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Advanced Formulation and Comprehensive Pharmacological Evaluation of a Novel Topical Drug Delivery System for the Management and Therapeutic Intervention of *Tinea Cruris* (Jock Itch)

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Abstract

Aim: *This research was initiated with an aim to formulate a controlled release local drug delivery system of luliconazole for the management of jock itch.* ***Methods:*** *To enable regulated medication release by using a quasi-emulsion solvent diffusion technique, microsponges containing liconazole were created and then implanted in transdermal gel. Total six formulations of Luliconazole microsponges were developed with different concentrations of drug and polymer and evaluated for size, shape, thermal characteristics, drug content and in-vitro drug release pattern.* ***Results:*** *The formulated microsponges' round shape and spongy texture were validated by the SEM assessment. Formulation LM 04 had the greatest drug content (93.58%), and the results of the in-vitro drug diffusion investigation show that 98.56% had been released after 12 hours. Drug release kinetics was monitored in all formulations. Formulation LMG 01 was chosen as the optimal formulation and integrated into a carbopol gel base based on drug content, in vitro drug release tests, and other assessment characteristics. When paired with a commercially available luteconazole gel, it was discovered that the in vitro drug release from the designed microsponge integrated gel was extended.* ***Conclusion:*** *The manufactured liconazole microsponge reduces the frequency of administration by delivering the medicine in a regulated release over an extended period of time.*

Keywords: *Topical, Transdermal, Microsponges, Luliconazole, Jock itch, Dermatophytes.*

1. INTRODUCTION

Fungal infections are a prevalent cause of morbidity and other health problems. There are two types of fungal infections: internal and exterior. Between 20% and 25% of people worldwide suffer from fungal infections that are external and are linked to daily activities, unhealthy lifestyles, and low health awareness. Malassezia spp. infections, dermatophytes, and candida infections can all result in external fungal infections. Some aerobic funguses are called dermatophytes. In the outer layers of the epidermis, the dermatophytes multiply and digest keratin for development (1) (2).

Luliconazole is an imidazole antifungal drug that has a distinct structure because it incorporates the imidazole moiety into the structure of ketene dithioacetate. The R-enantiomer, luconazole, is more effective against a wide range of fungi, particularly dermatophytes, and has stronger antifungal action. A 1% cream called luconazole is used to treat jock itch and athlete's foot, which are brought on by dermatophytes such Trichophyton rubrum, Microsporum gypseum*, and Epidermophyton floccosum (3)(4).

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A fungal infection of the groyne area, jock itch is characterised by a red, often ring-shaped rash that is itchy. Mostly affect the buttocks, inner thighs, and vaginal skin. People frequently wear clothing that is too tight and retains moisture inside of them (5)(6). It is extremely infectious and may spread to any portion of the body. The skin in the affected regions may flake, ripple, peel, iridescence, or fracture. The affected areas may appear reddish, tan, or brown (7)(8).

A micro sponge is a porous polymeric drug delivery technology that resembles a sponge and is frequently used to extend the duration and therapeutic index of drug release. Micro sponges regulate the amount of active substances delivered to minimise allergy, irritability, and other adverse effects while increasing dosage frequency and stability (9). The mixtures remain stable throughout a wide pH range. The current study's objective was to create micro sponges loaded with clozidonazole using a quassi-emulsion solvent diffusion method, then mix those sponges into a gel basis to increase their permeability and water solubility and assess them (10)(11).

2. MATERIALS AND METHOD

A free sample of leviconazole was obtained from CCSU Lab located in Meerut, India. Hydroxy propyl methyl cellulose (HPMC) and Carbopol 934 were the suppliers of ethylcellulose; PVA (poly vinyl acetic acid), PEG (poly ethylene glycol), dichloromethane, methanol, and triethanolamine were bought from Thapar nagar chemicals Pvt. Ltd. The remaining chemicals and reagents utilised in the study were all of analytical grade.

2.1. Identification of the drug and its purity confirmation

Differential Scanning Calorimetry (DSC) spectrum analysis Figures 1 and 2 were used in conjunction with Fourier-Transform Infrared spectroscopy (FTIR) to identify the medicine and excipients and evaluate their purity.

2.2. Studies on drug and excipient compatibility

Using infrared spectroscopy, the drug and excipient compatibility investigation was conducted. Micro sponges, physical mixtures, and pure drug samples were all documented. Samples were prepared by triturating them with KBr. They were then analysed using Differential Scanning Calorimetry (DSC) spectral analysis under nitrogen purging at a scanning rate of 10°C/m, covering the temperature range of 30-360°C, and Fourier-Transform Infrared spectroscopy (FTIR), with a scanning measurement range of 400 to 4000 cm-1 Figure 3.

2.3. Luliconazole micro sponges: assembly and preparation

The Quassi-emulsion solvent diffusion procedure produced the liconazole microsponge microstructures. The procedure consists of two steps: the first stage included dispersing the medication and a weighed quantity of ethylecellulose in the necessary amount of solvent. As a plasticizer, polyethylene glycol was used. In the second stage, PVA was dispersed using heat in 50 millilitres of deionized water to create the external phase, or continuous phase. After that, the produced internal phase was gradually added to the external phase. The mixture was then constantly agitated at 5000 rpm for six to seven hours, or until the internal phase had fully diffused out of the system and micro sponges had formed. To determine the manufacturing yield, the produced powdered micro sponges were weighed after being filtered using Whattman no. 40 filter paper, cleaned and dried for 12 hours at 40°C in a vacuum oven (12)(13). Table 1 shows the six micro sponge formulations that were created.

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Table 1: Composition of Luliconazole of Micro sponge Formulations

Ingredients	Formulation no					
	LM 01	LM 02	LM 03	LM 04	LM 05	LM 06
Luliconazole (g)	1	1	1	1	1	1
Ethyl cellulose (g)	0.25	0.5	0.75	1	1.25	1.5
Dichloromethane (ml)	50	50	50	50	50	50
Polyvinyl Alcohol (g)	0.8	0.8	0.8	0.8	0.8	0.8
Polyethylene glycol (ml)	5	5	5	5	5	5
Deionized water (ml)	q. s. to make 100ml	q. s. to make 100ml	q. s. to make 100ml	q. s. to make 100ml	q. s. to make 100ml	q. s. to make 100ml

2.4. Characterisation of micro sponges

2.4.1. Physical appearance: The formulated micro sponges were visually checked physical appearance.

2.4.2. Determination of Particle size: The particle size of the micro sponges was measured using an optical microscope equipped with a stage micrometre and a calibrated eye piece. A little quantity of micro sponge material was put on a sterilised slide, and the 100 particle sizes of each batch were recorded (14). Equation 1 was used to determine the micro sponges' average size, which is shown in Table 2.

$$dav = \frac{\Sigma nd}{\Sigma n} \qquad \text{Equation …… 01}$$

Where n is the number of particles per group, d is the middle value (μm), and dav is the average diameter of the particles (μm).

2.4.3. Surface morphology: Scanning electron microscopy (SEM) was used to assess the exterior properties of the prepared micro sponges. The samples were spread out on a double-sided adhesive tape that was adhered to a metal slab and put under a scanning electron microscope to show the micro sponges' spongy structure. Following that, photomicrographs were obtained and the samples of produced micro sponges were scanned at an acceleration voltage of 10.00 kV (15) Figure 4.

2.4.4. Determination of % yield: The weight of the micro sponges that were collected from each formulation batch was compared to the weight of the whole starting material (theoretical yield) to determine the practical per cent yield. The yield percentage was computed using Equation 02 (16) and recorded in Table 2.

$$\%\ \textbf{Yield} = \frac{\text{Practical yield}}{\text{Theoritical Yield (Drug+Excepients)}}\ X\ 100 \qquad \text{Equation ……..02}$$

2.4.5. Encapsulation efficiency: The Therapeutic effectiveness of any dosage form is relied on its capacity to release the drug for required period of time, at the required site of action and in the sufficient quantity needed. Therefore, the entrapment capacity of the active ingredient into the dosage form is considered to be of utmost importance for examining its in-vivo usefulness. The exactly weighed micro sponges equivalent to 10 mg of drug are dissolved methanol in a 10 ml volumetric flask and volume was made up to the mark. The solution was sonicated for 10 min and filtered using whattman no. 40 filter paper. All the formulated batches of Micro sponges was analysed using spectrophotometrically at 295 nm in triplicate (17). Using equation 03, the encapsulation effectiveness was determined and documented in Table 2.

$$\%\ \text{Encapsulation Efficacy} = \frac{\textbf{M}\ \text{Actual}}{\textbf{M}\ \text{Theoritical}}\ X\ 100 \qquad \text{Equation ……..03}$$

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Where M theoretical is the theoretical amount of liconazole in the micro sponge added throughout the procedure, and M actual is the actual liconazole content in a weighed quantity of micro sponges.

2.4.6. Determining the Drug Content

From each batch, precisely weighed amounts of specially prepared micro sponges corresponding to 10 mg of luliconazole were extracted. Using a mortar and pestle, the materials were triturated, and then they were fully dissolved in 100 millilitres of phosphate buffer solution (pH 7.4). Whattman No. 40 filter paper is used to filter the solution, and phosphate buffer solution is used as a blank in spectrophotometric analysis at 295 nm (18). The medication composition was computed and included into Table 2.

2.4.7. In-vitro diffusion study

The dialysis bag technique was used to conduct in-vitro diffusion investigations on the luliconazole-encapsulated micro sponges. To allow for the proper diffusion process, the dialysis membrane was immersed in newly made phosphate buffer solution (pH 7.4) for a whole night. The dialysis bag was filled with precisely weighed micro sponges that weighed 10 mg of luliconazole, and the micro sponges were allowed to suspend in the diffusion medium. By taking 5 millilitre samples of the diffusion medium at predetermined intervals for 12 hours, the drug's diffusion rate from the prepared micro sponges was determined. To keep the sink condition, the sample amount was always replaced with new diffusion medium. The samples were subjected to spectrophotometric analysis at 295 nm, with a blank of phosphate buffer solution (19). Calculations were made, and the results are shown in Table 3 and Figure 5.

2.4.8. Preparation of luliconazole micro sponge embedded gel

Hydroxy propyl methyl cellulose (HPMC) and Carbopol 934 were used to create two batches of micro sponges embedded in gel. The weighed quantity of carbomer and HPMC were soaked in required quantity of water overnight separately. The carbomer gel base was neutralised by thriethanolamine once the soaking was completed. The accurately weighed quantity optimised formulated micro sponges were suspended in required quantity of propylene glycol and Glycerine. Then the drug and solvent mixture was blended slowly followed by addition of other ingredients with continuous slow stirring, to avoid the formation of air bubble. For further research, the prepared luliconazole gel was kept in a cold, dry area in an airtight, collapsible tube (20)(21)(22).

The luliconazole micro sponge gel formula is shown in Table 4.

Table 4: Composition of Luliconazole micro sponges embedded gel Preparation.

Sl. No.	Ingredient	Formulation batch code	
		LMG-1	LMG -2
1	Luliconazole microsponges	Equivalent to 1 % of Drug	Equivalent to 1 % of Drug
2	Carbomer 934	1%	--
3	HPMC	--	1%
	Glycerine	5%	5%
4	Polyethylene Glycol	2%	2%
5	Ethanol	20%	20%
6	Triethanolamine	2%	2%
7	Methyl paraben	0.01%	0.01%
8	propyl paraben	0.10%	0.10%
9	Deionized water	q.s.	q.s.

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3. EVALUATION OF LULICONAZOLE EMBEDDED GEL

3.1. Physical properties of gels

Organoleptic parameters such as colour, consistency, homogeneity, texture, and presence of foreign particles were visually inspected and reported in Table 5 of the prepared luliconazole micro sponge embedded gel.

3.2. Determination of the pH

The formulated gel was subjected to pH measurement using a digital pH meter. The pH of topical drug delivery system is of importance as it should not cause any irritation to the skin upon application. 2 g of formulated gel was dissolved in 20 ml of distilled water and the pH was determined by digital pH meter (23) and was recorded in Table 5.

3.3. Determination of Spreadibility

Using the horizontal slide method, the spread ability of the prepared luliconazole gel was ascertained and quantified in terms of time in seconds. A glass slide that was adhered to a wooden surface was covered with one gram of gel. The gel was sandwiched between two slides by placing a second slide of the same dimensions on top of the fixed slide. For five minutes, a 125 g weight was placed over the upper slide in order to remove extra gel and provide a consistent layer of gel between the slides (24). After that, spread ability was determined using equation 04 and noted in Table 5.

$$\text{Spreadibility} = \frac{\mathbf{M\,X\,L}}{\mathbf{T}} \qquad \text{Equation ……..04}$$

Where M is the weight on the top slide, L is the length that the glass slide moves, and T is the time.

3.4. Viscosity Determination

The rheological characteristics of the prepared luliconazole micro sponge embedded gel were measured at 37°C ± 2°C 27 at a speed of 100 rpm using a Brookfield viscometer DV-III Programmable with spindle no. S-94. The results are shown in Table 5.

3.5. Determination of Extrudability

Any substance can be extruded through a nozzle with this property. The gel formulation was packaged in aluminium tubes that could be folded up. The weights in grams needed to extrude the contents through the tube's tip were used to calculate the extrudability (25).

3.6. Determination of swelling Index

After cleaning, a tea bag was immersed in distilled water for a whole day. After filling the soaked tea bag with a measured amount of the prepared gel, it was let to soak in 200 millilitres of distilled water for three hours at room temperature. Using equation 05, the gel's swelling index was determined to be (26) and entered into Table 5.

$$\text{Swelling index} = \frac{\text{weight of swollen gel} - \text{weight of dried gel}\ \text{X L}}{\text{Weight of dried gel}} \qquad \text{Equation …… 05}$$

3.7. Test for skin irritancy

The 0.5 g prepared gel sample was applied to the skin for four hours, during which time the skin was checked for signs of erythema and oedema. The reactions were then recorded at four, eight, and twelve hours (27).

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3.8. Determining the Drug Content

In order to determine the drug content of the luliconazole micro sponge embedded gel, a precisely weighed amount of gel was dissolved in 100 millilitres of phosphate buffer solution (pH 7.4) and then sonicated for ten minutes. Whattman No. 40 filter paper was used to filter the mixture and analysed spectrophotometrically at 295 nm calculated and was recorded in Table 5 (28).

3.9. In vitro diffusion Studies

Using a Franz diffusion cell and cellophane membrane, which functions as a semipermeable membrane, an in-vitro diffusion research of manufactured Luliconazole micro sponges embedded gel was carried out. A weighed quantity of the formulated gel (one hundred milligrams) was placed in the donor compartment of the cellophane membrane and fixed on the Franz diffusion cell mouth, which held 50 millilitres of phosphate buffer (pH 7.4) in the receiver compartment. The cellophane membrane was positioned so that it formed a pouch and hung inside the cell, touching the buffer solution's surface. The assembly was kept at 37 ± 0.5 °C, and a magnetic stirrer was utilised to continuously agitate the mixture at 300 rpm for 12 hours while employing a magnetic bead. To maintain sink conditions, a 5 ml sample was removed at predetermined intervals and replenished with an equivalent volume of phosphate buffer pH 7.4 at 295 nm, the samples underwent spectrophotometric analysis (29).

3.10. Ex vivo permeation studies

For the optimised gel formulation, ex vivo permeation tests were conducted using recently excised, cleansed, and cleaned goat abdomen skin. The modified Franz diffusion cell phosphate buffer pH 7.4 was used as the study's medium, and it was stirred continuously for 12 hours at 100 rpm on a magnetic stirrer at 37°C. To maintain sink conditions, a 5 ml sample was removed at predetermined times and replaced with an equivalent volume of phosphate buffer pH 7.4. The extracted sample was filtered using Whatman No. 40 filter paper, and its luliconazole content was measured spectrophotometrically at 295 nm(29) (30).

3.11. Antifungal Properties

The gel's optimal formulation was tested for antifungal properties using pathogenic Candida albicans and certain dermatophytes, such as Trichophyton rubrum and Microsporum gypseum (31). Using the "cup plate method," uniformly sized pre-sterilized petri dishes were incubated at 27 °C for 48 hours in Sabouraud's dextrose agar medium. In terms of inhibition zone, the antifungal activity of the prepared gel was compared to that of commercially available luliconazole cream (1%) and standard luliconazole gel (1%) (32-48). Each determination was triple-signed off on.

3.12. Stability Analysis

In accordance with ICH guidelines, accelerated stability investigations were conducted on the prepared micro sponge gel. Gel was subjected to 40°C ± 2°C temperatures and 75% ± 5% relative humidity. At 30, 90, and 180-day intervals, gel was inspected for indications of instability, polymeric phase separation, changes in drug content, and in vitro diffusion characteristics.

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4. RESULTS AND DISCUSSION

4.1. Drug identification and confirmation of Purity

Prior to developing a formulation, pre-formulation experiments were conducted to determine and validate the purity of luliconazole. The reference lulliconazole IR spectrum was compared to the infrared spectra of the medication sample. The fact that the sample's infrared spectrum matched the reference's showed that the compounds were extremely pure and safe to use. Figure 1

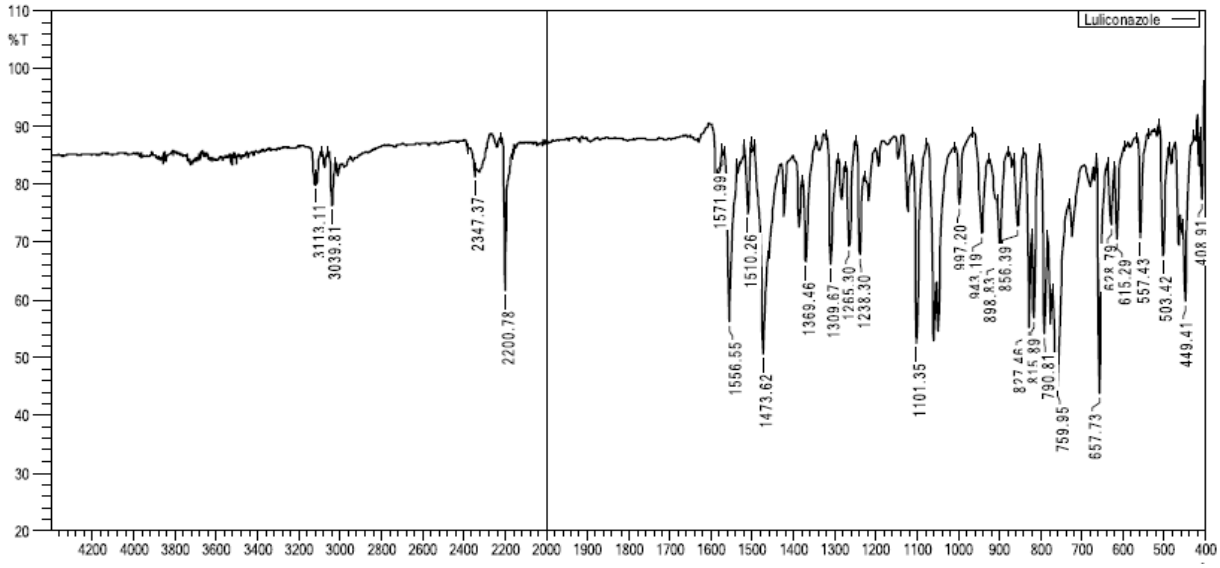

Figure 1: IR spectra of Luliconazole

4.2. Drug and Excipients compatibility studies:

FTIR spectroscopy was used to examine the drug polymer compatibility. In order to identify certain peaks based on the corresponding functional groups contained in their chemical structures, the FTIR spectra of the pure drug, physical combination of drug, and excipients were obtained and compared, as shown in Figure 2.

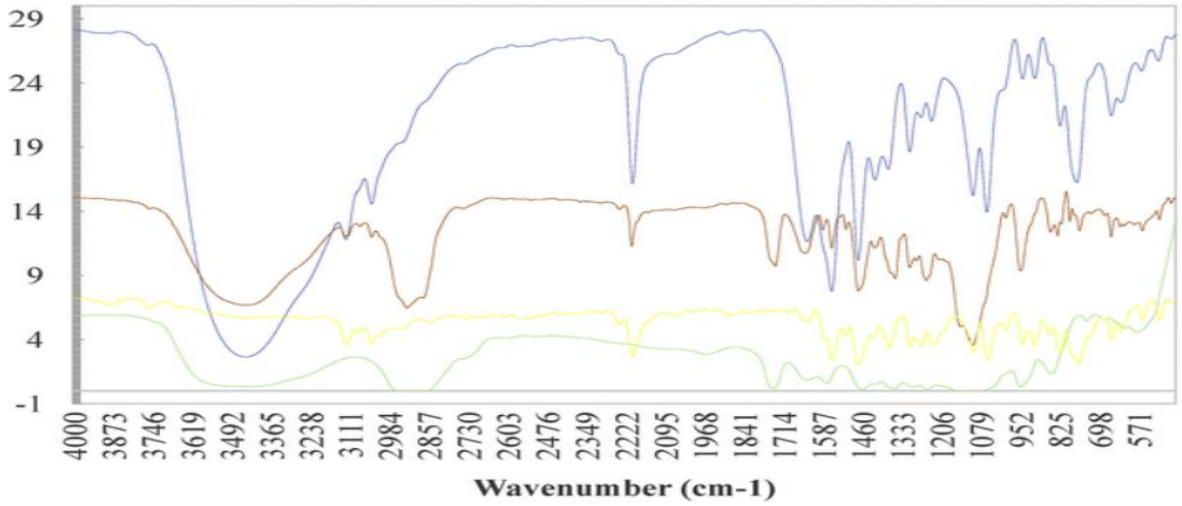

Figure 2: IR spectra of Luliconazole, Excipients used and Physical mixture of drug + excipients

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4.3. Differential Scanning Calorimetry study

There were no appreciable variations in the drug's melting point in the physical mixing of the drug and excipients, according to the pure drug's DSC thermo gram at 25 °C. This suggests that there is compatibility between the medication and the excipients utilised (Figure 3).

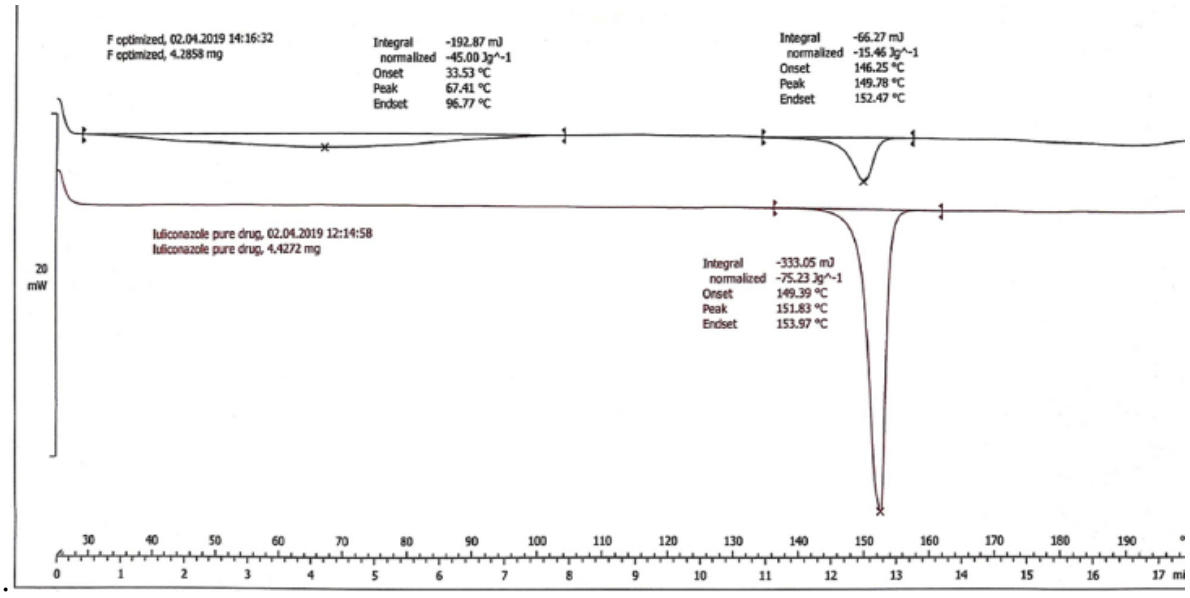

Figure 3: Thermo gram of luliconazole and excipients from DSC

4.4. Preparation of Luliconazole Micro sponges:

The micro sponges of Luliconazole were prepared in six batches with different concentration of polymer ranging from 0.25 – 1.5 g, by emulsion solvent diffusion method. Given that Table 1 shows the production of the micro sponge with the specified qualities, the employed procedure was feasible, simple, and repeatable.

5. CHARACTERISATION OF FORMULATED MICRO SPONGES

5.1. Physical appearance

Upon visually inspection the formulated micro sponges was found to white in colour uniform size powder.

5.2. Particle Size

The formulated micro sponges were examined under optical microscope. The average particle size for the formulated micro sponge batches was found in arrange of 0.75 µm to 1.2 µm. The micro sponges' size decreased as the polymer concentration increased. Hence, it was discovered that the drug polymer ratio affected the micro sponges' particle size Table 2.

5.3. Surface structure

The surface topography and morphology were examined using scanning electron microscopy (SEM). The created micro sponges were spherical in shape, smooth in texture, and porous, according to the scanned pictures of the micro sponges. The surface topography analysis showed that the microscopic holes that made up micro sponges. Ethanol is one type of volatile solvent that can evaporate and leave behind these pores. Figure 4 shows the drug crystals on the outside of the micro sponges at a greater resolution.

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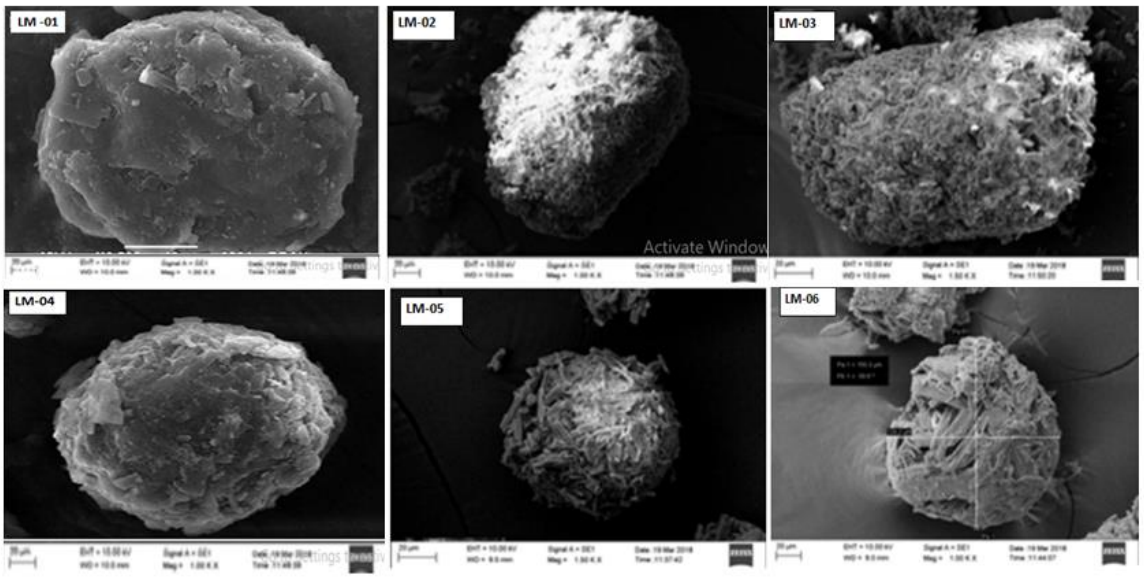

Figure 4: SEM photomicrographs for surface morphology of all six formulated micro sponge

5.4. Percentage (%) yield

After calculation, the percentage yield for each of the formed batches was discovered to be between 78.08 and 94.23%. The time it took for the solvent to spread from the droplet's core to its outside was the cause of this variation in manufacturing yield. Table 2 revealed that formulation LM 04 had the highest percentage yield.

5.5. Efficiency of entrapment

The range of 64.42 % to 92.23% was discovered to be the drug entrapment capability of the prepared batches. The difference in entrapment effectiveness was caused by the medication to polymer ratio. In formulation LM 04 Table 2, the drug and polymer 1:1 ratio exhibits the maximum entrapment efficacy of 92.23%.

5.6. Content of drugs

The formulated luliconazole micro sponges were found to have a drug concentration ranging from 54.65% to 93.56%. The formulated formulation LM 04 shows drug content of 93.58 %. The results revealed that drug content is related to the entrapment efficacy and the distribution of drug in micro sponges Table 2.

Table 2: Particle Size, Percentage Yield, Entrapment efficacy and Drug Content, formulated Luliconazole Micro sponge

Formulation Code	Average Particle Size (µm)	Percentage Yield (%)	Entrapment Efficacy (%)	Drug Content (%)
LM 01	0.75	82.46	64.42	54.65
LM 02	0.84	89.96	72.08	68.48
LM 03	0.91	88.08	78.42	73.96
LM 04	0.72	94.23	92.23	93.58
LM 05	1.1	78.08	69.35	58.89
LM 06	1.2	80.45	65.48	56.84

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5.7. Diffusion analysis of Micro sponge in vitro:

In vitro drug diffusion assays were conducted on all of the created micro sponges to monitor drug release. The results indicated that batches made with a larger proportion of polymer had drug release that was delayed by up to 12 hours. The formulation LM 04 showed the highest release up to 12 hr. due to particle size, highest entrapment capacity, and highest drug content and porous nature. The drug release from all the formulations was found to be in the range of 85.74 % -98.56% in 12hr Table 3 and Figure 5.

Table 3: In-vitro diffusion studies of formulated Luliconazole Microsponge

Formulation / Time (hr)	% cumulative drug Release					
	LM 01	LM 02	LM 03	LM 04	LM 05	LM 06
0.25	18.45	14.26	10.42	7.45	5.84	3.42
0.5	29.45	23.46	18.56	15.86	9.45	5.45
1	44.53	36.48	26.84	26.18	14.89	11.98
2	68.15	51.05	39.74	35.95	24.68	20.45
3	74.81	62.84	48.98	46.24	32.45	29.46
4	94.12	78.96	63.72	59.65	39.56	38.38
5	97.14	84.49	76.43	65.14	45.89	46.83
6		96.97	88.49	73.01	54.8	54.08
7			98.12	79.12	61.51	60.87
8				83.51	68.19	67.45
9				88.97	73.57	71.46
10				91.85	81.45	78.76
11				95.14	85.84	82.46
12				98.56	88.78	85.74

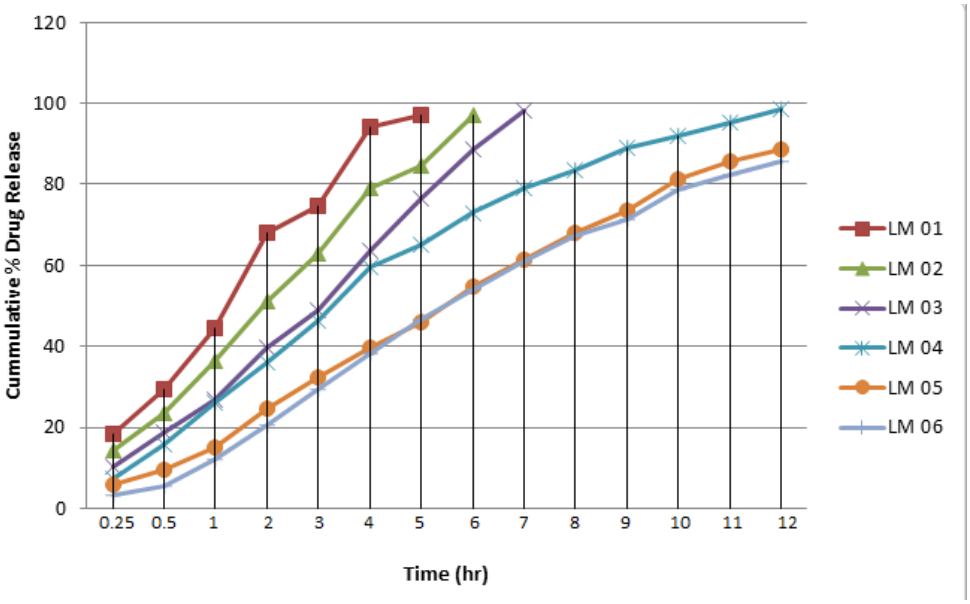

Figure 5: Plot of % cumulative drug released from all the formulated Luliconazole micro sponges

5.8. Preparation of Luliconazole embedded gel

Hydroxy propyl methyl cellulose (HPMC) and carbopol 934 were used to create two batches of micro sponges embedded gel, which were then kept in an airtight container in a cold, dry location for additional assessment Table 4.

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6. EVALUATION OF LULICONAZOLE MICRO SPONGE EMBEDDED GELS

6.1. Physical appearance of gels

Formulations LMG 01 and LMG 02 were homogeneous, smooth in substance, and glossy in appearance. Formulation LMG 01 was white in colour, whereas formulation LMG 02 was transparent.

Table 5: Physical Appearance of prepared gel

Formulation	Colour	Consistency	Homogeneity	Texture	Foreign Particles
LMG 01	Light green	Thick	Good	Smooth	Absent
LMG 02	Light Green	Thick	Good	smooth	Absent

6.2. pH, Spreadibility, Viscosity, Extrudability, Swelling Index and Skin irritancy test:

The pH values of 6.87 and 6.99 for the micro sponges embedded gel formulations LMG 01 and LMG 02, respectively, are deemed appropriate for topical use. A topical formulation's spread ability is crucial; a good formulation should spread readily at the application site. It was found that the formulation represents good spreading ability in a range of 16.25 – 18.85 g cm/sec. The prepared gel's viscosity was determined to be within the 6124–6137 cp range, which is deemed adequate for topical application. The range of 1.25 to 1.35 g/cm2 was determined to be the appropriate extrudability of the gel for a formulation intended to be packaged in tubes for convenient medication withdrawal. The gel's capacity to absorb secretions from the application site is shown by its swelling index. The developed gels showed a satisfactory swelling index between 0.876 and 0.963 g/g. At the application location, there was no indication of any erythema or oedema after 4, 8, or 12 hours. The results are reported in table 5.

Table 6: pH, Spreadibility, Viscosity, Extrudability and Swelling index of prepared Gel.

Formulation	pH	Spreadibility (g cm /sec.)	Viscosity (Cps)	Extrudability (g/cm2)	Swelling Index (g/g)	Skin Irritancy	% drug content
LMG 01	6.99	16.25	6124	1.25	0.876	Absent	93.58
LMG 02	6.87	18.85	6137	1.35	0.963	Absent	93.60

6.3. Diffusion studies for gel in vitro:

In vitro drug release profile evaluations were conducted for gel formulations LMG 01 and LMG 02. The study's results indicate that the formulation LMG 01 exhibits superior drug release in comparison to LMG 02. Table 6 and Figure 6 present the findings.

Table 7: In-vitro drug diffusion studies of the Formulated Gel

Formulation/ Time (Hr)	% Cumulative drug release	
	LMG-1	LMG -2
0.25	6.75	6.43
0.5	13.01	12.95
1	24.84	24.52
2	32.45	32.41
3	45.98	44.84
4	58.79	58.32
5	64.84	64.58
6	71.23	70.83
7	78.94	77.82
8	82.45	81.01
9	87.56	86.45
10	90.87	89.67
11	94.46	93.44
12	98.53	94.72

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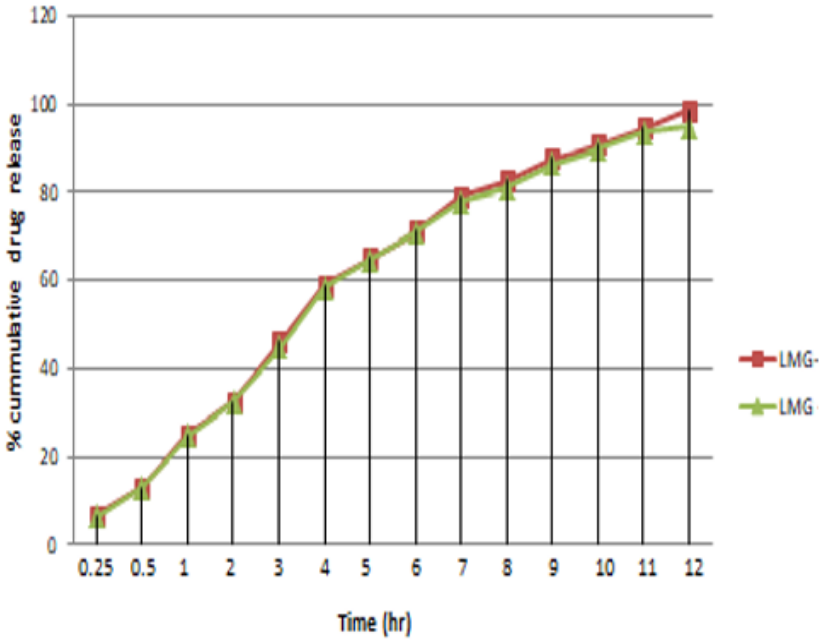

Figure 6: In-vitro drug diffusion studies, % cumulative drug release vs time (hr)

Ex vivo permeation studies

Along with other qualities, a good topical formulation should be able to penetrate the layers of the skin with ease. Thus, researches on in vitro permeability were carried out. In comparison to formulation LMG 02, the formulation LMG 01 shows a greater in vitro penetration rate of luliconazole from the gel. Table 7 and Figure 7 record the outcomes.

Table 8: E-vitro drug permeation Studies of the Formulated Gel

Formulation/ Time (Hr)	% Drug Permeation	
	LMG-1	LMG -2
0.25	7.32	7.68
0.5	14.56	13.99
1	25.73	25.71
2	33.48	33.36
3	46.66	45.64
4	59.74	59.12
5	65.62	65.33
6	72.46	71.54
7	79.89	78.29
8	83.51	82.15
9	88.49	87.3
10	91.74	90.17
11	95.83	94.56
12	99.14	95.88

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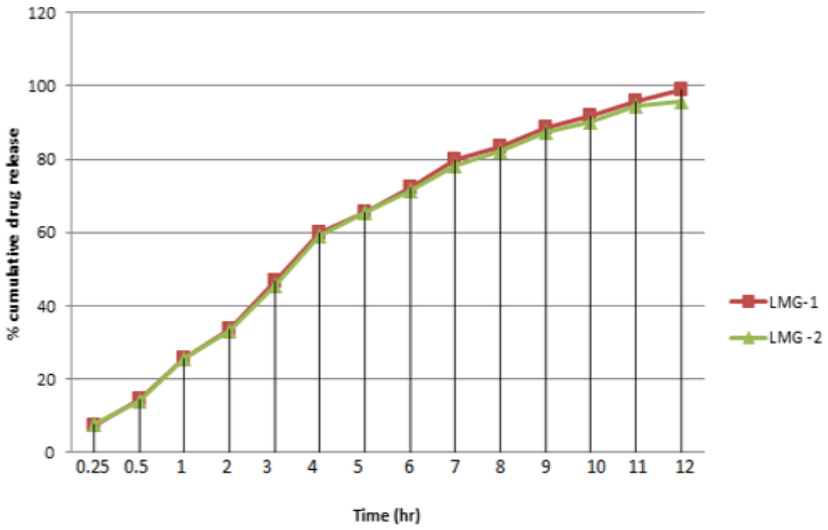


Figure 7: Ex-vivo permeability studies, % cumulative drug release vs time (hr)

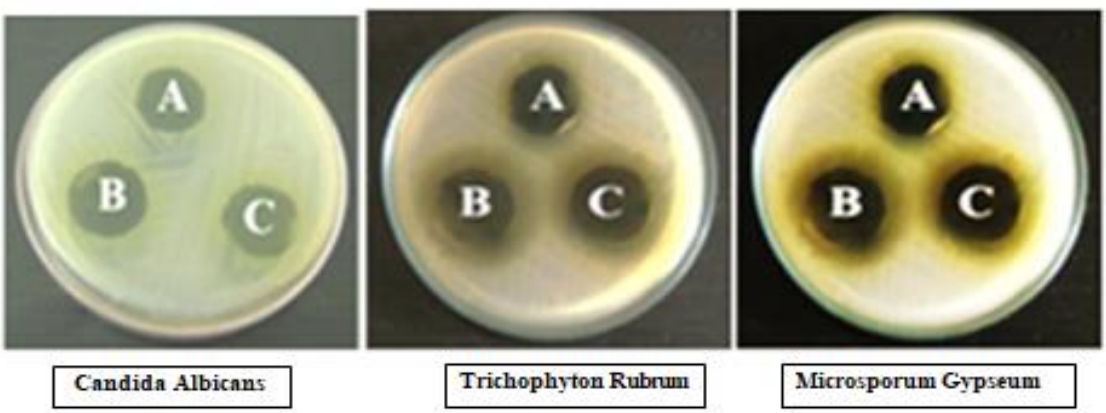
6.4. Antifungal activity

The optimised luliconazole micro sponge embedded gel (LMG 01) formulation has encouraging antifungal effectiveness against some dermatophytes such as Trichophyton rubrum and Microsporum gypseum, as well as fungal infections like Candida albicans. The in-vitro release pattern was used to select Formulation LMG 01 for antifungal activity. The zone of inhibition of commercially available luliconazole cream and conventional luliconazole gel did not significantly differ from one another; however, Table 8 and Figure 8 show that the optimised formulation showed a larger zone of inhibition, suggesting robust antifungal action.

Table 9: Observations of Antifungal activity

Formulation / Strains	Zone of inhibition (mm)		
	Candida Albicans	Trichophyton rubrum	Microsporum gypseum
Standard Luliconazole gel	3.4	4.1	4.3
Marketed Luliconazole cream	2.9	3.7	3.9
LMG 01	7.6	7.9	8.8

Figure 8: Antifungal activity of A) standard Luliconazole gel B) Optimised Formulation and C) Marketed Luliconazole cream.



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6.5. Stability study

Accelerated stability experiments were conducted on the optimised formulation LMG 01 for 180 days at 40°C ± 2°C and 75% ± 5% relative humidity. It was discovered that the formulation kept both its homogeneity of substance and its outward look. The formulation was found to have excellent release and to be stable throughout the stability investigation, with no changes or degradations noted. Figure 9, Table 9.

Table 10: In-vitro drug diffusion profile on 30th, 90thand 120th day of stability study

Days / Time (Hr)	% cumulative drug release		
	30 day	90 day	180 day
0.25	7.28	7.21	7.14
0.5	14.51	14.46	14.31
1	25.69	25.6	25.41
2	33.45	33.33	33.14
3	46.62	46.56	46.42
4	59.7	59.62	59.46
5	65.57	65.49	65.3
6	72.38	72.31	72.12
7	79.83	79.76	79.53
8	83.46	83.36	83.17
9	88.41	88.34	88.13
10	91.66	91.59	91.36
11	95.76	95.68	95.47
12	99.06	98.92	98.76

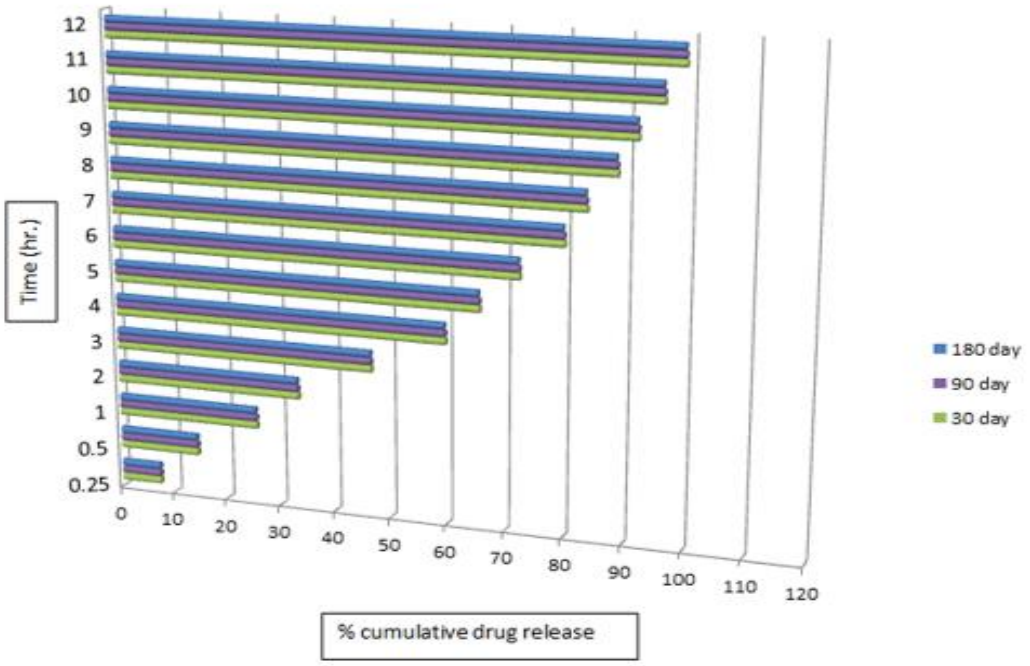

Figure 9: In-vitro drug diffusion studies at 30th, 90th and 120th day of stability study

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7. CONCLUSION

The development of the luliconazole micro sponges embedded gel emulsion solvent diffusion technique marked the successful conclusion of this investigation. The procedure was quick, simple, and repeatable. Upon examination, the created micro sponges were found to be porous, spherical in shape, and white in colour. Drug content, particle size, yield percentage, drug entrapment efficiency, and drug diffusion were among the characteristics that the variation in polymer concentration significantly affected. Excellent properties such as an appropriate pH range, good spread ability, viscosity, extrudability, and swelling index are displayed by the formulation LMG-01. Promising outcomes are seen in the drug content, drug diffusion, permeability, antifungal, and stability investigations. A unique local drug delivery method called micro sponges embedded gel is recommended to increase the therapeutic efficacy of the medications.

Conflict of Interest

The authors declare no conflict of interest.

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None

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