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Original Article

Herbal Nanoparticle-Embedded Film-Forming Spray: A Novel Topical Delivery System for Vitiligo Management

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ABSTRACT

Objectives: This study evaluated a topical film-forming spray designed to improve the skin permeation of curcumin and piperine-loaded nanoparticles, aiming to enhance therapeutic efficacy and reduce dosing frequency for managing vitiligo. **Materials and Methods:** The HPMC E15, Polyethylene glycol 6000 and Eudragit RS100, blended in cold water and ethanol (50:50). Six criteria were utilized for evaluation: drying time, viscosity, appearance, skin effect, stickiness and water washability. The study selected Propylene Glycol (PG) and Polyethylene Glycol (PEG) 400 as plasticizers, with camphor and menthol to enhance penetration. A 3^2 Factorial design was used to optimize the formulation using Polymer concentration (X1) and Plasticizer concentration (X2), focusing on drying time and *in vitro* drug release. The film-forming spray was evaluated. **Results and Discussion:** HPMC E15, in a blend of cold water and ethanol (50:50), satisfies the rating criteria. Increase propylene glycol concentration expands the spray area and preserve elasticity. The FTIR study shows no interaction. The drug content and average weight per dose in all formulated batches range from 93.5% to 95.5% and from 0.078±0.004 g to 0.098±0.002 g, respectively. The drying time ranged from 181.2 to 258 sec. The spray pattern exhibits good uniformity and is nonspherical. Spray angle, pH and leakage test are within acceptable limits. Viscosity ranges between 10648 to 10895 cp and shows good spray ability. The weight, thickness uniformity, folding endurance and tensile strength of the film were found to be satisfactory. All formulations showed drug release range of 82.34% to 96.88%. The TEM images showed irregular, non-porous structure, while XRD confirmed an amorphous nature. **Conclusion:** The developed film-forming spray demonstrated favorable physicochemical properties, enhanced drug release, and stability, indicating its potential as an effective topical delivery system for vitiligo.

Keywords: Curcumin, Piperine, Desolvation Method, Nanoparticles, Film-forming Spray.

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INTRODUCTION

Melanocytes, the cells that produce melanin, are destroyed in vitiligo, a chronic skin condition resulting in pigmentation loss. Because it is visible, this condition causes significant psychological and social distress for people of all ages and ethnicities.[1] Piperine, from black pepper, stimulates melanocyte proliferation and melanogenesis,[2] while curcumin, from turmeric, offers anti-inflammatory and antioxidant benefits, preventing oxidative stress on melanocytes and autoimmune damage. Together, these natural substances have the potential to effective treatment for vitiligo.[3,4]

Current developments in nanotechnology have enabled the development of delivery system-based nanoparticles, increasing the stability and bioavailability of therapeutic compounds.[5] Piperine-curcumin nanoparticles have shown potential in enhancing delivery and efficacy, offering new hope for vitiligo treatment.[6] Topical sprays for nanoparticle delivery provide localized application, reduced systemic side effects, and improved patient compliance. Encapsulating piperine and curcumin in nanoparticles and delivering them via sprays enables precise targeting of affected areas, thereby enhancing repigmentation.[7] This research focuses on developing, characterizing, and evaluating piperine-curcumin nanoparticle-loaded topical sprays to promote melanocyte regeneration and repigmentation, providing a promising solution for vitiligo management.[8,9]

MATERIALS AND METHODS

Material

Curcumin-Piperine Nanoparticles were prepared using sodium alginate and HPMC E15 as polymers, ethanol as a desolvating agent, glutaraldehyde for cross-linking, and propylene glycol as a plasticizer. Camphor and menthol acted as penetration

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enhancers. All reagents were of analytical grade, sourced from SDFCL, Mumbai, India.

Fabrication of Curcumin-Piperine Nanoparticles by Desolvation technique

Polymeric nanoparticles embedded with curcumin and piperine were synthesized using the desolvation method. A predetermined quantity of curcumin and piperine was incorporated into polymers such as sodium alginate, forming a 1% polymer solution with the pH adjusted to 7. The curcumin-piperine mixture was combined with 20 mL of ethanol (serving as the desolvating agent) and sonicated for 20 min. Subsequently, the desolvating agent was gradually introduced into 40 mL of polymeric solution while being continuously stirred mechanically at 800 rpm with the onset of turbidity marking the endpoint of the process. 0.3 mL of 25% glutaraldehyde was added as a cross-linking agent to stabilize the nanoparticle dispersion, and the mixture was agitated for 12 hr. The rotary evaporation was used to remove the solvent and aqueous components, free-flowing nanoparticles were obtained and further characterizations are performed.[10]

Screening of polymers

Different concentrations of HPMC E15, Polyethylene glycol 6000 and Eudragit RS100 were added to cold water and ethanol (50:50) to formulate film-forming solutions to ensure that polymers were completely dissolved. The solution was stirred constantly for about 6 to 8 hr.[11-13] The viscosity, drying time, stickiness, appearance of each polymer solution, and the films water washability and skin integrity were assessed after 12 hr of application. The formulations labelled as S1-S3 contained Eudragit RS100, HPMC E15 and Polyethylene Glycol 6000.

Screening of plasticizer

In the process of film formation, plasticizers play a critical role in maintaining elasticity and preventing the occurrence of film cracking. Additionally, they contribute to the stabilization of active pharmaceutical ingredients and enhance drug permeation. Propylene Glycol (PG) and Polyethylene Glycol (PEG) 400 were chosen as plasticizer for this study.[14,15] The plasticizer was incorporated into the polymeric solution, and the resulting film was assessed for tensile strength to determine the most suitable plasticizer for optimal film performance.

Screening of penetration enhancer

In this study, camphor, menthol, and their combination are used as penetration enhancers. The polymeric solvents system compromised propylene glycol, HPMC E15, and curcumin-piperine loaded nanoparticles in a 50:50 water-ethanol ratio, with each enhancer at a 0.5% concentration. Assessed the solution for flux, permeability coefficient, and *ex vivo* permeation studies.[16,17]

Optimization was performed using Design of Experiments (DoE)

The formulations were meticulously designed using a 3^2 full factorial approach, facilitating a comprehensive evaluation of two formulation variables and their interactive effects, as detailed in Table 1. This experimental framework provides a systematic representation of the formulations and their respective parameters. The study prioritized two critical dependent variables: drying time (Y_1) and percentage drug release (Y_2), to assess the performance of the formulations.[18,19]

Formulation of optimized film-forming solution

The weighed Polymer HPMC E15 with different concentration and Cur-Pip loaded nanoparticles were dissolved in cold water and ethanol (50:50) stirred for 2 hr at 100-120 rpm using magnetic stirrer, then the polymeric solution was mixed with a eutectic combination of camphor and menthol (1:1) to improve penetration.[20] The polymeric mixture is mixed with propylene glycol, a plasticizer, and stirred for 20 min. A refillable container with a plastic dip tube measuring (16 cm) 160 mm length and (4 cm) 40 mm diameter was filled with resultant solution.

Characterization and Assessment of the Developed Film-forming Spray

FTIR (Fourier Transform Infrared Spectroscopy)

To investigate the interactions of constituents in the formulations, drug-excipient interaction studies were performed using Fourier Transform Infrared (FTIR) spectroscopy with a Shimadzu FTIR instrument and KBr pellet method.[21] Samples and KBr were mixed in a 1:100 ratio, ground for even distribution, and then pressed into a disk under 5 tons of pressure for 5 min. This pellet was analyzed within the wave range of 400 to 4000 cm^{-1}.

Average Weight per Dose

The initial weight of the container was recorded and weighed again after applying the film-forming spray five times in succession. We calculated the average weight per dose by dividing the difference between the container's distinctive and final weight by the number of applications.[22]

$$Average\ weight\ per\ dose(W) = \frac{\{initial\ weight\ (W0) - final\ weight\ (W1)}{number\ of\ deliveries\ (N)} \quad \text{..... (1)}$$

Drug Content

Drug content was evaluated by dissolving a 1x1 cm^2 film in pH 7.0 buffer, stirring at 60-80 rpm for 1 hr at 35±2°C, and analyzing at 366 nm using a Shimadzu UV1900i.[23]

Drying Time

The drying time can be observed directly when a when film forming solution is applied to the skin. A glass plate was positioned against the film to check for drying. Note the drying time.[24]

Spray Pattern

The spray patterns were assessed by applying the formulation onto paper from a distance of 2.5 to 3.0 cm from the nozzle. The diameters of the spots were measured after three applications, and the average was calculated.[25]

Spray angle

This study utilized the spray impingement technique, using a sheet of white paper as the target surface. The spray was directed onto the paper, which was positioned at a fixed distance of 15 cm from the nizzle.[26] The radius of the resulting circular spray pattern was measured from multiple angles. This procedure was repeated three times, and the average of the measurements was recoded. The spray angles were then calculated using the following formula:

$$Spray\ angle\ (\theta) = tan^{-1}h/r \ldots\ldots\ldots\ldots\ldots\ldots \textbf{(2)}$$

pH of formulation

A Systronic Electrode pH meter was used to measure the pH of the formulation.[27]

Leak test

The test assessed the effectiveness of the pump seal in preventing product leakage and ensuring proper containment. To check for leaks, the filled test containers are left upright at 30° angle for three days. The container was weighed both before and after this three-day period to determine if any formulation had leaked out.[27]

Viscosity

The viscosity of the solutions was quantitatively measured at 25±1°C using a Brookfield LV model (DV-E Viscometer). The viscosity was measured using LV spindle number 64, rotating at 50 rpm.[28]

Weight Uniformity of Film

A random selection of 1 cm^2 films made from each batch, and film was weighed separately on an electronic balance after being cut at five different locations within the caste film. Noted the average weight of each formulation of film (n=6).[29]

Thickness Film

A digital screw gauge was utilized to measure the thickness of the drug-loaded films. Measurements was taken at six different locations on each film, and the average thickness was calculated.[30]

Folding Endurance

Folding endurance is a quantitative method used to evaluate the flexibility of a film. A small strip of the film measuring approximately 2x2 cm^2, is repeatedly folded at the same point until it breaks. The folding endurance is determined by counting the number of times the film can be folded at that same spot without tearing.[31]

Tensile strength

The tensile strength of the films was measured using a universal strength testing machine with a sensitivity of 1 g. The apparatus featured two load cell grips-a fixed lower grip and a movable upper grip. A test film strip measuring 4x1 cm^2 was positioned between the grips, and a gradual force was applied until the film ruptured. The tensile strength was directly recorded from the dial reading.[32]

In vitro release study

A cellophane membrane was used to cover the diffusion cell. The receptor chamber was filled with 50 mL of phosphate buffer (pH 7.0), while the donor chamber (upper reservoir) contained 1 mL of the formulation solution. The setup was maintained at 35±2°C and run for 24 hr. At predetermined intervals, 2 mL samples were withdrawn from the receptor compartment. After each withdrawal, a fresh phosphate buffer was replenished to maintain sink conditions. Drug concentrations in the collected samples were analysed using UV spectrophotometry at 366 nm.[33,34]

Kinetic Release Study

The data obtained from the *in vitro* release studies were evaluated using various kinetic models, including the Korsmeyer-Peppas, Higuchi, Zero-order, and first-order equations.

Ex vivo Diffusion Study

Goat skin, preserved in phosphate-buffered saline, was used after the underlying tissues were removed to isolate the epithelial membrane. A diffusion cell with a permeation area of 4.15 cm^2 was employed, with the formulation applied to the dermal side and phosphate buffer (pH 7.4) present in the receptor compartment. The setup is at 50 rpm. At intervals of up to 24 hr, 1mL samples were withdrawn and replaced with fresh buffer to maintain sink conditions. Drug release was analyzed using UV spectrophotometry at a wavelength of 366 nm, and cumulative permeability was plotted as the mean±standard deviation from three trials.[35]

Permeability Coefficient

The Permeability coefficient (P) represents the rate at which the drug traverses the membrane, expressed in cm/hr. It was determined from the slope of the plot of the percentage of drug permeated versus time using the following equation:[35]

$$P = \frac{Slope\ x\ Vd}{S} \ldots\ldots\ldots\ldots\ldots\ldots \textbf{(3)}$$

Where: *Vd* refers to the Volume of the donor phase, and *S* denotes the surface area of the membrane through which diffusion occurs.

Flux

Flux (J) represents the rate at which the drug diffuses across a unit area of the membrane over a given time.[35] It is determined using the following equation,

$$Flux\ (J) = P\ x\ CD \ldots\ldots\ldots\ldots (4)$$

Where: P = Permeability co-efficient, and CD = concentration of donor solution.

Enhancement Ratio

The impact of a permeation enhancer on the diffusion and permeation of the selected drug was evaluated.[35] The Enhancement Ratio (ER) was calculated using the following formula:

$$ER = \frac{Permeability\ coefficient\ with\ enhancer}{permeability\ coefficient\ without\ enhancer} \ldots\ldots\ldots\ldots (5)$$

X-ray Diffraction (XRD)

XRD analysis was performed at room temperature using a Bruker D8 Advance diffractometer equipped with Cu-Kα radiation. A LYNEXEYE XE-T detector and monochromated Kβ radiation were employed to scan both the pure drug and film samples across a 2θ range of 3° to 50°.[36]

Transmission Electron Microscopy

High-resolution TEM analysis was carried out using a JEOL JEM-2100 microscope operating at 200 Kv, equipped with a LaB6 electron gun. The instrument offers a point resolution of 0.23 nm and a lattice resolution of 0.14 nm. Selected Area Electron Diffraction (SAED) was also employed to examine the films microscopic morphology, surface texture, and uniformity.[37,38]

RESULTS AND DISCUSSION

Particle Size, PDI, Zeta Potential, Drug Content, and Entrapment Efficiency

Curcumin-Piperine-loaded sodium alginate nanoparticles had an average size of 168.5 nm, as measured using DLS (Malvern Zetasizer, ver.7.13, MAL1200116). The polydispersity index was 0.422, indicating moderate size distribution. The zeta potential was -57.9 mV, indicating good stability. The drug content of the nanoparticles was found to be 70%, while the drug entrapment efficiency was 79%, suggesting effective encapsulation of the active phytoconstituents within the polymer matrix.

Scanning Electron Microscope (SEM) Analysis

SEM analysis conducted at Cochin University, Kochi, Kerala, confirmed that the nanoparticles prepared by the desolvation method were irregular in shape and non-porous. At higher magnification (X5,000, the surface appeared rough with variable particle sizes, indicating heterogeneity. At lower magnification (X1,500), scattered crystalline structures were observed, suggesting the presence of unencapsulated drugs (Figure 1). The observed aggregation may be attributed to high surface energy and insufficient stabilizers, which promote particle clustering and affect formulation stability.

Formulation development and optimization of curcumin piperine nanoparticles loaded topical spray

Assessment of the different polymeric solution

The film-forming polymeric solutions were evaluated based on six key rating parameters: viscosity, drying time, appearance, stickiness, integrity, and washability. Parameter I showed low viscosity, fast drying, good appearance, low stickiness, strong flexible film, and easy washability. Parameter II had moderated results with medium viscosity, drying time, appearance, and washability and showed slight cracks. Parameter III performed poorly, exhibiting high viscosity, slow drying, poor appearance, high stickiness, weak or absent film, and was hard to wash off.

Preliminary Selection of polymer and solvent

A preliminary solvent screening revealed that a 50:50 cold water and ethanol blend demonstrated higher solubility and faster film formation (under 5 min) for a topical solution. Among the tested polymeric solutions, batch S1, formulated with HPMC E15, showed superior performance compared to batches S2 and S3. S1 achieved the fastest drying time (198-540 sec), low stickiness, and low viscosity. Additionally, it produced shiny, transparent films with complete polymer dissolution in the solvent system. In integrity tests after 12 hr, S1 maintained strength and flexibility without cracking or flaking, unlike S2 and S3. S1 also exhibited excellent water washability due to its high-water affinity. These consistent top ratings across all evaluation criteria led to the

Table 1: Parameters used for three square factorial design.

Independent variables	Levels		
	(-1) Low	(0) Medium	(+1) High
Polymer concentration (%)	4	5	6
Plasticizer %	5	7.5	10
Dependent variables	Drying time in seconds (Y_1) Drug release in % (Y_2)		

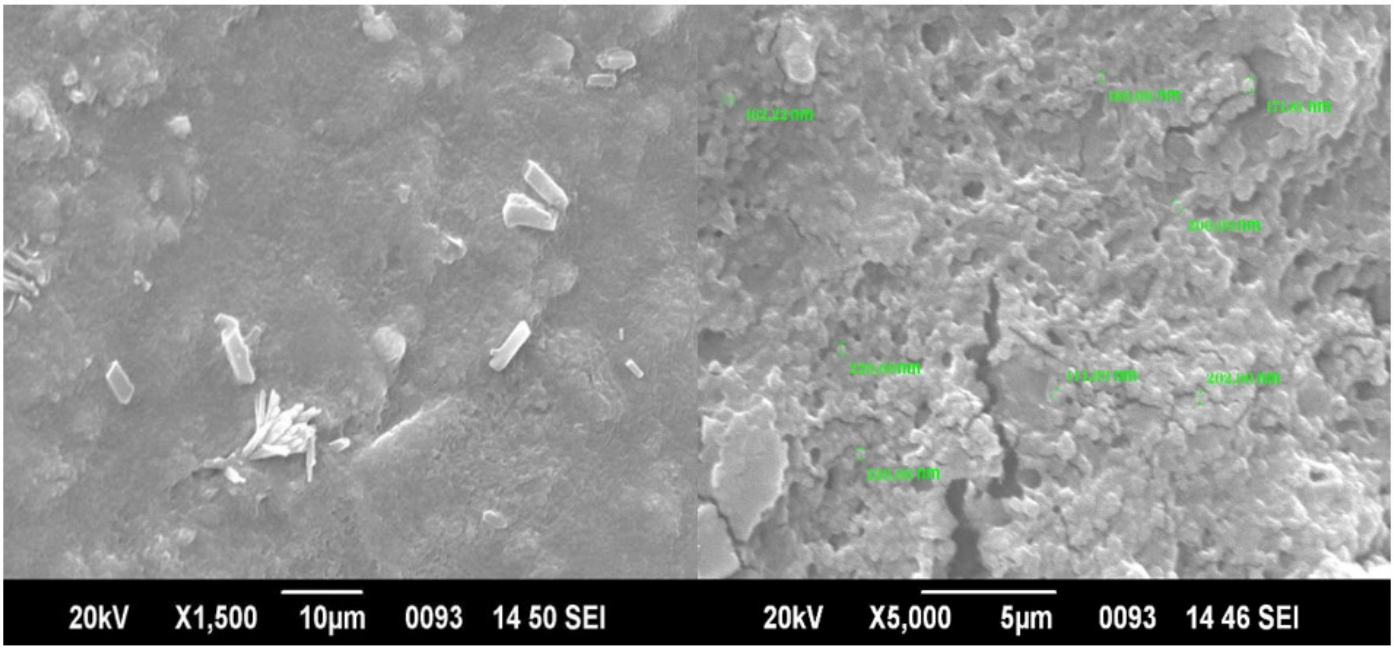

Figure 1: SEM analysis of Nanoparticles.

selection of batch S1 as the most promising film for further development. Batch S1, formulated with HPMC E15, was identified as the most suitable film-forming agent based on its consistent top rating (score I) across all evaluation criteria in the screening study.

Selection of Plasticizer

PEG 400 in a water-ethanol mix produce an unsatisfactory film, indicating incompatibility. Propylene glycol improved spray volume and coverage while maintaining film elasticity at higher concentrations.

Selection of Penetration Enhancer

Camphor, Menthol, and their 1:1 combination (each at 0.5%) were evaluated as penetration enhancers based on *ex vivo* permeation studies. Parameters assessed included drug permeation, flux, permeability coefficient, and enhancement ratio (Table 2, Figure 2). Camphor: Menthol exhibited the highest drug permeation (90.88% at 24 hr), flux (7.9±0.15 µg/cm^2/hr), and permeability coefficient (0.79±0.07 cm^2/hr), with an enhancement ratio of 1.92. Thus, the camphor: menthol blend was selected as the most effective enhancer.

Optimization of formulation variables

To optimize formulation variables, a 3^2 full factorial design was used, with drying time and percentage of drug release as dependent variables and polymer concentration and plasticizer concentration as independent variables at three levels each. Table 3 displays the coded and actual values of three levels of independent variables, a 3^2 factorial design from Expert Version 13.0 software, which identified nine experiments with polynomial equations for each response explained the main interaction, quadratic, and linear effects.

To determine the importance of each variable and the effects of their interactions, an ANOVA (Analysis of Variance) was utilized. ANOVA results for the Response Surface Quadratic model concerning Response 1, which relates to drying time and the linear model for Response 2, which pertains to drug release, respectively.

The high F-value (29.94) for drying time confirms the models significant (p< 0.05). Factors A, B, AB, and A^2 significant effects. Drying time, while B^2 is not significant.

The complete regression equation for drying time, expressed using coded variables, as follows:

$$\text{Drying Time} = +198.37-31.17*A-0.833*B-2.95*AB+15.48*A^2+9.48*B^2$$

The ANOVA results demonstrate the suitability of the linear model for drug release. For response 2 (Drug release), the models F-value of 29.36 indicates strong statistical significance, with only a 0.02% chance that such a result could occur due to variation. In this analysis, both A and B are identified as significant model factors (p<0.05).

The complete regression equation for drug release, expressed using coded variables, is as follows:

$$\text{Drug Release} = +90.52+5.75*A+0.1500*B$$

The regression model was used to generate contour and 3D surface plots for drying time and drug release (Figures 3a and 3b) and an overlay plot (Figure 3c). Analysis of interactions of the

Table 2: Comparison of Flux, Permeability Coefficient, and Enhancement Ratio for various Penetration Enhancers.

Parameters	Without Enhancer	Menthol	Camphor	Camphor: Menthol
Flux (μg/cm²/hr)	4.1	4.9	6.21	7.9
Permeability coefficient (cm²/hr)	0.41	0.49	0.62	0.79
Enhancement ratio		1.19	1.51	1.92

Table 3: 3² Factorial Design of curcumin-piperine nanoparticles loaded film forming spray with Independent and Dependent Variables.

Formulation batches	X1	X2	Concentration of polymer (%)	Concentration of plasticizer (%)	Drying time (s)	Drug release (%)
	Coded values					
FCPS1	-1	-1	4	5.0	258.0±1.15	86.1±1.52
FCPS2	-1	1	4	10.0	256.0±0.25	82.3±1.23
FCPS3	-1	0	4	7.5	240.0±1.68	84.2±1.11
FCPS4	0	+1	5	10	214.8±1.12	93.6±0.25
FCPS5	0	-1	5	5.0	204.0±0.45	91.2±0.48
FCPS6	0	0	5	7.5	198.0±0.47	90.8±0.52
FCPS7	1	-1	6	5.0	195.0±0.18	94.5±0.47
FCPS8	1	0	6	7.5	190.8±0.68	95.8±0.95
FCPS9	1	+1	6	10.0	181.2±1.12	96.8±1.02

Mean±SD, *n*=3.

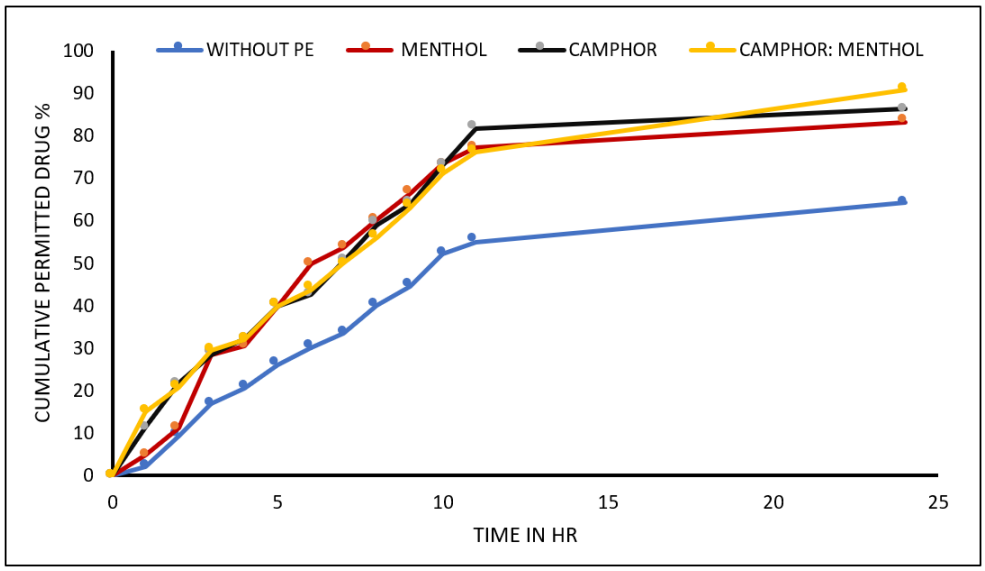

Figure 2: Cumulative Drug Release Profile Using Different Enhancement Ratio for various Penetration Enhancers.

independent factors was done. The counter plots and 3D surface plots showed that the polymer and plasticizer concentration increased, the drying time decreased, and linearity was observed in drug release as an increase in release was observed with increased concentration of polymer and plasticizer.

Experimental validation of design space

The overlay plot shows the design space required to achieve the desired response based on three checkpoint batches recommended by the Design of Experiments (DoE) software. The experimental values for drying time and drug release closely matched the predicted values, validating the reliability of the optimization process.

Fourier Transfer Infrared Spectroscopy (FTIR) Evaluation Component Compatibility

The FTIR spectra of Curcumin, Piperine, their Nanoparticles (NPs), and the nanoparticle-loaded polymeric film show distinct

characteristics peaks without significant shifts. This indicates that there were no major chemical interactions between the drug components and the excipients used in the formulation. Therefore, the integrity and compatibility of their ingredient were retained in the final formulation shown in Figure 3d.

Characterization and evaluation of topical spray

The average weight per dose and drug content in all the formulated batches (FCPNS1 to FCPNS9) ranges from 0.078±0.004 to 0.098±0.002 g and 93.5% to 95.5%, respectively. The drying time for formulations was found to be 181.2 to 258 sec to dry. Spray pattern for all formulations exhibits the good uniformity and nonspherical patterns due to viscosity, which increases the coverage area. The spray angle for all formulations ranges from 74.6° to 84.47° and the spray angle should be less than 85° for easy, even coverage, reducing overspray and waste. The pH of all formulations ranges between 5 to 6, which is very close to the skin pH making it even more suitable for sensitive skin and

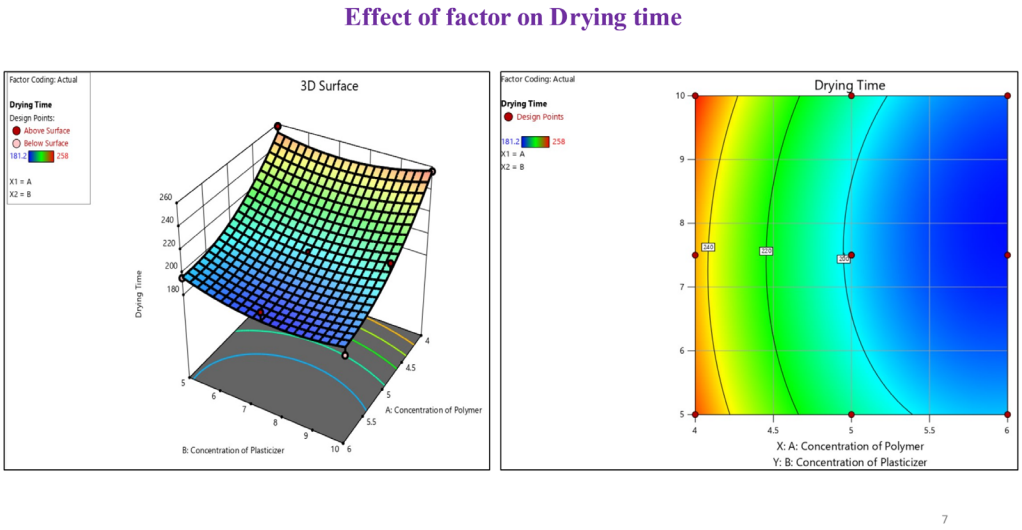

Figure 3a: Contour and 3D Surface Plots Representing Drying Time.

Table 4a: Average Weight Per Dose, Drying time, Spray pattern, Spray angel, pH, Leakage test and Viscosity of Film Forming Spray.

Formulation code	Average Weight Per Dose (g± SD)	Drug content	Drying Time (s± SD)	Spraying pattern	Spray Angle (θ± SD)	pH	Leakage Test %	Viscosity cp
FCPS1	0.098± 0.002	93.14 ±0.21	258.0± 1.05	Uniform, non-spherical	80.53± 0.50	5.8	0.02	10648
FCPS2	0.095±0.002	95.4 ±1.02	256.2± 1.50	Uniform, non-spherical	81.83± 0.26	5.6	0.01	10692
FCPS3	0.094±0.002	93.05 ±1.42	240.0± 0.40	Uniform, non-spherical	82.59± 0.28	5.5	0.03	10784
FCPS4	0.078±0.004	94.4 ±1.20	214.8± 0.93	Uniform, non-spherical	82.40± 0.68	6.0	0.01	10674
FCPS5	0.080±0.004	95.0 ±1.25	204.0± 0.53	Uniform, non-spherical	84.09± 0.99	5.0	0.02	10651
FCPS6	0.085±0.005	93.2 ±0.84	198.0± 1.32	Uniform, non-spherical	84.47± 0.39	5.0	0.02	10777
FCPS7	0.095±0.006	93.7± 0.77	195.0± 0.50	Uniform, non-spherical	80.3± 0.61	5.0	0.02	10760
FCPS8	0.094±0.002	94.9± 1.07	190.8± 1.06	Uniform, non-spherical	75.8± 0.11	6.0	0.01	10759
FCPS9	0.085±0.002	95.05 ±2.01	181.2± 1.02	Uniform, non-spherical	74.6± 0.18	6.0	0.01	10895

Mean±SD, n=3.

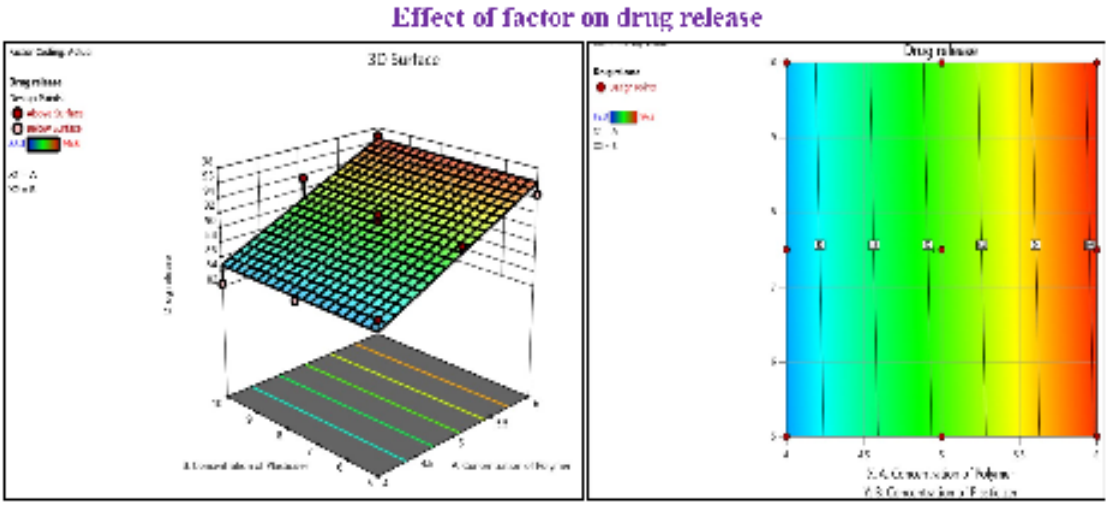

Figure 3b: Contour and 3D Surface Plots Representing Drug Release.

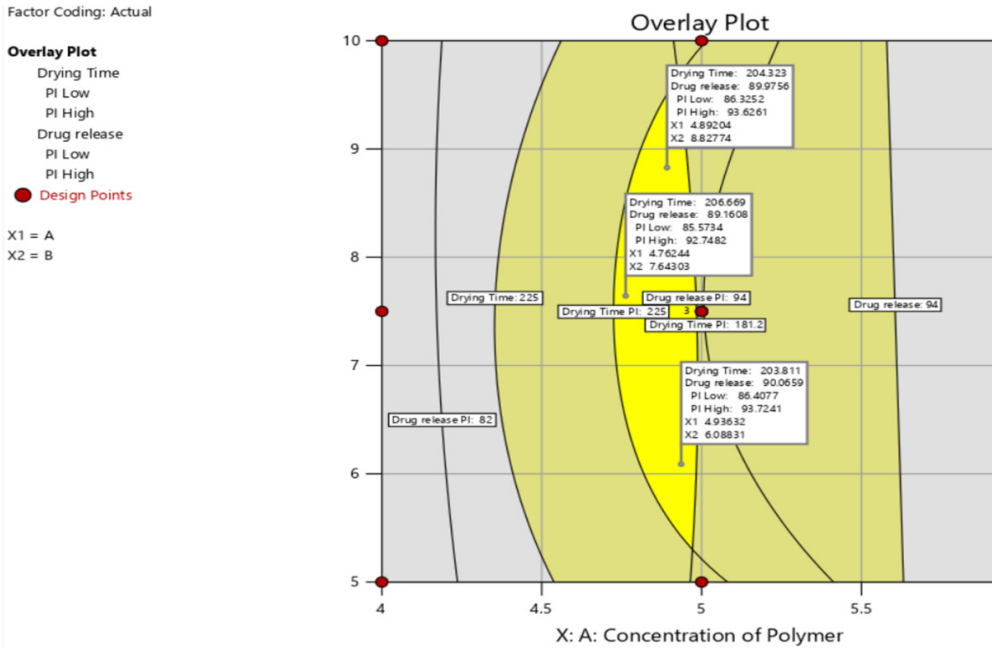

Figure 3c: Overlay plot for formulation variables optimization.

Table 4b: Weight Uniformity, Thickness, Folding Endurance and Tensile strength of Polymeric Film.

Formulation Code	Weight uniformity (mg) ±SD	Thickness (mm± SD)	Folding Endurance ±SD	Tensile strength (Kg/ sq mm)
FCPS1	0.0418±0.0027	0.056± 0.0049	240± 2.08	0.53±0.22
FCPS2	0.0422±0.0044	0.058±0.0067	245±2.51	0.57±0.12
FCPS3	0.0503±0.0018	0.063±0.0043	248±0.57	0.66±0.18
FCPS4	0.0466±0.0029	0.057±0.0010	244±2.51	0.59±0.24
FCPS5	0.0512±0.011	0.069±0.0030	259±1.52	0.67±0.14
FCPS6	0.0624±0.0041	0.074±0.0023	262±2.0	0.71±0.36
FCPS7	0.0496±0.0027	0.059±0.0042	250±1.0	0.56±0.28
FCPS8	0.0542± 0.0019	0.068±0.0032	249±2.64	0.64±0.08
FCPS9	0.0608±0.0019	0.078±0.0014	251±1.73	0.69±0.16

Mean±SD, n=3.

reducing skin irritation. A negligible leakage of 0.01% to 0.03% occurred from a spray container placed upright for three days at 30°. Viscosity measurements with a Brookfield viscometer ranged from 10,648 to 10,895 cp. Indicating good spreadability, as shown in Table 4a.

Weight uniformity, Thickness, Folding Endurance and Tensile Strength of Film

All films (FCPS1-FCPS9) showed weight (0.0418±0.0027 to 0.0624±0.0041mg), thickness (0.056±0.0049 to 0.078±0.0014 mm), increasing with higher polymer concentration. Folding endurance (240±2.08 to 262±2.00) and tensile strength (0.53±0.22 to 0.70±0.36 kg/sq mm) were satisfactory, with improved strength attributed to hydrogen bonding between polymer and drug, as shown in Table 4b.

In vitro Diffusion Profile

All formulations (FCPS1-FCPS9) showed sustained drug release over 24 hr, with cumulative release ranging from 84.26% to 96.88%. FCPS9 exhibited the highest release, suggesting an optimal polymer concentration and a strong drug-polymer interaction, as shown in Figure 4a.

Drug Release Kinetics

Drug release followed the Korsmeyer-Peppas model best (R^2=0.999), indicating a diffusion-controlled mechanism. The Higuchi model also showed a good fit (R^2=0.959), while lower R^2 values for the zero and first order models suggest less accurate fitting, as shown in Figure 4b.

Ex vivo Permeation Profile

The *ex vivo* permeation study revealed that the curcumin-piperine nanoparticle-loaded film-forming spray showed significantly enhanced drug permeation compared to pure piperine and curcumin sprays (80.52% and 61.02%, respectively). After 24 hr, the nanoparticle-loaded spray achieved the highest cumulative permeation (89.77%), indicating an improved skin permeation ability. Flux and permeability coefficients were also highest for the Curcumin piperine nanoparticle-loaded film-forming spray formulation. The enhancement ratios (1.29 for curcumin and 1.08 for piperine) confirm improved topical delivery from the formulation, as shown in Figure 4c. While the ex vivo model reflects a static equilibrium system using isolated skin tissue, it provides relevant preliminary insights into the potential dynamic behaviour of the formulation under *in vivo* conditions, particularly regarding drug diffusion, retention, and permeation enhancement through the stratum corneum.

X-ray Diffraction

The characterization of FCPNS3 was carried out. It was found that the 2θ of 10° to 80° diffraction of the film shown plane of 20 confirmed that amorphous nature. The outlined peaks 2θ of 10° to 80° show poor periodicity, as shown in Figure 4d.

Transmission Electron Microscope

The HR-TEM analysis of the curcumin and piperine nanoparticle-loaded film revealed uniformly distributed, spherical nanoparticles, indicating successful nanoformulation and embedding within the film matrix. The SAED pattern displayed distinct concentric rings, confirming the polycrystalline of the nanoparticles, as shown in Figure 4e.

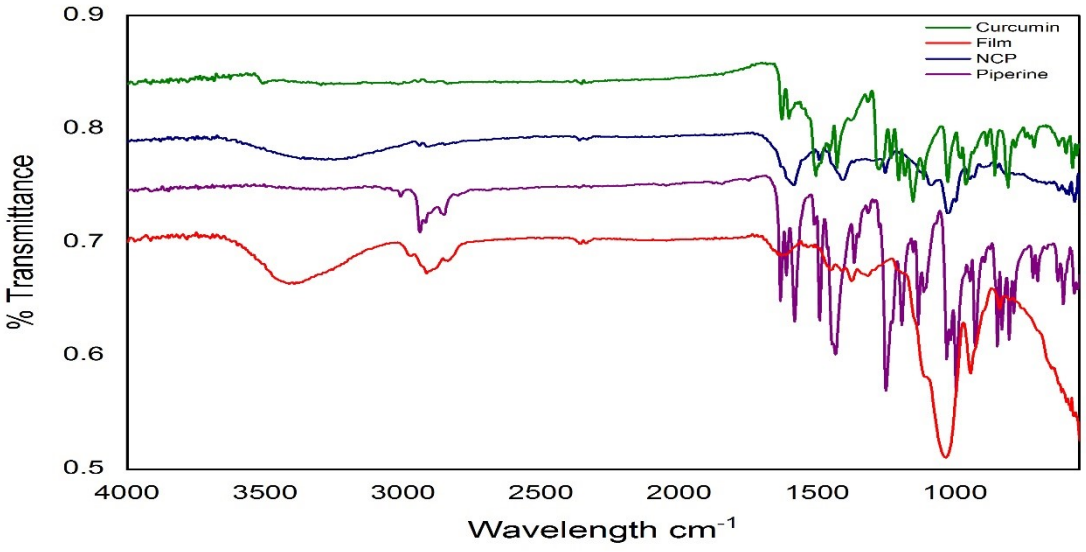

Figure 3d: FTIR of extracted curcumin, piperine, curcumin and piperine loaded Nanoparticle and curcumin piperine nanoparticle loaded polymeric film.

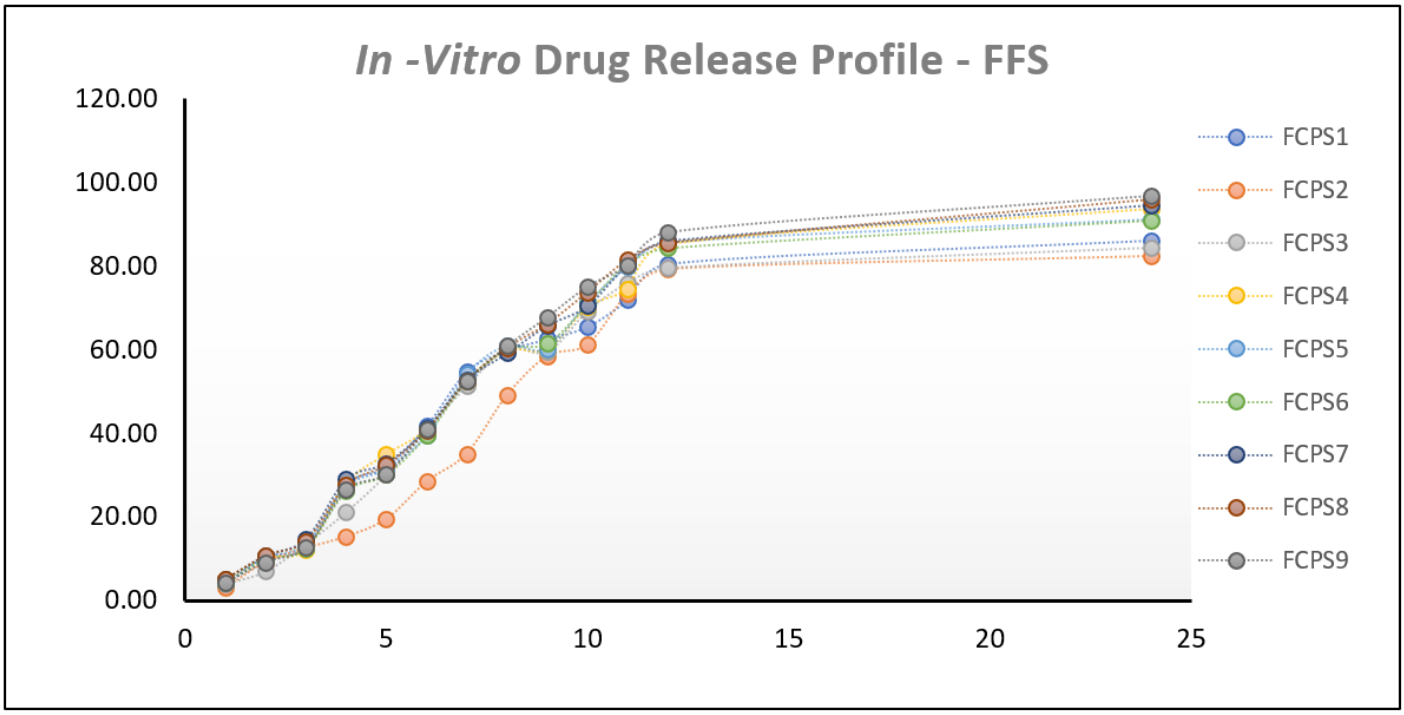

Figure 4a: *In vitro* diffusion profile for FCPNS1 to FCPNS9.

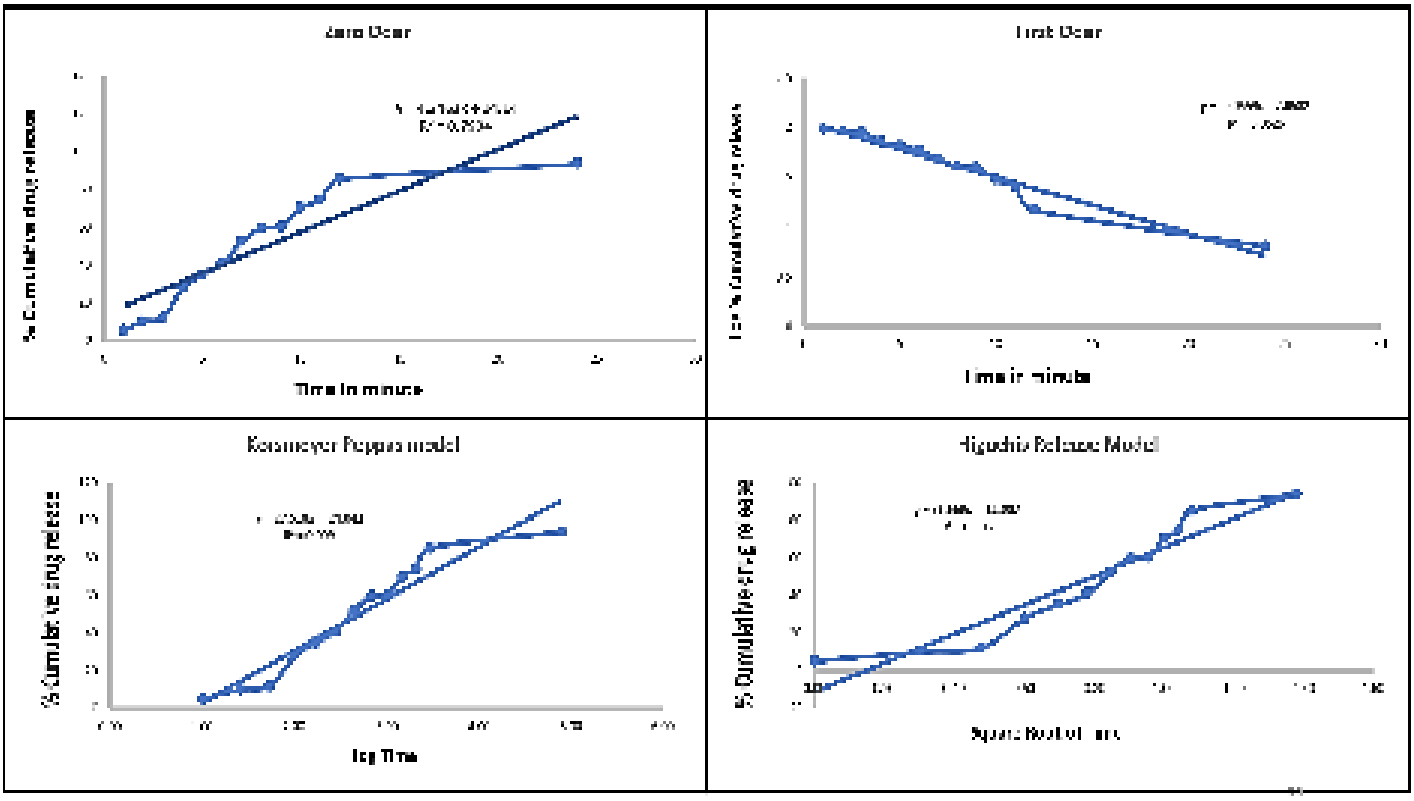

Figure 4b: Kinetic release of prepared FCPNS.

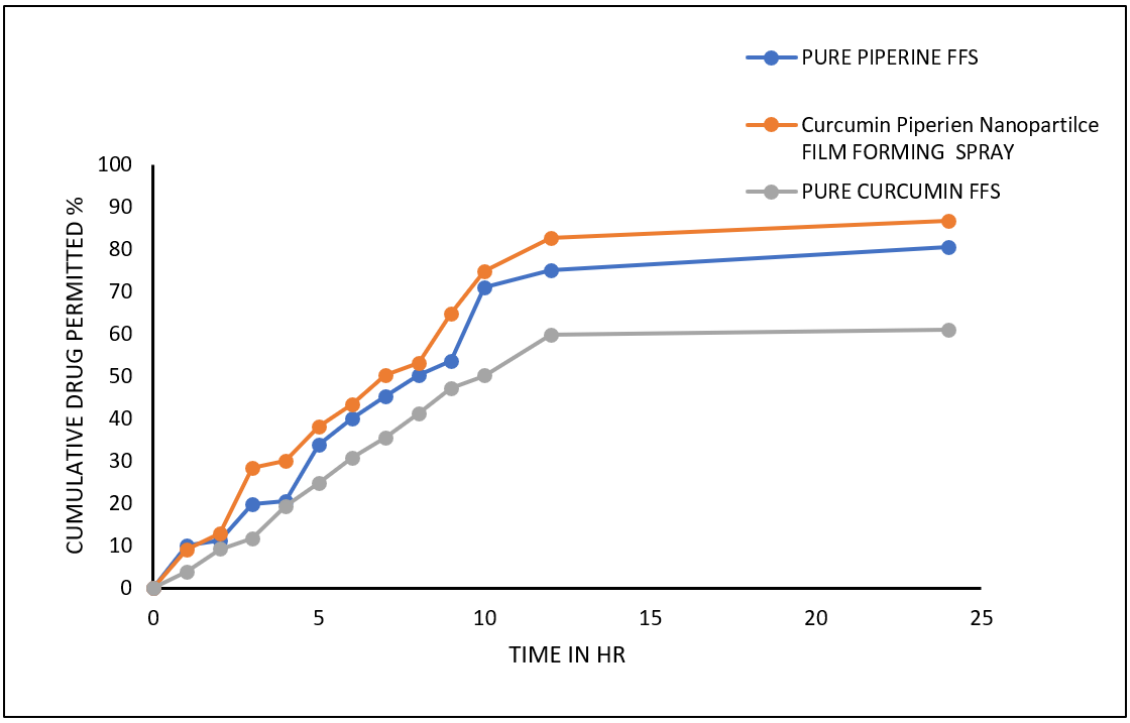

Figure 4c: *Ex vivo* Permeation Study.

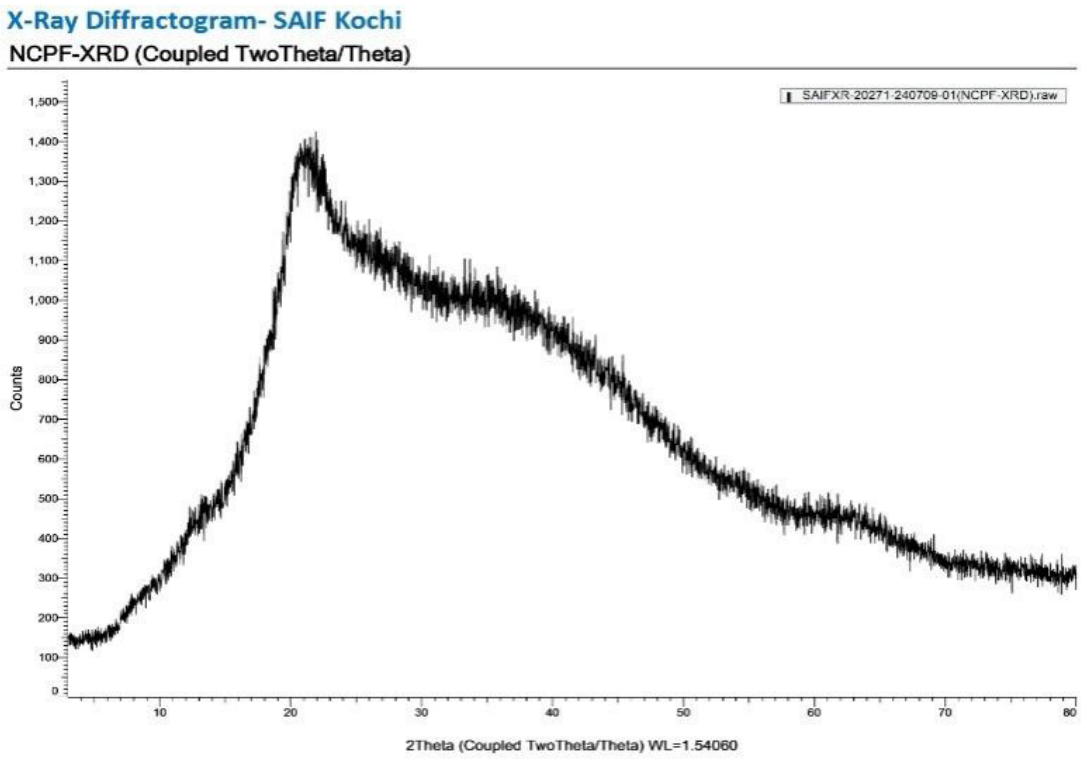

Figure 4d: X-ray Diffraction pattern of curcumin piperine nanoparticle loaded film forming spray.

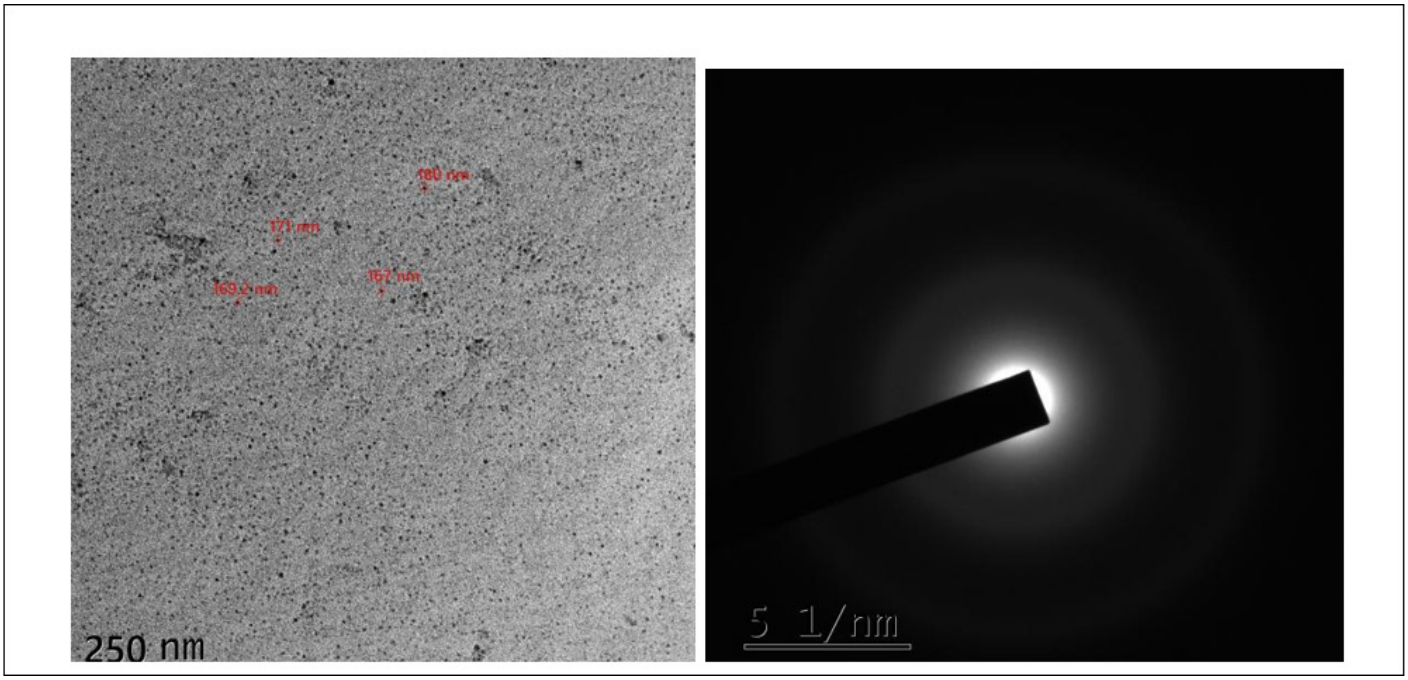

Figure 4e: TEM and SAED images of curcumin and piperine nanoparticle-loaded film showing uniform spherical particle and polycrystalline structure.

CONCLUSION

The study successfully formulated and evaluated a topical film-forming spray incorporating curcumin and piperine-loaded nanoparticles for vitiligo management. The optimized formulation, using HPMC E15 in a cold water-ethanol blend (50:50), met the desired criteria for viscosity, drying time, and skin integrity. Propylene glycol effectively enhanced spray coverage and elasticity, while a camphor-menthol combination improved drug permeation through goat epithelial membranes. Characterization results confirmed the formulation's stability, uniformity, and effective drug release (82.34%-96.88%). XRD confirmed an amorphous state, and HR-TEM supported the nanostructural integrity of the formulation. The findings demonstrate that this nanoparticle-based spray offers a promising, efficient, and patient-compliant approach to enhancing drug delivery and addressing vitiligo treatment challenges.

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ABBREVIATIONS

FTIR: Fourier Transform Infrared Spectroscopy; **HPMC:** Hydroxypropyl Methylcellulose; **PEG:** Polyethylene Glycol; **PG:** Propylene Glycol; **SEM:** Scanning Electron Microscopy; **TEM:** Transmission Electron Microscopy; **XRD:** X-ray Diffraction; **UV:** Ultraviolet; **DoE:** Design of Experiments; **SAED:** Selected Area Electron Diffraction; **PDI:** Polydispersity Index; **NP:** Nanoparticles; **DLS:** Dynamic Light Scattering; **ANOVA:** Analysis of Variance; **SD:** Standard Deviation; **FCPS:** Formulation Code of Curcumin-Piperine Spray; **FCPNS:** Formulated Curcumin-Piperine Nanoparticle Spray; **ER:** Enhancement Ratio; **X_1:** Polymer Concentration; **X_2:** Plasticizer Concentration; **Y_1:** Drying Time; **Y_2:** Drug Release; **cm:** Centimeter; **rpm:** Revolutions per minute; **°C:** Degrees Celsius; **µg/cm²/hr:** Micrograms per square centimeter per hour.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL STATEMENT

The study did not involve human or animal subjects. All experimental procedures, including *ex vivo* permeation studies, were conducted using goat skin obtained ethically from a licensed abattoir. The research adhered to institutional guidelines for the responsible use of biological materials and complied with ethical standards for laboratory studies.

SUMMARY

The study presents the development and evaluation of a novel topical film-forming spray containing curcumin and piperine-loaded nanoparticles for effective vitiligo management. Curcumin and piperine, known for their antioxidant and melanogenic properties respectively, were incorporated into nanoparticles using the desolvation technique with sodium alginate and HPMC E15 as polymers. The optimized nanoparticle-loaded film-forming spray was formulated using HPMC E15, a water-ethanol solvent system, propylene glycol as a plasticizer, and a camphor-menthol blend as a penetration enhancer. A 3^2 factorial design was employed to optimize polymer

and plasticizer concentrations, evaluating drying time and drug release as key parameters. The optimized formulation exhibited desirable physicochemical properties, including acceptable drying time (181.2-258 s), pH, viscosity, and spray angle. *In vitro* and *ex vivo* studies showed sustained drug release (up to 96.88%) and enhanced skin permeation (up to 86.77%) compared to pure drugs. Characterization techniques, such as FTIR, XRD, and TEM, confirmed the amorphous nature, compatibility, and uniform nanoparticle dispersion. Drug release followed the Korsmeyer-Peppas model, indicating diffusion-controlled kinetics. Overall, the nanoparticle-embedded film-forming spray offers a promising, stable, and patient-compliant delivery system for the topical treatment of vitiligo, potentially improving therapeutic outcomes and patient adherence.

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