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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation evaluation and development of Econazole Hydrogel by using Solid Dispersion Method

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ABSTRACT
For a medication's local or transdermal action, or for its moisturizing or protective role, topical gel formulations are designed to be administered to the skin or to certain mucosal surfaces. For effective drug administration, to avoid first pass metabolism, and to increase local action for treating skin problems and pain, topical medication delivery can be achieved by incorporating the medicine into the gel matrix. However, when used topically, antifungal medications have excellent antifungal action. This study's objective was to describe solid dispersion technique formulation, development, and assessment of an econazole topical hydrogel. Method: In the current work, an attempt was made to develop a hydrogel-based topical drug delivery system for the medication econazole. The formulation method involved the usage of 9 batches. All of the hydrogel formulations that were created demonstrated acceptable physical characteristics, consistency, spreadability, viscosity, and hydrogel pH. When compared to commercially available econazole medications, the most optimized formulation is F5. Using a Franz diffusion cell and phosphate buffer pH 7.4 as the receptor media, the in-vitro release rate of hydrogel was assessed. It was discovered that the improved F1 formulation's release rate followed the Higuchi Model. At room temperature and under standard settings for one month, the hydrogel was determined to be stable in terms of colour, pH, and drug content.
Keywords: *Lipophilic, Hydrophilic, Polymetric Network, Solid dispersion*

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INTRODUCTION

In three dimensions, hydrogels are hydrophilic polymeric networks that can absorb huge volumes of water or biological fluids. Due to the existence of physical crosslinks, such as entanglements or crystallites, or chemical crosslinks, such as tie-points or junctions, the networks, which are made up of homopolymers or copolymers, are insoluble. The latter offers physical integrity and network structure. These hydrogels' thermodynamic compatibility with water allows them to swell under watery environments [1].

The use of hydrogels in biomedical applications is widespread due to their biological compatibility with human bodies and similarity to real tissue. Hydrogels are become more crucial in pharmacological and biological applications [2]. As a result, they are used in a variety of applications, including those for implanted devices (such contact lenses, biosensors, artificial skin, catheters, and controlled drug delivery systems) and diagnostic and therapeutic procedures [3].

Recent achievements in science and technology have increased the local activity of hydrogel drug delivery systems and helped them overcome physiological obstacles including first pass metabolism. There are several ways to treat fungi nowadays, however studies have been done on the development of transdermal anti-fungal gels using various polymer types. The current study includes the development of Econazole transdermal hydrogels using polymers of both biological and semi-synthetic sources [4].

When water is the dispersion medium, a hydrogel is a configuration of water-insoluble polymer chains that occasionally appears as a colloidal gel4. Hydrogels are very absorbent polymers that can contain over 99% water. They can be made from natural or synthetic materials. Hydrogels also have a degree of flexibility that is quite like that of real tissue because of their high-water content. Hydrogels are crosslinked polymer

networks that can hold a lot of water in liquid form. Hydrogels were essential in the creation of its medication delivery system [5].

The present effort's objective was to create and evaluate topical hydrogel drug delivery systems. An effort has been made to increase drug exposure and absorption to enhance therapy by controlling the pace at which medications release from dosage forms. Agents that promote cross-linking, thickening, or gelling were used to change drug release rates. The ultimate objective was to combine hydrophilic polymers to improve the market formulation and raise the drug's bioavailability [6,7].

MATERIAL AND METHODS

Materials: Econazole was procured from Maharshi Laboratories Pvt. Ltd. Ankaleshwar, Polyethylene glycol (Research Lab Fine Chem Industries, Mumbai), Carbopol 940 (Loba Chemie Pvt. Ltd. Mumbai), Glycerin (Research Lab Fine Chem Industries, Mumbai), Isopropyl Myristate (Research Lab Fine Chem Industries, Mumbai), Triethanolamine (Research Lab Fine Chem Industries, Mumbai), Poloxamer 188 (Research Lab Fine Chem Industries, Mumbai), Sodium Hydroxide (Research Lab Fine Chem Industries, Mumbai) were procured and used in this investigation.

PRE-FORMULATION STUDY:

Examining the physicochemical properties of the pharmacological ingredient both by itself and in combination with excipients is known as pre-formulation research. Identification of physicochemical properties that may influence formulation design, production process, and pharmacokinetics profile of finished product is the aim of preformulation parameter study [8].

Drug Characterization:

A small quantity of drug powder was taken on butter paper and observed in well illuminated place.

- Colour: A little amount of Econazole was taken in butter paper and examined under well lighted area.
- Odour: Small amount of Econazole sample was smelled to get the odour.
- Appearance: A pinch of Econazole was taken between two fingers and appearance was observed.

Determination of melting point:

The melting point of the sample is the first indication of its purity. The open capillary technique was used to determine the melting point of econazole. Through a glass capillary with a flame-sealed aperture, Econazole was delivered. The melting point of the capillary was then measured after it had been inserted into the melting point apparatus.

UV-visible spectrophotometric analysis:

UV spectroscopy in Water:

Method: 10 mg of Econazole was dissolved in 100 ml of solvent (Polymeric solution) to produce 100 µg/ml and spectra was observed.

Calibration Curve in water:

Stock Solution: 10 mg of Econazole was dissolved in 100 ml of solvent to produce 100µg/ml.

Dilutions: From stock solution 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml solution were withdrawn and diluted up to 10ml with solvent to produce 5 ppm, 10 ppm, 15 ppm, 20 ppm and 25 ppm and absorbances were measured at 220nm.

FT-IR of Econazole:

Econazole's IR spectra was captured by the Shimadzu IR Affinity-1. Using potassium bromide (KBr) as a blank, the spectrum was captured with a resolution of 4 cm over a 400–4000 cm range. The principal peaks of the IR spectrum provided in the monograph or literature were compared with the peaks in the spectrum of econazole [8].

FORMULATION OF ECONAZOLE TOPICAL HYDROGEL BY USING SOLID DISPERSION TECHNIQUE:

The topical hydrogel using solid dispersion method by using different proportions were prepared as follows:

- Solid dispersions were made by using econazole with different polymers (PEG 6000 and Poloxamer 188)
- 1, 1.5, 2.0 % concentration of Carbopol 940 colloidal dispersion were prepared using distilled water.
- 2, 3, 4 % Concentration of Polyethylene glycol were mixed with enough water.
- After complete dispersion both the polymer solutions were kept aside for complete swelling.
- Dispersion of polymers were made using magnetic stirrer. After dispersing Carbopol 940 in distilled water, colloidal dispersion of water and polyethylene glycol was added to it under magnetic stirring. 5 % isopropyl myristate and 3 % glycerine were added. And aqueous solution was added to polymeric dispersion after addition of sodium hydroxide solution.
- Finally, after remaining distilled water with solid dispersion added to obtain a homogenous dispersion of gel under magnetic stirring [9,10].

EVALUATION OF SOLID DISPERSION AND TOPICAL ECONAZOLE HYDROGEL.

EVALUATION OF SOLID DISPERSION:

Physical evaluation: Visual observations were used to test the physical evaluation parameters of colour, smell, and appearance of the created solid dispersion.

Determination of percent practical yield: The weight of the dried finished product and the initial weight of the medication and polymer used to create the solid dispersion were used to calculate the percent practical yield of solid dispersions created using various procedures [11].

Saturation solubility study: Using water as the solvent, the solubility research of the solid dispersion was carried out. Both solid dispersion and physical mixture solubility studies were conducted using the shake flask method [12].

Determination of drug content of solid dispersion: Solid dispersion corresponding to 10 mg of Econazole was collected and diluted in 100 ml of methanol for the assay of the medication in solid dispersion. Filtered and further diluted, the solution now falls within the standard curve's range of absorbance. Using a UV-visible double beam spectrophotometer (Shimadzu Corporation, Japan), the absorbance of the solution was evaluated at 220 nm [13].

In vitro dissolution study: Solid dispersions and physical mixes containing 10 mg of Econazole were dissolved in water (900ml) at 50 rpm using a USP type 1 apparatus, basket type (LAB INDIA DS 8000) kept at 370.5°C. For 60 minutes, the sample was extracted at regular intervals. The sink state was maintained by pipetting out 5 ml of dissolve media and refilling the same volume of solvent. Withdrawn material was filtered through 0.45 Whatman filter paper and analysed at 220 nm in a UV-visible double beam spectrophotometer (Shimadzu Corporation, Japan) using water as a blank. The batch with the highest drug release was designated as the optimized batch, and the solid dispersion was characterized [14].

FT-IR spectroscopy: The IR spectrum of the optimized batch was recorded using a Shimadzu IR Affinity Spectrum, with potassium bromide (KBr) as the blank, at a resolution of 4 cm and a range of 400-4000 cm[15].

Differential scanning calorimetry (DSC): The differential scanning calorimetry (DSC) measurement was carried out with the help of a Mettler Toledo Differential scanning calorimeter, which was purchased in Mumbai, India. A 6-7 mg optimized solid dispersion was heated in sealed aluminium pans with nitrogen gas across a temperature range of 100-150 °C, and thermograms were measured at a heating rate of 40 °C/min[16].

X-ray diffraction study: The improved solid dispersion was studied using X-ray diffraction (XRD). To obtain the diffractogram, an Empyrean, Malvern paralytical multifunctional diffractometer with Multicore Optics (United Kingdom) was employed. The sample was examined in the 0-100° angle range [17].

EVALUATION OF TOPICAL ECONAZOLE HYDROGEL:

Physical evaluation: Visual observations were used to assess the physical evaluation characteristics of the manufactured solid dispersion, such as colour, odour, and appearance.

pH determination: The pH meter (Labman pH system LMPH-10) was calibrated with pH 4, 7, and 9 standard buffer solutions. The pH of the Hydrogel was determined after 1 gram of it was weighed and dissolved in 10.0 ml of pure water.

Viscosity determination: The hydrogel's viscosity was measured using a Brookfield Viscometer (Amtech Model Number. LVDVE) at various rpms and spindle number-64. The spindle was revolved at 10, 50, 60, and 100 rpm to determine viscosity (cP) and torque (%). The lower the torque, the higher the viscosity.

Spreadability test: One gram of Hydrogel was placed between two slides. On the upper slide, a 100-gram weight was inserted. Extra formulation was scraped off and the weight was eliminated. The bottom slide was secured to the apparatus's board, and the top slide was secured with a non-flexible string to which a 20g force was applied. The time it took the upper slide to fall off was recorded [9].

$$S = ML/T$$

Determination of drug content of hydrogel: In a 10ml volumetric flask containing 5ml methanol, a hydrogel corresponding to 10 mg of Econazole was placed and the volume was brought up to the mark with methanol to get a concentration of 1000g/ml. An aliquot of 0.1ml was transferred to a 10ml volumetric flask and filled with methanol to achieve a concentration of 10g/ml. The absorbance of the prepared solution was measured using a UV visible spectrophotometer at a maximum wavelength of 220 nm.

In vitro diffusion test: To assess the drug release profile from Hydrogel, a laboratory-assembled equipment mimicking a Franz diffusion cell was employed. Phosphate buffer solution pH 5.8 (PBS) was utilized as the diffusion medium. The donor compartment was filled with 10 mg of the drug containing Hydrogel (1gm), which was separated from the receptor compartment by the cellophane membrane [10].

RESULTS AND DISCUSSION

The purpose of present research work was to create and test topical hydrogel medication delivery systems. Efforts have been made to adjust medicine absorption and exposure by manipulating the rate of drug release from dosage forms in order to enhance pharmacokinetics and pharmacodynamics. Cross-linking, thickening, or gelling agents will be used to control the rate of medicine release.

The ultimate objective is to give patients with acute and elegant dose forms that meet the demand for a steady blood concentration of the medicine, leading in increased adherence to therapy. Topical hydrogels were created using various polymer ratios and then examined.

Econazole topical hydrogels with different polymer: econazole ratios were developed.

From the developed gels, gels with enhanced physicochemical properties were chosen. Table 1 shows the various polymer ratios used to make gels, and Table 7 shows the outcomes of formula optimisation based on the physical properties of the gel.

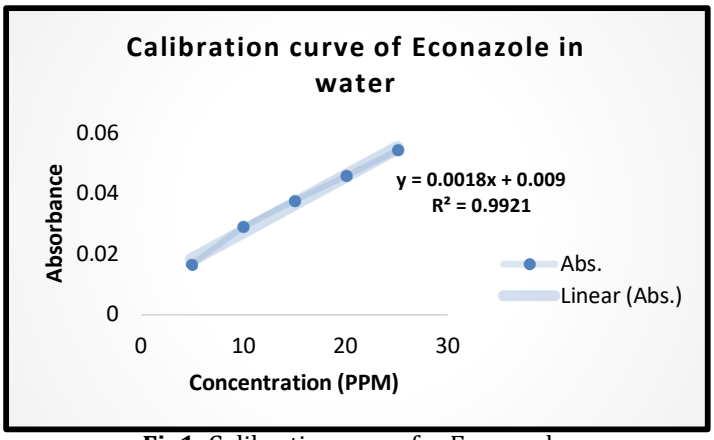

Fig1. Calibration curve for Econazole

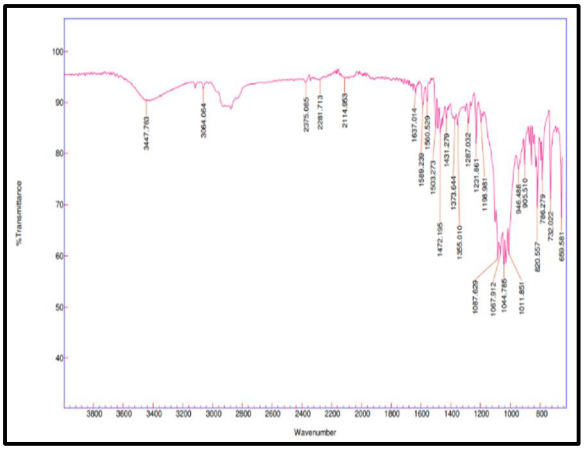

Fig2. IR of pure Econazole

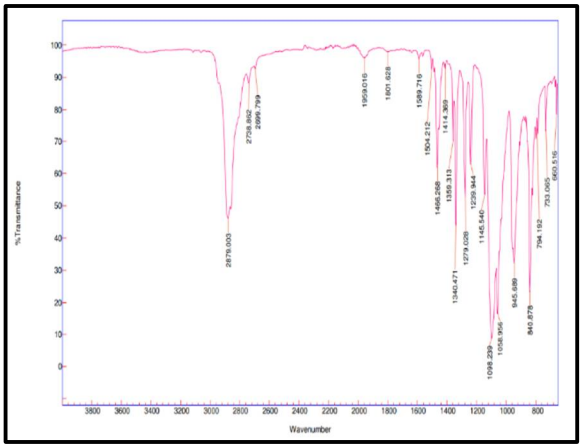

Fig3. IR of Optimized batch

Differential Scanning Calorimetry (DSC) Study: Figure 4 depicts a DSC thermogram of pure medication (Econazole), whereas **Fig. 5** depicts an optimum batch of solid dispersion. The presence of a strong endothermic peak at roughly 86.15^{0}C in pure econazole and 62.640C in optimal solid dispersion batch makes it easy to identify.

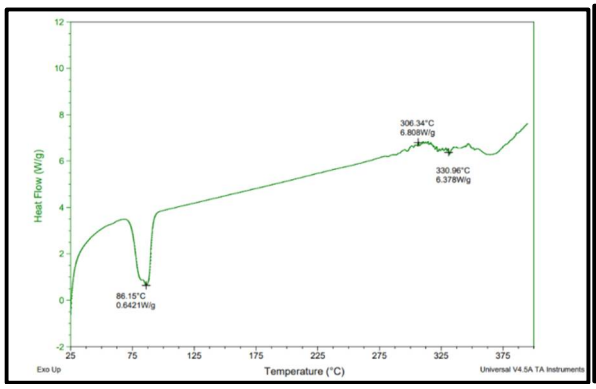

Fig4. DSC of Pure Econazole

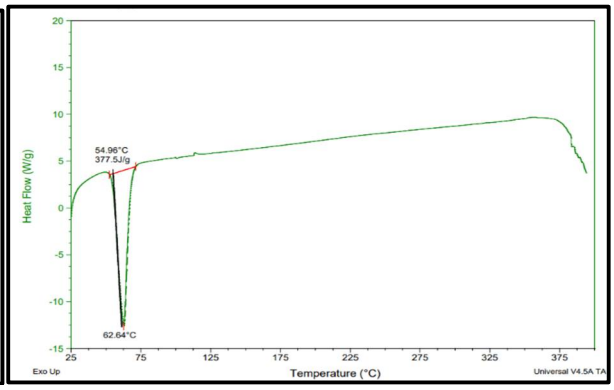

Fig5.DSC of Optimized batch of S.D

X-ray diffraction study: The X-ray diffraction analysis was carried out on both the pure drug sample (Econazole) and the optimized batch of solid dispersion. **Figures 6 and 7** depicts the outcomes. The total number of peaks for the pure drug sample and the optimized solid dispersion batch were determined to be 22 and 10, respectively.

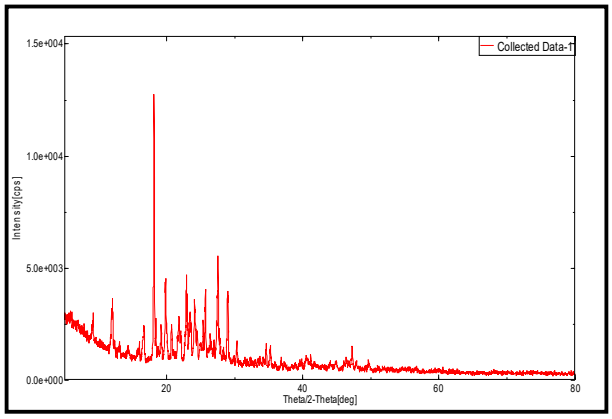

Fig6. XRD of Pure Econazole

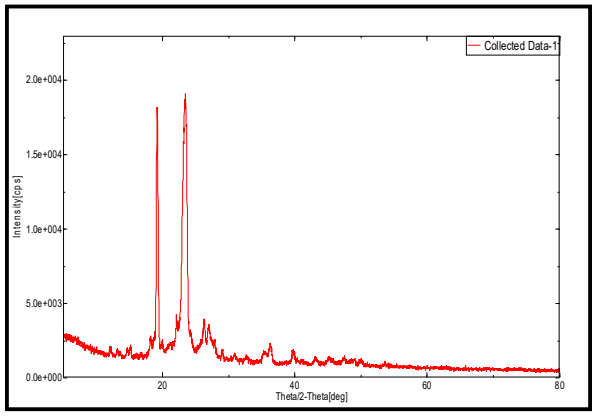

Fig 7. XRD of Optimized solid dispersion of Econazole

Table 1: Composition of Hydrogel (%)

Ingredients (in mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Econazole S. D	1	1	1	1	1	1	1	1	1
Polyethylene Glycol	2	2	2	3	3	3	4	4	4
Carbopol 940	1	1.5	2	1	1.5	2	1	1.5	2
Glycerin	3	3	3	3	3	3	3	3	3
Isopropyl Myristate	5	5	5	5	5	5	5	5	5
Sodium Hydroxide	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

Table 2: Physical characteristics of formulation batches

Batch Code	Colour	Odour	Appearance	pH	Viscosity	Spreadability	Drug content
F1	White	Characteristic	Smooth	5.84 ± 0.1	8212 ± 98	9.2 ± 0.2	97.25
F2	White	Characteristic	Smooth	5.62 ± 0.1	8936 ± 112	8.9 ± 0.1	97.77
F3	White	Characteristic	Viscous	5.75 ± 0.1	9428 ± 84	8.4 ± 0.2	99.84
F4	White	Characteristic	Smooth	5.68 ± 0.1	8471 ± 97	9.1 ± 0.2	100.92
F5	White	Characteristic	Smooth	5.79 ± 0.1	9065 ± 101	9.0 ± 0.2	99.91
F6	White	Characteristic	Viscous	5.85 ± 0.1	9385 ± 85	8.3 ± 0.1	98.15
F7	White	Characteristic	Smooth	5.96 ± 0.1	8684 ± 98	8.9 ± 0.2	100.33
F8	White	Characteristic	Smooth	5.98 ± 0.1	9212 ± 105	8.6 ± 0.1	99.35
F9	White	Characteristic	Viscous	5.89 ± 0.1	9655 ± 85	8.2 ± 0.1	101.92

Determination of % drug diffusion: Drug diffusion was determined to be between 89.13 and 99.11% for all prepared batches. As the viscosity of the formulation rises, the drug diffusion process slows down over time and has a longer impact. According to the results of the in vitro diffusion research, formulations F1 and F2 did not maintain drug release for more than 8 hours. This might be related to the formulations' low viscosity and low quantities of drug release modifying polymers. F4, F5, and F6 formulations provided continuous medication release for 8 hours. Formulations F7 through F9, on the other hand, maintained drug release but did not entirely release the medication. At intermediate polymer levels, drug release was observed to be maintained.

Table 3: Determination of % drug diffusion

Time (Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	16.46	15.58	14.45	15.68	15.28	14.45	14.38	13.45	12.35
2	31.27	29.14	26.69	27.16	28.16	26.69	25.16	25.36	24.69
3	49.79	48.68	42.24	41.05	42.05	39.04	38.35	38.67	36.28
4	65.78	64.78	58.27	56.06	56.36	54.27	52.46	49.72	47.41
5	79.45	77.58	77.39	68.78	67.88	67.59	64.28	61.16	59.25
6	92.28	90.46	88.13	80.28	80.38	76.13	74.78	73.25	70.03
7	98.06	97.02	91.34	90.06	91.16	86.64	85.25	82.67	79.92
8	98.23	97.41	96.74	98.32	99.11	97.33	92.15	91.45	89.13

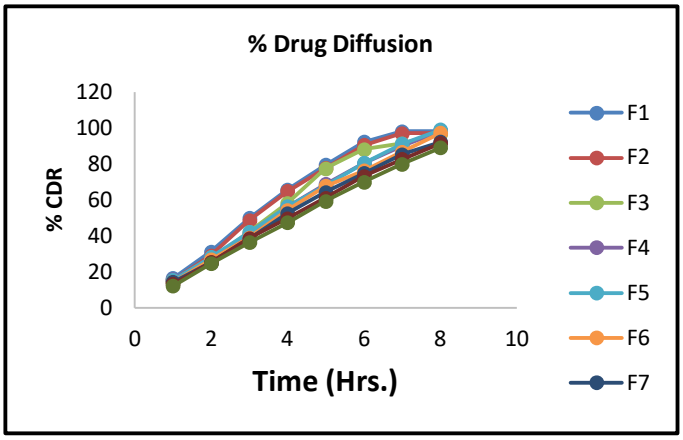

Fig 8. % CDR vs Time for drug diffusion

Antifungal study for optimized batch (F5): The antifungal investigation was carried out in accordance with the standard technique outlined under experimental work. The zone of inhibition for the improved batch was determined to be 34 mm. The zone of inhibition for a conventional antifungal drug (Nystatin) was determined to be 27mm. Based on antifungal findings, it was determined that the optimized batch of film forming gel had enough antifungal efficacy.

Stability study: After a month of stability testing at temperatures ranging from 0 to 40 degrees Celsius, the manufactured Econazole topical hydrogel formulation was confirmed to be stable. There was no significant change in the parameters assessed for colour, pH, and spreadability of formulations.

CONCLUSION

The current work attempted to develop an Econazole topical medication delivery system in the form of a hydrogel. Econazole is a popular antifungal medication that is generally used to treat fungal infections. The sample Econazole was originally identified utilizing physical characterisation tests such as melting point, UV absorption in phosphate buffer 7.4, and FTIR. Polyethylene glycol as a sustained release agent, Carbopol 940 as a gelling agent, Glycerine as a humectant, isopropyl myristate as a penetration enhancer, and sodium hydroxide as a pH adjusting agent were determined to be within the standard limit and in conformity with the findings of these full tests. All formulations were examined for post-formulation investigations such as colour, pH, viscosity, spreadability, drug content, and in-vitro drug release as well as stability tests. And all of the findings were discovered inside the stipulated time limit. The right polymer choices and proportions are required for designing and developing transdermal medication delivery systems. When compared to the commercial formulation, the formed gels demonstrated superior homogeneity, stability, and drug release rates.

Based on its test criteria, the formulation F5 (optimal formulation) of 1.5% Carbopol and 3% polyethylene glycol was deemed to be appropriate for topical application.

DECLARTION OF COMPITING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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