Formulation and Evaluation of Topical Microsponge Based Gel of Clotrimazole

Jitendra Shinde [1*], Rakesh Patel [2], Shweta Shriwas [3]

[1] Ph.D. Scholar, School of Pharmacy, Dr. A. P. J. Abdul Kalam University, Indore, Madhya Pradesh, India. jitushinde29@gmail.com

[2] Professor, School of Pharmacy, Dr. A. P. J. Abdul Kalam University, Indore, Madhya Pradesh, India.

[3] Associate Professor, School of Pharmacy, Dr. A. P. J. Abdul Kalam University, Madhya Pradesh, India.

Abstract: The study's overarching goal is to develop a novel medication delivery method based on microsponge gel containing clotrimazole. Clotrimazole is poorly absorbed from the gastrointestinal tract (GIT), has a short half-life of only 2 h, & is metabolized into inert molecules by the liver. Therefore, clotrimazole's drug delivery method must be modified for topical application. Microsponge delivery is a novel approach to sustained drug release. Microsponges were made with a polymer solution of Eudragit RS 100 in dichloromethane (DCM) and ethanol (1:1) using a quasi-emulsion solvent diffusion technique. A number of metrics, including production yield, entrapment efficiency, particle size measurement, and in vitro drug release studies, were used to each microsponge formulation. For topical administration, the optimized microsponge formulation F6 was transformed into a gel formulation. Prepared gel was compared to a commercially available formulation based on physical factors such as pH, viscosity, spreadability, drug content, and an in vitro diffusion investigation. Most of the formulations were discrete and spherical in shape, indicating a satisfactory production yield, suggesting quasi-emulsion solvent diffusion method is a promising methodology for the fabrication of microsponge. Clotrimazole was released steadily over the course of 12 hours from the microsponge gel formulation MGI (F6). Therefore, the medicine in the form of a microsponge can reduce the risk of adverse effects and increase patient compliance by avoiding skin contact.

Keywords: Clotrimazole, Microsponge, Antifungal drug, Microsponge gel, Topical delivery.

1. INTRODUCTION

Candida is the most common fungus that causes illness all over the world. Candida is the fourth most common pathogen to enter the circulation during hospitalisation (also known as a "nosocomial" infection or a "hospital acquired infection") in the United States. Candida is a genus that includes 17 distinct species. Whether a particular medicine is used to treat our infection depends on the severity of our symptoms or the species of Candida that is most likely responsible [1]. Infected keratinized tissues include the epidermis, hair, and nails. This condition is known as dermatophytosis. It is a common misconception that these are 'tinea infections' [2–3]. Most contemporary, wide-spectrum antifungals work by interfering with various stages of membrane production in fungal cells [4]. Caused by dermatophytes, tinea infections affect the skin's outermost layer and are a major public health concern [5, 6]. Topical antifungals are effective for treating mild to moderate tinea infections, but oral medications are often reserved for treating severe or resistant infections [6, 7].

The precise, effective, and targeted drug delivery systems have been a dream for a long time, but the complexity of developing new systems has mainly thwarted this hope [8-9]. The development of microsponges represents a major advancement in the battle against these issues. For medications with low solubility [8, 9], these microscopic sponges can be adhered to the skin and then slowly release the drug over time. The creation of cutting-edge drug delivery systems based on microsponges, allowing for more precise regulation of drug release. When medicines are

incorporated into a carrier system, their therapeutic index and duration of activity can be modified [10]. Cardinal Health, Inc. has just acquired a licence to use this technology in topical products [11]. They are tiny spherical particles with a large porous surface [12] and a non-collapsible structure that resembles a sponge. Drug stability, toxicity, and pharmacokinetics may all improve with their addition [13, 14]. When applied, microsponges release their active contents, creating a thin, concentrated layer of the substance that the body quickly absorbs. The disadvantage of applying the ointment with a microsponge delivery device was addressed in [15]. Active substances with particular properties can also be trapped by microsponges [16]. Microsponge polymers may have already been loaded with active chemicals during production [17, 18]. Since many cosmetic components and most pharmacological ones would degrade at the temperatures of polymerization, post-loading is the recommended approach. When in contact with skin, the polymer slowly releases the microsponge particles it has been loaded with via diffusion, much like a typical sponge. Treatment of vaginal yeast infections, dermatophytes, Candida infections, oral thrush, ringworm, athlete's foot, and jock itch, as well as a wide variety of other fungal infections in people and animals, is common use for the antifungal drug clotrimazole. An efficient antifungal agent in topical infections, it is generally recognised as safe [20–23] and is on the World Health Organization's (WHO) list of essential medications. Improving medication residence time and decreasing absorption into systemic circulation by controlling the release of a drug from the topical formulation to the epidermis/topical layer of the skin would lessen side effects. Clotrimazole is the medicine of choice for treating fungal infections due to its broad spectrum antifungal activity. Clotrimazole is poorly absorbed from the gastrointestinal tract (GIT), has a short half-life of only 2 hours, and is metabolised into inert molecules by the liver. Therefore, clotrimazole's drug delivery method must be modified for topical application. Cream, lotion, troche, lozenges, and solution are all commercially available formulations, but none of them offer continuous release. Due to their low efficiency, many traditional delivery systems necessitate a large concentration of active ingredient to be included for successful therapy [24–27]. So, clotrimazole is employed in microsponge manufacture to improve the therapeutic system by delivering the medicine in a controlled and sustained manner. The current study is predicated on the concept that clotrimazole integration into microsponges will enhance the quantity of drug residence on the skin and decrease the toxicity that occurs due to burst release, hence increasing the therapeutic efficacy of the drug. Encapsulated drugs can be released slowly and steadily from a microsponge. When compared to traditional dose forms, the microsponge system permits a significant concentration of medication in the skin at a low permeability flux [28]. With the use of the quasi-emulsion solvent diffusion method, clotrimazole microsponges were successfully generated in the present work employing polymers such as Eudragit RS-100 at varying quantities.

2. MATERIALS AND METHODS

For this project, we worked with Encube Pharmaceutical Pvt Ltd. in Verna, Goa to get clotrimazole. The Mumbai branch of Evonik Industries supplied the Eudragit RS-100. Loba Chemie Pvt. Ltd., Mumbai supplied the Carbapol-940, while Cosmo chem supplied the polyvinyl alcohol. The analytical quality of all other reagents used was ensured.

Preparation of Microsponges

The quasi-emulsion solvent diffusion method was used to make the microsponges. The quasi emulsion solvent diffusion technique was used to create a clotrimazole microsponge. Since it is simple, repeatable, and quick, with the added benefit of eliminating solvent toxicity, the quasi emulsion solvent diffusion approach was investigated for the manufacture of Clotrimazole microsponges. The internal phase is made by dissolving Eudragit RS 100 in a 1:1 mixture of dichloromethane (DCM) and ethanol. The medication can then be added to the solution and ultra-sonicated for 20 minutes to dissolve. About 1% triethycitrate is added to formulation to increase its malleability. Polyvinyl alcohol served as an emulsifying agent as the internal phase containing the medication (100mg) was added progressively to the 200 ml distilled exterior phase. To get rid of the DCM and Ethanol, the liquid was agitated for 8 hours at 500 rpm using a magnetic stirrer. The microsponges that resulted from the process were weighed after being dried at 40 degrees Celsius for 12 hours, washed with distilled water, and filtered through Whatman filter paper no. 41 (Whatman, UK).

Table 1: Composition of formulation batches of clotrimazole microsponge

Formulation code	Clotrimazole: Eudragit RS100 (mg)	Dichloromethane (ml)	Dibutyl Phthalate (% w/v)	Polyvinyl alcohol (mg)	Stirring Speed (RPM)	Water (ml)
F1	1:1	5	1	50	500	200
F2	1:1	10	1	50	500	200
F3	1:1	15	1	50	500	200
F4	1:2	5	1	50	500	200
F5	1:2	10	1	50	500	200
F6	1:2	15	1	50	500	200
F7	1:3	5	1	50	500	200
F8	1:3	10	1	50	500	200
F9	1:3	15	1	50	500	200

Evaluation of clotrimazole microsponges

Determination of Production Yield

The percentage of production yield (wt./wt.) was calculated from the weight of dried microsponges (W1) recovered from batches and the sum of initial dry weight of starting materials (W2) as the following equation:

% production yield = Practical mass of Microsponge/Theorotical mass (polymer + Drug)*100

Production yields were determined by comparing the total amount of Clotrimazole and polymer used in the formulation to the weight of the finished product after drying.

Actual drug content

The following method was used to analyse the actual drug loading: Clotrimazole was extracted from a microsponge and diluted in phosphate buffer pH 6.8 at a concentration of 100 mg per 100 ml. The clotrimazole in the phosphate buffer pH6.8 was allowed to dissolve completely over night. A solution with a concentration of 10 g/ml was prepared by filtering and diluting the original solution. The drug concentration was determined by comparing the absorbance of the solutions at 264 nm with that of phosphate buffer at pH 6.8 (the blank).

Entrapment efficiency

Crushing and dissolving 10 mg of microsponges in 50 ml of phosphate buffer pH6.8 yielded a clear solution. The fluid was subsequently filtered via a 0.45-micron membrane filter. The concentration of the medication was measured spectrophotometrically at 264 nm after being appropriately diluted.

Entrapment efficiency =Actual drug loading/Theoretical drug loading× 100

Particle size analysis

Using optical microscopy with a stage micrometre, the average particle size of microsponges was calculated. An average of 200 microsponges from each batch were measured after being spread out on a glass slide.

Infrared spectroscopy

It was found by employing the KBr pellet method with a Fourier Transform Infrared Spectrophotometer (FTIR-Shimadzu). In the wavenumber range of 4000 to 400 cm^{-1}, FTIR spectra were acquired for Clotrimazole, physical mixture(s) of clotrimazole and eudragit RS-100, carbapol 940, and microsponge formulation..

Differential scanning colorimeter

Clotrimazole's purity was determined with the help of a Differential Scanning Calorimetry (DSC) thermogram recorded on a METTLER TOLEDO Star SW 920. At a scanning rate of 100C/min in an environment of nitrogen flow (40mL/min),

7 mg of clotrimazole was heated in a crimped aluminium pan with a punctured cover throughout a temperature range of 40-350°C.

Formulation of gel of optimized batch

Method of preparation

The quantities of each item were meticulously measured. After being left in distilled water overnight to hydrate, carbopol 940 was once again dispersed in distilled water, this time with the help of a magnetic stirrer, for about an hour before the addition of propylene glycol and other excipients like Butylated Hydroxy Toulene and Methyl paraben. The mixture was then neutralised by the slow, steady addition of triethanolamine. The amount of base was adjusted until a translucent gel formed with a pH of around 6.8 [29], and mixing was continued until the gel hardened. After measuring out 1% Clotrimazole in microsponges, they were mixed with carbopol gel with a magnetic stirrer for 20 minutes to ensure that the microsponges were evenly scattered throughout the gel.

Evaluation of basic gel parameters

Physical examination

The colour, homogeneity, consistency, and aesthetic appeal of the created gel compositions were evaluated.

pH

Using the digital pH metre, we poured 10 g of the gel formulation into 10 millilitres of the beaker. The ideal PH range for a topical gel is between 3 and 9.

Viscosity

The produced gel formulation's viscosity (in cps) was measured using a Brookfield digital viscometer (DVII+PRO). At 10 rpm, the spindle (T-D) was being turned. It took 30 seconds of running the motor before a reading was reported. The measurements were taken three times to get an accurate average.

Spredability

In order to determine how easily 0.5 g of clotrimazole gel could be dispersed throughout a 2 cm diameter circle marked on a glass plate, a second glass plate was used. For 5 minutes, a half-kilogram weight was allowed to sit on the top glass plate. After the gel was spread into a circle, its diameter was measured. It is calculated using the formula:

$S = M \times L / T$

Where, S = is the spredability, M = is the weight in the pan (tied to the upper slide), L is the Length moved by the glass slide and T represents the time in seconds taken to separate the slide completely.

Diffusion study

The Franz diffusion cell and the cellophonic membrane were used to conduct the diffusion research. We developed, manufactured, and tested a vertical Franz diffusion cell. Approximately 2.5 cm2 of cellophonic membrane was sliced and hydrated in phosphate buffer (pH-6.8) overnight before being used in a diffusion research. After putting together the rest of the cell, we slathered 100mg of gel sample onto the membrane attached to the base of the donor compartment. The receptor volume was maintained at 25 ml. In order to facilitate permeation, the completed cell was placed in a bath of permeation fluid (phosphate buffer pH-6.8) maintained at 37°1°C and swirled constantly on a magnetic stirrer at 50 rpm. The spectroscopic approach was used to determine the drug concentration in the 1ml sample that was taken. After each collection, the fluid was replaced with an identical volume of new buffer. To determine the optimal gel formulation, samples were taken at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours. At each sampling point, the total amount of medication that diffused through the membrane was determined and recorded.

In Vitro Drug Release of Microsponges

The current research made use of the USP apparatus II. The dissolution basket was filled with microsponges containing 100 mg of Clotrimazole. The dissolution test was conducted at 370.5°C and 100 rpm in a phosphate buffer solution. At regular intervals throughout the course of 12 hours, 1 ml aliquots of the solution were removed from the dissolving device and replaced with fresh dissolution media to keep the sink condition constant. Filters with a micron

rating of 0.45 were used on the samples. The solutions were tested for their absorbance at 264 nm. An equation derived from a standard curve was used to determine the cumulative percentage of medication release.

Kinetics of drug release

The findings of the in vitro dissolution investigation of the optimised batch of microsponges (batch) were fitted with several kinetic equations to better understand the mechanism and kinetics of drug release.

3. RESULTS & DISCUSSION

Determination of production yield and encapsulation efficiency

Production yield, particle size, drug content, entrapment efficiency, and in vitro drug release of formulated clotrimazole microsponges were all assessed.

Table 2: Evaluation of Formulated Clotrimazole Microsponges

Formulation Code	Drug: polymer ratio	Actual drug content (%)	Entrapment Efficiency (%)	Production yield (%)	Particle size (μm)
F1	1:1	30.35±0.01	60.70±0.02	48.95	42.35
F2	1:1	38.99±0.02	77.98±0.01	62.6	39.76
F3	1:1	42.80±0.03	85.60±0.02	68.50	38.25
F4	1:2	20.23±0.02	60.75±0.04	67.06	74.10
F5	1:2	25.28±0.02	75.91±0.02	75.16	56.33
F6	1:2	29.45±0.02	88.45±0.01	80.00	50.44
F7	1:3	20.6±0.15	82.4±0.04	70.00	80.33
F8	1:3	24.17±0.02	86.40±0.02	87.62	76.66
F9	1:3	20.80±0.01	83.20±0.04	98.52	72.10

The average batch yield was 48.95%, and the highest was 98.52%. It was discovered that the drug:polymer ratio and polyvinyl alcohol concentration had significant impacts on production yield. Production yield was shown to rise with polymer concentration while decreasing with polyvinyl alcohol concentration. A small increase in the viscosity of the dispersed phase resulted from the use of higher volumes of PVA while making microsponges at higher drug: polymer ratios. Diffusion of the inner phase's solvents led to the formation of solid microsponges and the separation of particles. The ratio of polymer to drug in some formulations was higher than in others, which may account for their superior drug loading efficiency.

In vitro drug release study

All formulations' cumulative drug release (% CDR) was determined. Table 3 shows the summative percentage of medication release for each formulation.

Table 3: Result of In-Vitro drug release of Formulated clotrimazole microsponge

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.83± 0.12	17.33± 0.35	21.60± 0.45	12.61± 0.22	16.51± 0.41	19.61± 0.44	8.90±0. 23	13.30± 0.12	15.22± 0.19
2	28.60± 0.54	31.28± 0.29	32.83± 0.42	20.32± 0.31	25.57± 0.12	29.88± 0.41	13.60± 0.64	18.20± 0.17	23.54± 0.64
3	35.18± 0.45	38.70± 0.64	43.80± 0.57	29.57± 0.12	31.39± 0.42	38.88± 0.42	19.40± 0.49	23.12± 0.10	28.63± 0.98

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
4	46.43± 0.53	49.93± 0.42	55.19± 0.13	37.65± 0.24	43.90± 0.21	46.39± 0.21	24.98± 0.80	28.90± 0.31	32.21± 0.35
5	55.29± 0.45	59.60± 0.56	67.33± 0.19	43.85± 0.42	49.51± 0.23	53.54± 34	30.21± 0.34	33.01± 0.15	38.13± 0.11
6	66.21± 0.21	69.96± 0.23	74.42± 0.43	50.94± 0.39	55.33± 0.29	61.72± 0.42	37.58± 0.39	39.56± 0.36	43.29± 0.43
7	74.62± 0.58	77.65± 0.03	81.59± 0.36	55.80± 0.21	61.88± 0.17	66.98± 0.43	43.15± 0.40	45.36± 0.49	49.12± 0.23
8	81.05± 0.13	84.72± 0.72	87.62± 0.17	63.92± 0.23	70.92± 0.35	73.56± 0.67	50.87± 0.67	49.29± 0.29	55.37± 0.47
9	88.70± 0.42	91.58± 0.98	92.48± 0.31	68.55± 0.23	74.61± 0.18	79.92± 0.98	53.66± 0.67	55.30± 0.18	60.23± 0.43
10	98.08± 0.32	98.81± 0.65	96.46± 0.23	75.30.1 95±	81.23± 0.11	85.93± 0.25	58.23± 0.98	61.48± 0.25	66.52± 0.27
11				80.23± 0.22	87.89± 0.23	91.32± 0.39	61.65± 0.61	66.15± 0.42	70.19± 0.23
12				84.04± 0.10	92.79± 0.22	99.59± 0.28	64.02± 0.11	71.09± 0.45	77.61± 0.19

Based on these findings, it can be concluded that Formulation F6 is both aesthetically pleasing and functionally optimal, with maximum medication release occurring after 12 hours. Therefore, this was the chosen formulation for making clotrimazole gel-loaded microsponges.

Kinetics of drug release

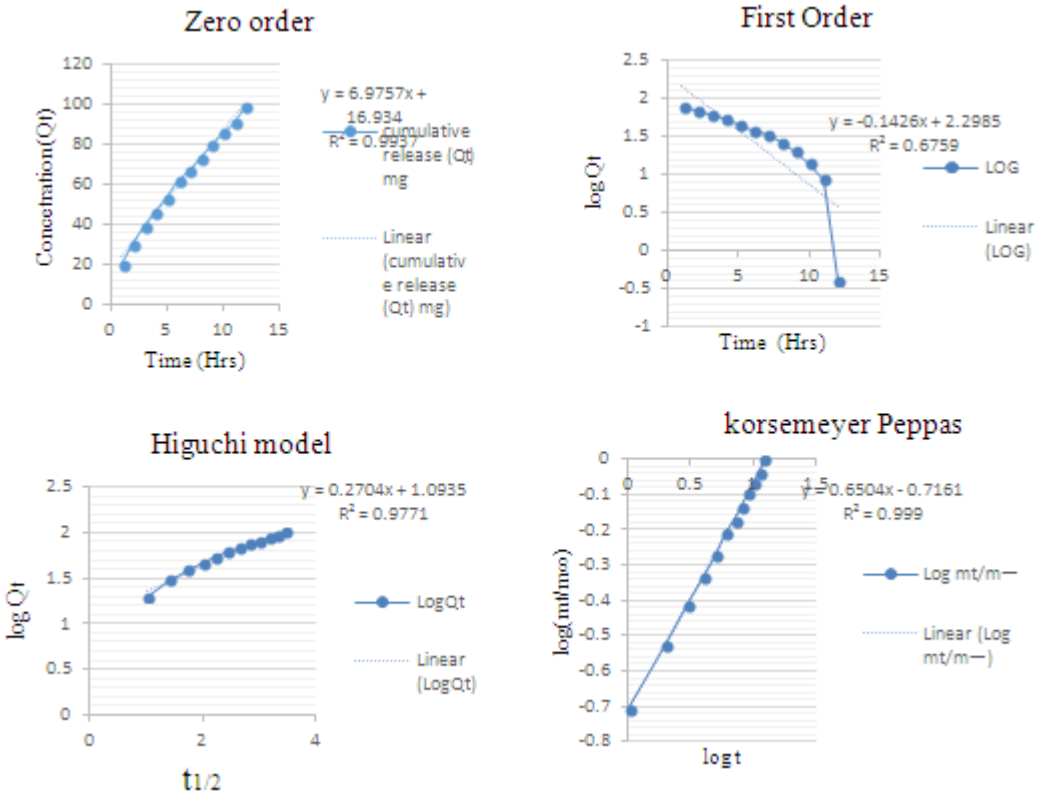

Figure 1: Kinetics of drug release

Table 4: Release kinetic data of Clotrimazole microsponges

Formulation	Zero Order	First Order	Highuchi Matrix	Korsemeyer Peppas
F6	0.9937	0.6759	0.9771	0.999

Zero-order, first-order, Highuchi matrix, and Korsemeyer Peppas model kinetic evaluations were performed on the optimised batch. As shown in table no. 2, the best-fitting model has a high value for the correlation coefficient (R2). Korsmeyer-Peppas release model suggested that the medication was released by a diffusion process, and formulation f6 fit this model very well. The concentration of the medicine in the formulation affects how well it diffuses into the diffusion medium. The drug is released and the diffusion distance increases as the gradient changes. To confirm the diffusion mechanism, the data were fitted to Korsmeyer's equation;

$Qt / Q\alpha = K\ tn$

Where, Q is the amount of drug released at time t, Qα is overall released amount, K is a constant incorporating the properties of macromolecular polymeric system and the drug, and n is a kinetic constant or diffusion exponent that depends on the transport mechanism. The exponent n gives information about the release mechanism; n = 0.5 characterizes diffusion Controlled release, $0.5<n<1.0$ indicates anomalous (non-Fickian transport), and n = 1.0 indicates swelling controlled release (zero-order kinetics). Formulation f6 showed a diffusion controlled-release mechanism as reflected by their n value which indicating drug release by non-fickian mechanism.

FTIR Spectroscopy

Figure 2 depicts the clotrimazole drug's spectral range. These peaks only appear for certain functional classes. The FTIR spectrum of the drug's functional groups shows that the obtained drug's observed peaks correspond with the reported peaks. Based on these findings, it was determined that the clotrimazole medication had no impurities and was of adequate quality.

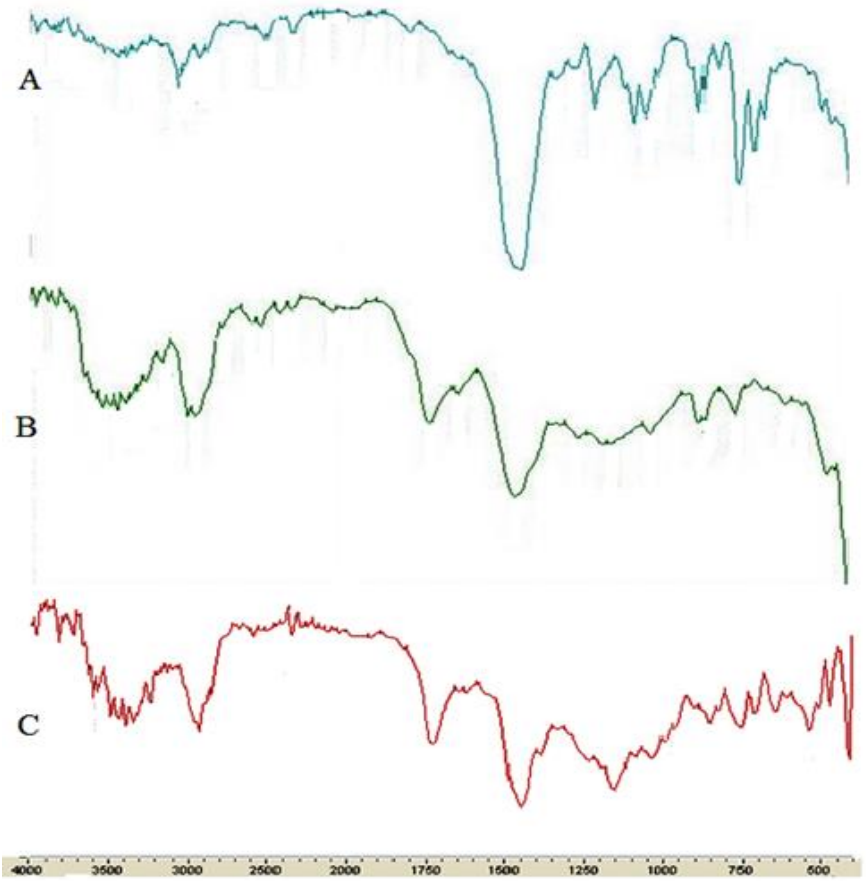

Figure 2: FT-IR spectra of A) Clotrimazole, B) Eudragit RS 100 & C) Optimized Formulation

FTIR spectroscopy showed that there was no chemical interaction between the medication and polymer since no new peaks appeared and no peaks disappeared. The IR spectrum exhibited distinctive peaks at 1797.72 (cm^{-1}) due to C=N stretching. The peaks at 1450.52 (cm^{-1}) is due to the C=C stretching and at 756.12 (cm^{-1}) is due to the C-Cl stretching. The peak at 3063.06 is due to the C-H methylene stretching. During the compatibility examination, the IR spectra of both the physical combination and the clotrimazole-loaded microsponges showed all of the typical peaks of clotrimazole. Therefore, the results of the IR spectroscopy demonstrated that the medicine was compatible with the excipients and polymer of choice. Based on these results, it appears that clotrimazole is stable in microsponges and is compatible with specific polymers.

Differential Scanning Colorimeter (DSC)

The purity of the Clotrimazole sample was validated by DSC thermogram analysis, which showed that a pure clotrimazole thermogram reflected an endothermic peak at 149 °C, which corresponded to its standard melting point range.

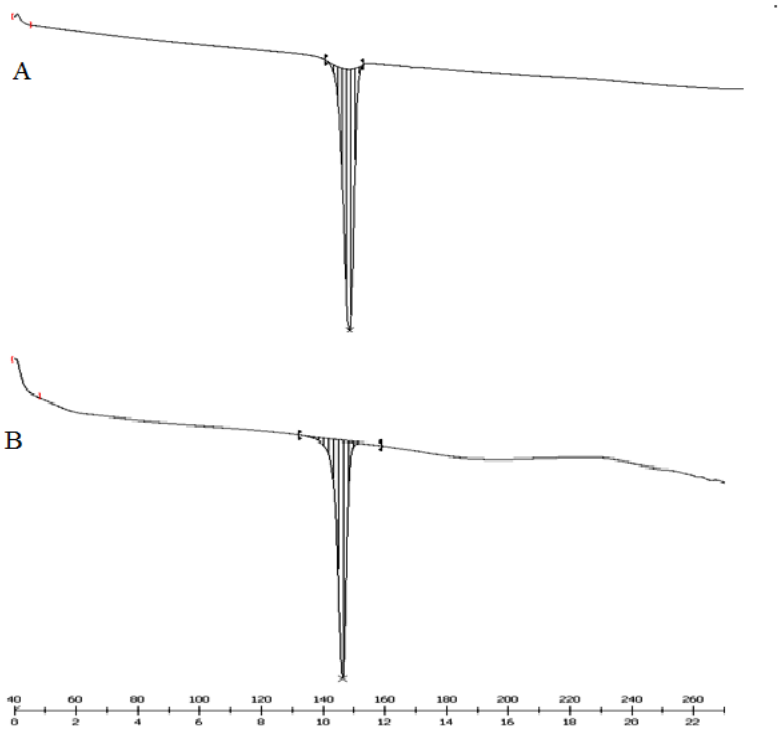

Figure 3: DSC Thermogram of A) Clotrimazole, B) Eudragit RS100 and C) Clotrimazole

DSC shows a potential interaction between the medication and other excipients in microsponges and offers information about the sample's physical qualities, such as its crystalline or amorphous nature. Clotrimazole and eudradgit RS 100, as a physical mixture, exhibit the temperature behaviour depicted in figure. The drug's melting point in crystal form corresponds to an endothermic peak measured at 1480C. The peak temperature of the Clotrimazole/eudradgit RS 100 physical mixture was determined to be 148 degrees Celsius. There is no obvious discrepancy between this peak and the conventional peak. Because of this, we know that the polymer and the medication can work together safely.

Evaluation of gel parameters [30-31]

1. Appearance: The formulated gel was analysed and determined to be clear, refined, homogeneous, and consistent.

2. pH: PH of formulated batch was found to be 6.8.

3. Viscosity: The developed batch had a viscosity of 19996 cps. When drug diffusion through the gel is the rate-determining step, the viscosity of cream may have a significant role in regulating the release of drug into the receptor compartment.

4. Spredability: The batch's spreadability was measured at 7.8gm.cm/sec after it was formulated. It represents the surface area across which the gel can be applied without difficulty. A formulation's medicinal efficacy is affected by its dispersal value as well. The rate at which two slides can spread apart under a given force is measured in seconds and is known as the "slip off time" from gel placed between the slides. Better spreadability is achieved with faster slide separation times.

5. In vitro diffusion study

Table 5: In vitro diffusion study- Amount of drug diffused per unit area of microsponge gel formulations

Time(hr.)	Drug release (%) of batch F6	Drug release (%) MP
1	18.26±0.44	20.77±0.65
2	25.19±0.41	29.36±0.45
3	31.15±0.42	35.41±0.85
4	39.85±0.21	46.85±0.89
5	46.53±0.34	57.25±0.54
6	52.65±0.42	72.35±0.53
7	59.43±0.43	88.87±0.40
8	67.29±0.67	99.26±0.52
9	72.18±0.98	
10	80.72±0.25	
11	85.46±0.39	
12	93.14±0.28	

All formulations were tested for diffusion in PBS (pH 7.4) in vitro tests. Table 5 displays the results of batch F6 and formulation MP's in vitro diffusion.

4. CONCLUSION

These days, topical gels are preferred over other semisolid preparations because they are more stable and enable controlled release of the medicine. Clotrimazole is an antifungal medication that has been shown to be effective. It's strong and picky, and it works. It is effective against all three types of tinea infections (pediculosis, ringworm, and body fungus). In order to improve medication solubility, microsponge gel was utilized as a topical drug delivery method. This research used eudragit RS100 as a polymer to create a microsponge of Clotrimazole. The quasi emulsion solvent diffusion method was used to create the microsponge. The primary objective of this study was to determine the best solvent and polymer concentration combinations for producing Clotrimazole microsponges using ethanol and dicyclohexane (DCM). The results showed that Clotrimazole release might be improved upon for greater therapeutic effect. The quasi emulsion solvent diffusion technique was used successfully to prepare clotrimazole microsponges. Clotrimazole microsponge containing gel also demonstrated sustained release activity, as did microsponge made using eudragit RS100 polymer and solvent ethanol and DCM. Therefore, the medicine in the form of a microsponge can reduce the risk of adverse effects and increase patient compliance by avoiding skin contact.

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