\ Drug\ in\ Microsponge}{Mass\ of\ Microsponges\ Recovered}\ X\ 100\ \ldots\ldots [13]$$

In this context, M_{actual} refers to the actual Tolnaftate content in the weighed quantity of microsponges, $M_{microsponge}$ is the weighed quantity of powdered microsponges, and $M_{theoretical}$ is the theoretical amount of Tolnaftate in microsponges, calculated based on the quantity added during the process.

The particle size was determined using an optical microscope with PixelPro software. The average particle size was expressed in micrometers (µm). Microsponges were mounted on a slide and placed on the microscope stage. Each determination was conducted on a minimum of 100 particles, and their mean size was reported [14, 15]. The particle surface morphology was analyzed using scanning electron microscopy (SEM) [9]. Microsponges were mounted on double-sided adhesive tape, coated with a thin gold-palladium layer using a sputter coater, and examined with a scanning electron microscope (Jeol JSM-6360A). Powder X-ray diffraction patterns for the pure drug, ethyl cellulose, and microsponges were recorded using an X-ray diffractometer (PW 1729 Philips, Netherlands) [9].

Carbopolgel Formulation

Carbopol 940 (0.25%) was soaked in distilled water for 2 hours, then agitated with a digital mechanical stirrer to create a smooth dispersion. The viscous solution was then neutralized to pH 7 with triethanolamine while stirring slowly. Prepared Tolnaftate microsponges (equivalent to 1% w/w Tolnaftate) were added to the Carbopol gel with continuous stirring to form the Tolnaftate microsponge gel (TNFMG) [9].

TNFMG Evaluation [3-10]

The pH of TNFMG was evaluated using a digital pH meter (Equip-Tronics model EQ-614). Spread ability was determined using a wooden block and glass slide apparatus by placing an excess amount of the sample between two glass slides [9-18]. A one-kilogram weight was placed on the top slide for 5 minutes to achieve uniform thickness. After adding weight to the pan, the distance traveled on the glass slide and the time required to separate the slides were measured. Spread ability was calculated using the formula:

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

Where S is spreadability, W is the weight added to the pan, L is the length traveled on the glass slide, and T is the time taken for the slides to completely separate.

The viscosity of the prepared gel was measured using a Brookfield viscometer (DV-II+ Viscometer) at room temperature. The gel sample was placed in the sample holder, and viscosity was measured by inserting the spindle into the sample and rotating it at a speed.

In Vitro Release Experiments

In vitro release studies were performed using an artificial cellophane membrane (molecular weight 12,000) and a vertical Franz diffusion cell with a 2.5 cm^2 area and a 15 ml receptor compartment [3-12]. The artificial membrane was carefully positioned between the two halves of the diffusion cell. The receptor compartment, filled with phosphate buffer (pH 5.8), was maintained at 37±0.5°C and continuously stirred with a magnetic stirrer. A predetermined amount of TNFMG containing 10 mg of Tolnaftate was placed on the donor side above the cellophane membrane. One milliliter of the sample was withdrawn from the receptor compartment at specific time intervals over 8 hours and replaced with an equal volume of fresh receptor fluid. The aliquots were appropriately diluted with the receptor medium and analyzed by UV. The release of TNFMG was measured using a spectrophotometer and the results were compared to the release profile of a marketed Tolnaftate cream (TNFMC, 1% w/w).

Ex Vivo Study on Drug Deposition

The ex vivo diffusion study was conducted on excised Wistar rat skin [3]. The abdominal skin of the rat was shaved and placed carefully 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 of the diffusion cell was filled with phosphate buffer pH 5.8 and stirred continuously. A sample was applied to the donor compartment, and after 8 hours, the diffusion cell was dismantled. The skin was removed gently and washed with distilled water to remove any gel present on the skin surface. The skin was then chopped into small pieces, homogenized with 10 ml of methanol, and diluted with phosphate buffer. The drug content in the extract was appropriately diluted, and absorbance was measured using UV spectroscopy. The ex vivo diffusion study was performed in accordance with the protocol approved by the Institutional Animal Ethics.

Antifungal Activity

The optimized formulation was assessed for its antifungal properties using the cup plate method against Aspergillus niger [5-20]. Fungal culture was inoculated into Sabouraud dextrose agar medium and poured uniformly into sterile petri dishes, allowing the agar to solidify. Under aseptic conditions, the optimized formulation gel, marketed gel, pure drug, and placebo were inoculated onto the agar using the cup plate method. The plates were then incubated at 25°C for 24 hours, after which the inhibition zone was measured.

Stability

A batch of optimized Tolnaftate microsponge gels was monitored for 3 months at 40±2°C and 75±5% relative humidity following International Conference on Harmonisation guidelines. Samples were taken at monthly intervals (1, 2, and 3 months) and analyzed for physical appearance, pH, viscosity, and drug content. Stability studies are crucial for evaluating the formulation's long-term stability [3].

Table 1: Drug polymer ratio selection

Formula Code	Drug polymer (mg)	Erap Effec. (%)	Mean particle size (µm)	Active drug content (%)
TNFM1	2:1	69.9669± 0.660	25.809± 3.449	52.389±1.489
TNFM2	1.5:1	81.839± 1.649	21.869±2.729	69.519±5.479
TNFM3	1:1	78.799± 2.049	36.069±3.799	59.949±2.419
TNFM4	1:1.5	72.50 ± 3.000	35.889±4.469	65.249±1.969
TBFM2 shows smaller particle size and highest entrapment efficiency and actual drug content				

Table 2: Box-Behnken design for optimization

No.	Factor A PVA (mg)	Factor B DCM (mL)	Factor C (RPM)	Response 1 Erap Effec.(%)	Response 2 particle size (µm)	Response 3 Active drug content (%)
1.	500	10	1500	87.169±**1.945**	23.869±**3.229**	61.390±**1.000**
2.	600	10	1800	88.529±**2.479**	22.299±**2.479**	66.000±**1.939**
3.	600	5	1500	83.019±**2.989**	23.799±**2.649**	60.959±**0799**
4.	400	5	1500	85.179±**2.839**	15.540±**0849**	56.919±**2.859**
5.	500	10	1500	87.169±**3.849**	23.869±**5.089**	61.389±**2.489**
6.	500	5	1800	85.869±**3.319**	20.779±**3.850**	62.699±**2.239**
7.	500	5	1200	72.494±**4.989**	27.690±**7.360**	49.370±**2.910**
8.	400	15	1500	87.699±**4.819**	11.840±**2.189**	66.839±**5.580**
9.	600	10	1200	72.869±**4.089**	38.079±**4.010**	49.410±**3.080**
10.	500	15	1200	78.869±**4.089**	24.129±**6.169**	54.270±**4.490**
11.	500	10	1500	87.169±**3.679**	23.869±**2.140**	4.389±**1.100**
12.	500	15	1800	82.090±**6.050**	16.129±**4.639**	71.250±**3.919**
13.	500	10	1500	87.169±**2.010**	23.876±**2.829**	61.390±**4.750**
14.	600	15	1500	83.589±**3.379**	20.429±**4.750**	61.400±**4.320**
15.	400	10	1800	87.720±**0.0580**	22.910±**4.319**	68.260±**3.880**
16.	500	10	1500	87.169±**8.049**	23.870±**2.839**	61.390±**1.050**
17.	400	10	1200	85.889±**2.119**	22.140±**2.459**	52.069±**2.020**

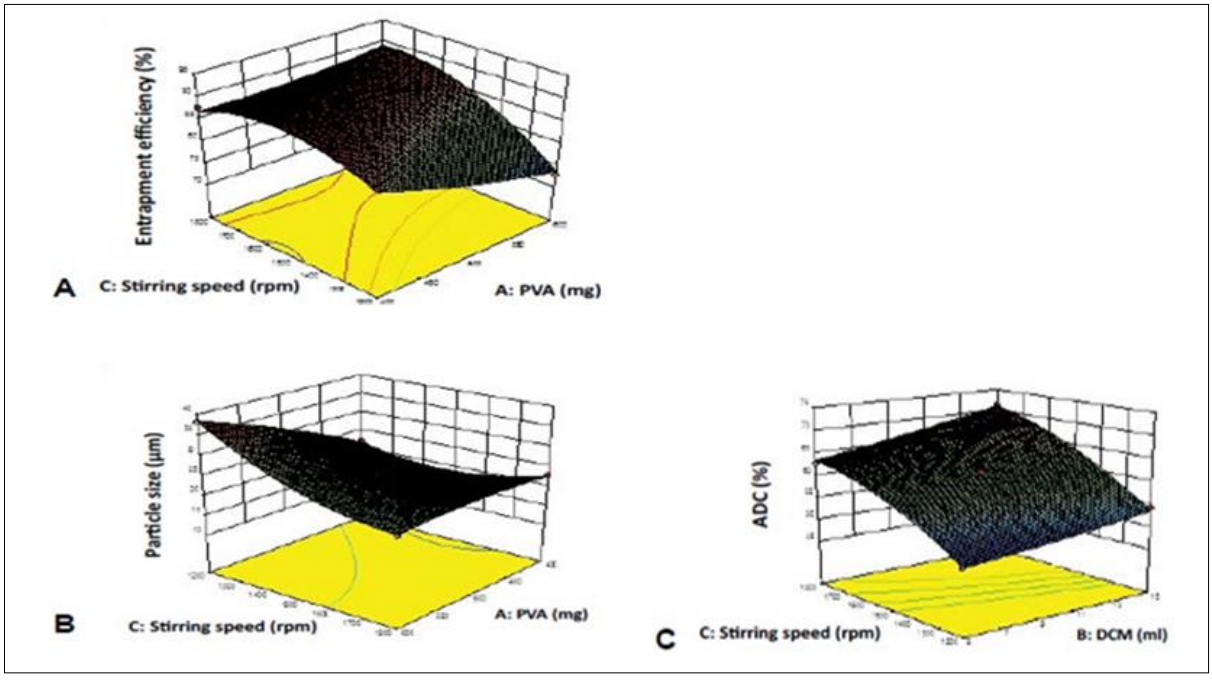

Figure 1: 3D response plots of entrapment efficiency, particle size, and active drug content. The plots illustrate the effects of stirring speed and PVA on (A) entrapment efficiency, (B) particle size, and the effects of stirring speed and DCM on (C) active drug content

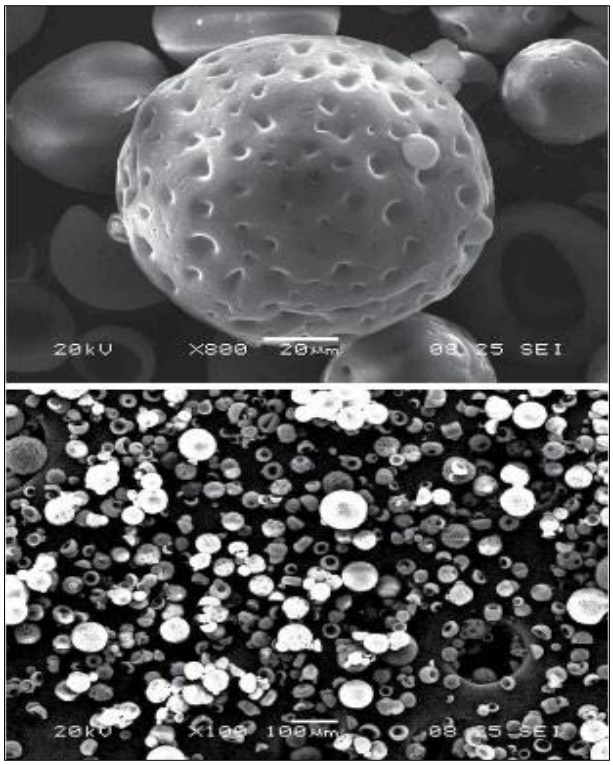

Figure 2: SEM micrographs of microsponges

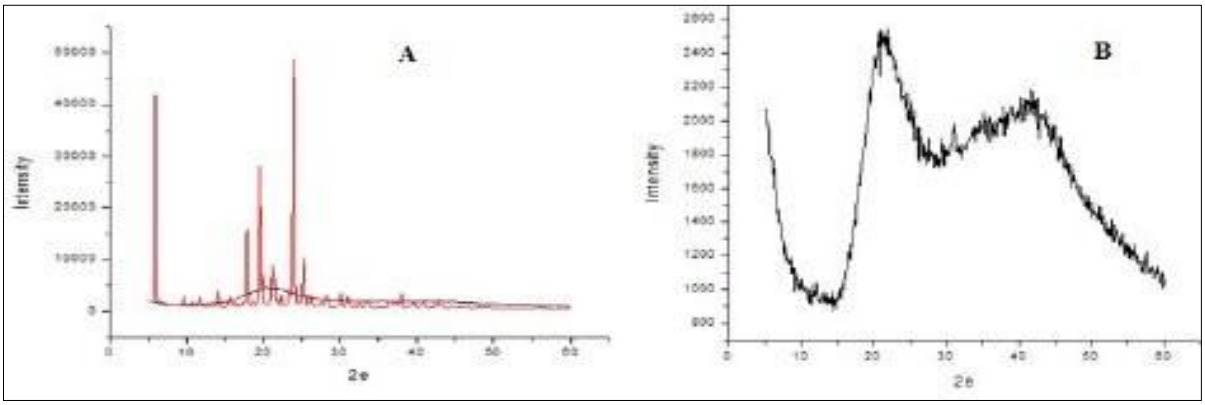

Figure 3: PXRD patterns of (A) Tolnaftate and Ethyl cellulose, and (B) the microsponge formulation

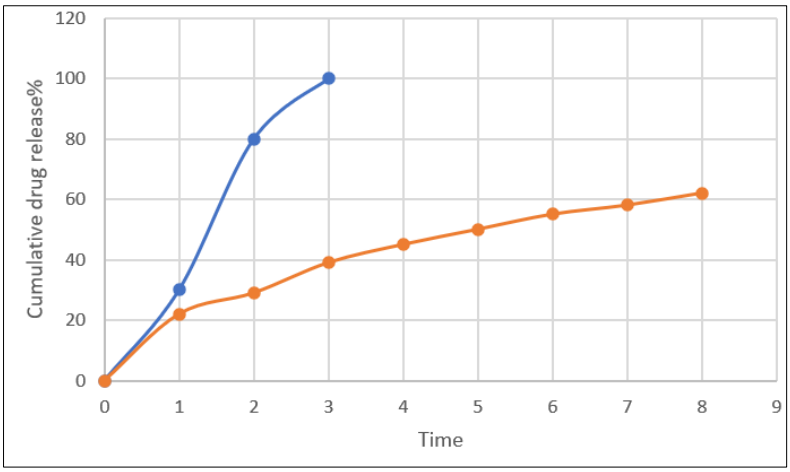

Fig. 4: In vitro drug release profiles of TNFMG and TNFMC (Tolnaftate microsponge gel and Tolnaftate marketed cream, respectively)

RESULTS AND DISCUSSION

Tolnaftate microsponges were prepared using different polymer ratios of 2:1, 1.5:1, 1:1, 1:1.5, and 1:2. These formulations were evaluated for active drug content (ADC), entrapment efficiency, and particle size, as detailed in Table 1. TNFMG2 exhibited the highest ADC, entrapment efficiency, and smaller particle size, prompting the selection of a 1.5:1 drug-to-polymer ratio for optimization studies. The impact of independent factors (PVA, DCM, and stirring speed) on entrapment efficiency, particle size, and ADC is summarized in Table 2. Equations derived for entrapment efficiency, particle size, and ADC are as follows: Equation 1, entrapment efficiency = +87.17 – 2.31×A + 0.70×B + 4.27×C, indicates an inverse relationship between A (PVA) and entrapment efficiency, and a direct relationship between B (DCM), C (stirring speed), and entrapment efficiency. Equation 2, particle size = +23.87 + 4.09×A – 1.85×B – 3.74×C, shows a direct relationship between A (PVA) and particle size, and an inverse relationship between B (DCM), C (stirring speed), and particle size. Equation 3, ADC = +61.39 – 0.79×A + 2.98×B + 7.89×C, demonstrates an inverse relationship between A (PVA) and ADC, and a direct relationship between B (DCM), C (stirring speed), and ADC.

Formulation No. 8 demonstrated satisfactory entrapment efficiency, active drug content, and particle size. This optimized batch underwent further characterization studies and was incorporated into a Carbopol gel base. The entrapment efficiency was found to have an inverse relationship, while particle size was directly proportional to the quantity of the emulsifier (PVA). The non-ionic nature of the emulsifier (PVA) allows its molecules to aggregate away from the oil-water interface at higher concentrations. This phenomenon can lead to the dissolution of some portions of the drug, resulting in reduced entrapment efficiency, as shown in Figure 1A [10-14]. The results indicated that higher concentrations of PVA resulted in larger microparticles, as illustrated in Figure 1B. The increase in the mean particle size of microsponges with increasing emulsifier concentration can be attributed to an increase in apparent viscosity. This increased viscosity causes larger emulsion droplets and ultimately leads to larger microsponge size.

The particle size was observed to decrease with an increase in the quantity of internal phase (DCM), indicating an inverse relationship. This negative correlation suggests that as the volume of the internal phase increases, the particle size of microsponges decreases. The particle sizes of microsponges can be directly linked to the apparent viscosity of the internal phase. When a lower viscosity internal phase was introduced into the continuous phase, the resulting emulsion globules could more easily separate into smaller droplets, thereby decreasing the mean particle size [3-21], (see fig. 1C). Additionally, the particle size was found to be inversely proportional to the stirring rate. Higher stirring rates imposed vigorous and uniform mechanical shear, which facilitated rapid division of formed droplets. This reduced the likelihood of droplet coalescence into larger entities, resulting in a decrease in particle size with increasing stirring rate [14], (see fig. 2). The SEM images of Tolnaftate-loaded microsponges shown in Fig. 2 revealed that the microsponges were uniform, spherical, and porous. The pores were created by the diffusion of the solvent from the surface of the microparticles. The X-ray powder diffractogram of the pure drug and ethyl cellulose is shown in Fig. 3. The pure drug displayed a sharp endothermic peak, indicating a crystalline state, while ethyl cellulose did not show sharp peaks, indicating its amorphous nature. The decreased intensity of the peaks in the microsponge confirmed that Tolnaftate was entrapped in the ethyl cellulose polymer [9]. The microsponge-loaded gel was white, smooth, and homogeneous. The formulation's pH, viscosity, and spreadability were found to be 7.1, 2976±1.52 cps, and 21.3±0.03 gcm/s, respectively.

An in vitro drug release study was conducted using an artificial cellophane membrane and phosphate buffer at pH 5.8. The release profiles of TNFMC and TNFMG were evaluated. TNFMC released the drug within 4 hours, whereas TNFMG showed sustained release for up to 8 hours, with 59.70% of the drug released, as illustrated in Fig. 4. The mechanism of drug release was analyzed using various kinetic models (zero-order, first-order, matrix, Peppas, and Hix-Crowell). The findings indicated that the release kinetics from the microsponge gel followed Peppas kinetics (r^2: 0.9963). At the end of 8 hours, the amount of drug deposited in rat skin was 0.841 mg/cm² for TNFMG and 0.357 mg/cm² for TNFMC, as shown in Fig. 5. The higher amount of Tolnaftate deposited from TNFMG compared to TNFMC indicated that microsponges enhanced drug residence in the skin [3-15]. The zones of inhibition measured 19.34 mm for the microsponge gel, 23.66 mm for the marketed gel, and 25.12 mm for the pure drug. The microsponge gel exhibited a relatively smaller zone of inhibition, likely due to the controlled release of Tolnaftate, leading to sustained antifungal activity. The formulation effectively inhibited the growth of A. niger, suggesting its potential use in treating fungal infections.

Tolnaftate-loaded microsponges of ethyl cellulose were prepared using the quasi-emulsion solvent diffusion method. The drug-to-polymer ratios, internal solvent volume, emulsifier concentration, and stirring speed significantly influenced the physical and chemical properties, including particle size, entrapment efficiency, and active drug content of the microsponges. The internal phase volume and stirring rate had a negative impact on the particle size of the microsponges, while the concentration of PVA had a direct effect on particle size. The X-ray powder diffractogram confirmed the entrapment of Tolnaftate in ethyl cellulose. SEM analysis revealed that the microsponges were spherical, porous, and rigid. The optimized microsponge formulation was dispersed into a Carbopol gel, which demonstrated sustained release of Tolnaftate and satisfactory drug deposition within animal skin.

REFERENCES

1. Pradhan, S. K. (2011). Microsponges as the versatile tool for drug delivery system. *Int J Res Pharm Chem*, *1*(2), 243-58.
2. Aloorkar, N. H., Kulkarni, A. S., Ingale, D. J., & Patil, R. A. (2012). Microsponges as innovative drug delivery systems. *Int J Pharm Sci Nanotechnol*, *5*(1), 1597-1606.
3. Nokhodchi, A., Jelvehgari, M., Siahi, M. R., & Mozafari, M. R. (2007). Factors affecting the morphology of benzoyl peroxide microsponges. *Micron*, *38*(8), 834-840.
4. Özcan, İ., Abacı, Ö., Uztan, A. H., Aksu, B., Boyacıoğlu, H., Güneri, T., & Özer, Ö. (2009). Enhanced topical delivery of terbinafine hydrochloride with chitosan hydrogels. *Aaps Pharmscitech*, *10*, 1024-1031.
5. Charyulu, N. R., Satveek, M., Harish, N. M., & Patil, A. B. (2013). Comparative study of Tolnaftate ethosomal formulations: A Novel Approach. *Nitte Univ J Health Sci*, *3*, 23-29.
6. Chakraborti, P. (2013). A Textbook of Microbiology. London: New Central Book Agency (P) Ltd. 616-619.
7. Tortora, G. J., Funke, B. R., & Case, C. L. (2004). Microbiology: An Introduction. 9th ed. San Francisco: *Pearson Benjamin Cummings*, 629-632.
8. Rajeshree, M., Harsha, P., & Vishnu, P. (2014). Photostability enhancement of miconazole nitrate by microsponge formulation. *Int J Curr Trends Pharm Res*, *2*, 437-458.
9. Bothiraja, C., Gholap, A. D., Shaikh, K. S., & Pawar, A. P. (2014). Investigation of ethyl cellulose microsponge gel for topical delivery of eberconazole nitrate for fungal therapy. *Therapeutic delivery*, *5*(7), 781-794.
10. Jain, V., & Singh, R. (2010). Dicyclomine-loaded Eudragit®-based microsponge with potential for colonic delivery: preparation and characterization. *Tropical Journal of Pharmaceutical Research*, *9*(1).
11. Çomoğlu, T., Gönül, N., & Baykara, T. (2003). Preparation and in vitro evaluation of modified release ketoprofen microsponges. *Il farmaco*, *58*(2), 101-106.
12. Swetha, A., Rao, M. G., Ramana, K. V., Basha, B. N., & Reddy, V. K. (2011). Formulation and in vitro evaluation of etodolac entrapped in microsponge based drug delivery system. *Int J Pharm*, *1*(2), 73-80.
13. Dora, C. P., Singh, S. K., Kumar, S., Datusalia, A. K., & Deep, A. (2010). Development and characterization of nanoparticles of glibenclamide by solvent displacement method. *Acta pol pharm*, *67*(3), 283-290.
14. Jain, V., & Singh, R. (2010). Development and characterization of eudragit RS 100 loaded microsponges and its colonic delivery using natural polysaccharides. *Acta Pol Pharm*, *67*(4), 407-15.
15. Orlu, M., Cevher, E., & Araman, A. (2006). Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. *International journal of pharmaceutics*, *318*(1-2), 103-117.
16. NN, V., & Saudagar, R. B. (2014). Formulation, development and evaluation of film-forming gel for prolonged dermal delivery of terbinafine hydrochloride.
17. Abdelmalak, N. S., & el-Menshawea, S. F. (2011). New topical fluconazole microsponge loaded hydrogel: preparation and characterization. *Int J Pharm Pharm Sci*, *4*, 460-468.
18. D'souza, J. I., & More, H. N. (2008). Topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system. *Research Journal of Pharmacy and Technology*, *1*(4), 502-506.
19. Delahaye, C. H., Rainford, L., Nicholson, A., Mitchell, S., Lindo, J., & Ahmad, M. (2009). Antibacterial and antifungal analysis of crude extracts from the leaves of Callistemon viminalis. *Journal of Medical and biological sciences*, *3*(1), 1-7.
20. Kim, D. M., Suh, M. K., Ha, G. Y., & Sohng, S. H. (2012). Fingernail onychomycosis due to Aspergillus niger. *Annals of dermatology*, *24*(4), 459-463.
21. Maiti, S., Kaity, S., Ray, S., & Sa, B. (2011). Development and evaluation of xanthan gum-facilitated ethyl cellulose microsponges for controlled percutaneous delivery of diclofenac sodium. *Acta Pharmaceutica*, *61*(3), 257-270.