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Formulation and Characterization of Simvastatin Transdermal Patches by Central Composite Design

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Abstract: The study aimed to develop transdermal patches containing Simvastatin and evaluate their characteristics and drug release profile. The researchers used the solvent evaporation and tested different polymer ratios and solvents to prepare the patches. They also conducted FTIR studies to ensure compatibility between the drug and excipients. Various parameters were evaluated to assess the quality of the patches. The thickness of the patches ranged from 0.31±0.01 to 0.37±0.02mm, indicating consistency in thickness across different formulations. The weight of the patches varied from 0.29±0.02 to 5.01±0.02mg, reflecting the various amounts of drug and excipients in each formulation. The folding endurance values, which indicate the ability of the patches to withstand repeated folding without breaking, ranged from 253±3 to 289±2, suggesting good mechanical strength. In vitro diffusion studies were conducted to measure the release of Simvastatin from the patches over time. The cumulative percentage of drug release after 74 hours ranged from 82.3% (F8) to 85.7% (F6) for the transdermal films. The formulation F6 exhibited a higher drug release percentage than F8, indicating a more rapid and sustained release of Simvastatin. Based on the results, the researchers concluded that formulation F5 demonstrated favorable characteristics, such as appropriate thickness, weight, folding endurance, and *in vitro* drug diffusion. However, it is essential to note that additional studies, including in vivo evaluations and stability testing, would be necessary to assess the potential of the transdermal patches containing Simvastatin fully.

Keywords: permeation; Simvastatin; *Ocimum bacilicum*; patch; Simvastatin; transdermal.

1. Introduction

A transdermal drug delivery system (TDDS) is a well-established method of delivering drugs to the body. It offers several advantages, such as improved patient compliance and bypassing first-pass metabolism. TDDS is designed to facilitate the entry of drugs into the bloodstream through the skin while minimizing drug retention and metabolism in the skin itself. The primary route of drug penetration through the skin is the intercellular micro route, and permeation or penetration enhancers play a crucial role in reducing the barrier resistance of the outermost layer of the skin, called the stratum corneum, without causing harm to the underlying viable cells [1,2].

Transdermal patches are a commonly used form of TDDS, delivering drugs either locally to the skin or systemically to target tissues beneath the skin. Transdermal patches offer substantial benefits compared to conventional dosage forms or controlled-release oral systems. Depending on the intended target location, skin-care formulations can have systemic or local effects. Transdermal drug delivery can closely mimic the slow infusion of drugs intravenously but with fewer potential risks. Importantly, transdermal patches also allow patients to discontinue drug therapy easily by simply removing the patch if any adverse effects occur[3,4].

Simvastatin is a medication commonly used in combination with a balanced diet to lower "bad" cholesterol and fats in the blood, such as LDL and triglycerides while increasing "good" cholesterol (HDL). It belongs to a class of medications known as "statins." Users of Simvastatin may occasionally experience mild disorientation or memory issues. In rare cases, this drug can cause muscle problems, including a serious condition called rhabdomyolysis and autoimmune myopathy. There is also a small risk of liver problems, which may manifest as stomach or abdominal pain, nausea, vomiting, yellowing of the eyes or skin (jaundice), and dark urine. It is essential to consult a healthcare professional for proper monitoring and management when taking SSimvastatin to ensure safety and address potential side effects. The average half-life of short-acting statins is 6 hours. The time it takes for the body to digest and eliminate half of the medicine is known as the half-life. Simvastatin, when taken as a prodrug, is hydrolyzed in the liver to create its active beta-hydroxy acid metabolite, which has a plasma half-life of about 5 h and reaches peak plasma concentrations in 2-4h [5].

A factorial design experiment is indeed a research design that involves multiple independent variables or components. It allows researchers to analyze the main effects of these variables and their interactions. In a factorial design, there are at least two independent variables, also referred to as factors or components [6].

The central composite design (CCD) is a specific experimental design used in statistics, particularly in response surface methods. It is employed to develop quadratic models for response variables without conducting a complete three-level factorial experiment. CCD is a valuable tool for optimizing processes and understanding the relationship between independent variables (factors) and the response variable [7].

In a central composite design, each factor is set at five levels: extreme high (often denoted by a star point), higher point, low point, extreme low star point, and center point. The center point is typically replicated to estimate the experimental error. Using these levels, the contour of the response surface can be determined, allowing for the visualization of the relationship between factors and the response variable within the experimental domain [8].

Overall, factorial designs, including the central composite design, provide researchers with a powerful tool to investigate the main effects of multiple independent variables and their interactions, allowing for testing hypotheses and conclusions.

2. Materials and Methods

2.1. Materials.

Simvastatin was gifted from Actavis Pharma, Bangalore. *Ocimum bacilicum* seeds (OBS) were collected from the local market of Anantapur, India. Span 20, Dichloromethane, Ethanol, Ethylcellulose, Potassium dihydrogen phosphate, NaOH, and Disodium hydrogen phosphate, and double distilled water and analytical reagent grade chemicals were employed throughout the trials—the composition of the patches as per table 1.

Table 1. Composition of transdermal patches.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Simvastatin	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Ethylcellulose	300	600	300	600	237.86	662.32	450	450	450
OBS	300	300	400	400	350	350	279.28	420.71	350
Span 20	2	2	2	2	2	2	2	2	2
Dichloromethane	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Ethanol	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

2.2. Formulation of transdermal patches.

2.2.1. Basil seeds extraction.

Use a weighing scale to measure out 20g of basil seeds accurately. Place the measured basil seeds in a container or beaker and add 400ml of water. Make sure the seeds are fully submerged in the water. Set up a magnetic heater or a hot plate with magnetic stirring capabilities. Place the container with the basil seeds and water on the magnetic heater. Turn on the magnetic heater and set the temperature and stirring speed as required. Heat and stir the mixture for 60 minutes, ensuring the temperature is maintained consistently. During the heating and stirring process, observe the mixture. After approximately 60 min, the white mucilage from the basil seeds should start to appear. Once the white mucilage has appeared, carefully remove the container from the magnetic heater. Take a cotton cloth or cheesecloth and strain the mixture to separate the liquid extract from the basil seeds and mucilage. Squeeze the cloth gently to extract as much liquid as possible. Transfer the extracted liquid into a tray dryer or a similar drying apparatus. Make sure to spread the liquid evenly on the tray. Set the tray dryer to the appropriate temperature and time settings. Allow the liquid extract to dry for 24 h, ensuring proper ventilation and air circulation. After 24 h, check if the extract has completely dried. It should have transformed into a solid or semi-solid form. Carefully collect the dried extract from the tray using a spatula or suitable tool [9].

It's worth noting that the specific temperature, stirring settings, and drying conditions may vary depending on the equipment available and the desired outcome. Following any specific instructions or guidelines the manufacturer provides or relevant references for best results is recommended.

2.2.2. Preparation of transdermal patches.

Preparing transdermal patches containing Simvastatin using the solvent evaporation method. Firstly, rathered the required materials and ingredients: Simvastatin (drug), OBS (*Ocimum bacilicum* seeds), water, dichloromethane, ethanol, ethyl cellulose, span 20, petri dish, glycerine, beaker, magnetic stirrer, and desiccator. Measure the required amount of OBS and water. Place them in a beaker. Add the necessary amount of dichloromethane and ethanol to the OBS and water mixture. Add Simvastatin to the mixture in the beaker and triturate (mix) thoroughly until there are no lumps, ensuring a uniform drug distribution. In a separate beaker, dilute ethyl cellulose in dichloromethane. Stir until it is well dissolved. Add the OBS mixture (containing Simvastatin) to the diluted ethyl cellulose solution in the beaker. Mix them well. Place the beaker on a magnetic stirrer and continue stirring to ensure thorough mixing. After the solution is well mixed, add span 20 to the beaker and stir again. Prepare the petri dish by lubricating it with glycerine. This will prevent the patches from sticking to the dish. Pour the resulting uniform solution into the lubricated petri dish. Place an inverted funnel over the petri

dish. This helps prevent rapid evaporation of the solvent. Allow the solution in the petri dish to dry at room temperature for 24 h. This will facilitate the formation of transdermal patches. After 24 h, carefully remove the dried patches from the petri dish. Store the patches in a desiccator to protect them from moisture and further study them for various parameters. Following these steps, you can prepare transdermal patches containing Simvastatin using the solvent evaporation [10,11].

2.2.3. Drug-excipient compatibility studies by FTIR.

The FTIR technique can be used to assess drug excipient compatibility investigations. Examining a physical mixture of the drug and the excipients and the drug in its purest form.

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beaker on a magnetic stirrer and continue stirring to ensure thorough mixing. After the solution is well mixed, add span 20 to the beaker and stir again. Prepare the petri dish by lubricating it with glycerine. This will prevent the patches from sticking to the dish. Pour the resulting uniform solution into the lubricated petri dish. Place an inverted funnel over the petri dish. This helps prevent rapid evaporation of the solvent. Allow the solution in the petri dish to dry at room temperature for 24h. This will facilitate the formation of transdermal patches. After 24h, carefully remove the dried patches from the petri dish. Store the patches in a desiccator to protect them from moisture and further study them for various parameters. Following these steps, you can prepare transdermal patches containing Simvastatin using the solvent evaporation method [1,13].

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2.4. Evaluation studies.

2.4.1. Folding endurance.

The strip's section (2 x 2 cm) was uniformly cut and repeatedly folded until it broke. The number of folds required to either break the film or cause it to show apparent cracks was used to calculate the folding endurance value [14].

2.4.2.Thickness.

Using a micrometer allows for precise measurement of the thickness of the patches. By taking measurements at multiple locations on each patch, potential variations in thickness across the surface can be identified and accounted for. This helps obtain a representative measurement that reflects the overall thickness of the patch. The mean values of the measurements are calculated by summing up the thickness measurements at each location and dividing by the total number of measurements taken. This provides an average thickness value that represents the overall thickness of the patch more accurately than a single measurement.

2.4.3. Percentage of moisture content.

Firstly, each film is weighed using an analytical balance or a precise weighing scale. The weight of each film is recorded. The weighed films are placed in a desiccator containing fused calcium chloride. The desiccator creates a controlled environment with low humidity, allowing moisture to be removed from the films. The films are kept inside the desiccator at room temperature for 24 hours. This duration allows sufficient time for moisture in the films to be absorbed by the calcium chloride, resulting in moisture removal. After the 24-hour desiccation period, the films are removed from the desiccator. The same weighing procedure as before is followed to measure their weight again. The percentage moisture content in the films can be calculated using the formula [15]:

$$\%\ moisture\ content\ \frac{(\text{Weight before desiccation} - \text{Weight after desiccation})}{\text{Weight before desiccation}} X100 \ldots..(1)$$

2.4.4. Percentage of moisture uptake.

To maintain a relative humidity (RH) of 84%, the weighted films were placed in desiccators containing a saturated potassium chloride (KCl) solution. These desiccators create a controlled environment with a specific humidity level. The films were kept in the desiccators at room temperature for 24 hours. After 24 hours, the films were removed from the desiccators and reweighed using the same method. The difference in weight before and after the desiccation period allowed the calculation of the percentage moisture uptake using the following formula [16,17]:

$$\% \text{ moisture uptake} = \frac{\text{Weight after desiccation} - \text{Initial weight}}{\text{Initial weight}} X100 \text{--- (2)}$$

2.4.5. Determination of flatness.

Longitudinal strips were taken from each film, one from the middle and two from either side. The length of each strip was measured to assess the flatness of the film. The percent constriction was calculated to determine the variance in length due to nonuniform flatness. The percent constriction measures how much the strip deviates from perfect flatness, with 0% constriction indicating 100% flatness. The calculation of percent constriction is typically done by comparing the actual length of the strip to the expected length based on perfect flatness. The formula for percent constriction is as follows [18,19]:

$$\% \text{ Constriction} = \frac{\text{Expected Length} - \text{Actual Length}}{\text{Expected Length}} X100 \text{--- (3)}$$

The variance in length due to nonuniform flatness can be determined by measuring and calculating the percent constriction for each strip.

2.4.6. *In-vitro* permeation studies.

Permeation investigations are used to identify how the medicine gets from the patch to the skin's microcirculation. In this study, a synthetic membrane consisting of cellulose nitrate was used to divide the donor and receptor compartments of the Franz diffusion cell. A phosphate buffer with a pH of 7.4 was present in the receptor compartment. The donor compartment of a transdermal patch was oriented outward on the cellulose nitrate membrane. The receptor compartment holding the phosphate buffer was on the other side of the cellulose nitrate membrane. The receiver chamber was maintained at room temperature by continuous agitation using a magnetic stirrer. Conditions in the washbasin were preserved [4,20]. After samples were taken out, their absorbance was examined, and concentration was estimated (Table 4).

2.4.7. Weight variation.

To assess the weight uniformity of the patches, 10 patches from each formulation were individually weighed, and the average weight was calculated. This step aims to ensure that the individual weights of the patches do not deviate significantly from the average weight. Ten patches from each formulation were selected randomly. Each patch was weighed individually using a weighing balance with appropriate precision. The weight of each patch was recorded. The weights of the 10 patches were added together to obtain the total weight. The average

weight was calculated by dividing the total weight by the number of patches (in this case, 10). By comparing the individual weights of the patches to the average weight, one can determine if there is any significant deviation. Ideally, the individual weights should be relatively close to the average weight, indicating uniformity in the manufacturing process. Any substantial deviation from the average weight could indicate inconsistencies in the formulation or manufacturing process and may require further investigation [21,22].

2.4.8. *In vitro* drug release studies.

The dissolution of patches was performed using the USP Type of Dissolution Apparatus. The patches were placed in respective jars with their drug matrix exposed to phosphate buffer, pH 6.8. All dissolution studies were performed at 50 rpm, with each dissolution jar carrying 900 mL of buffer. Samples were withdrawn at different time intervals and analyzed using a UV spectrophotometer at 238 nm against blank. Cumulative amounts of drug released were plotted against time for different formulations [23].

2.4.9. Drug content.

In the given experimental procedure, a beaker holds 100ml of a buffer solution with a pH of 7.4. The purpose of the buffer solution is to maintain a stable pH environment for the experiment. A patch, which is not specified, is placed in the buffer solution and left to incubate for 24 hours. This period allows any relevant interactions or reactions between the patch and the buffer solution. After the 24-hour incubation, the sample is filtered to remove any solid particles or impurities that may have formed during the experiment. Filtration helps ensure that only the desired components of the solution are used for analysis. Next, the filtered sample is analyzed using a UV (Ultraviolet) spectrophotometer. The spectrophotometer is a device that measures the absorbance or transmission of light at specific wavelengths. In this case, the analysis is carried out at a wavelength of 238nm. To determine the particular properties or characteristics of the sample, a comparison is made against a blank. The blank represents a control or reference solution without the patch, allowing for measuring any changes or effects explicitly caused by the patch in the sample. Overall, this procedure describes incubating a patch in a buffer solution, filtering the resulting solution, and then analyzing it using a UV spectrophotometer to assess its properties at a wavelength of 238nm regarding a blank solution[24,25].

2.4.10. Surface pH.

In the experimental procedure, films measuring 2cm square are placed in a glass tube containing 0.5 ml of double distilled water. The purpose of this step is to allow the films to interact with the water, potentially causing any chemical or physical changes in the films. After the films have been submerged in the water for approximately 1 hour, the pH of the film is determined using a pH meter. A pH meter is a device that measures the acidity or alkalinity of a solution on a logarithmic scale from 0 to 14, where pH 7 is considered neutral, values below 7 indicate acidity, and values above 7 indicate alkalinity. The pH meter is used to measure the pH value of the water in which the films have been immersed directly. This provides information about any changes in the acidity or alkalinity of the films due to their interaction with the water. By calculating the pH of the film, researchers can gain insights into the effect of the water on the film's chemical properties. This information can be valuable in various

research fields, such as materials science, surface chemistry, or the study of film degradation or stability. It's important to note that this description assumes the film is intended to have a potential pH change or that its pH value is relevant to the study. If the film is pH-sensitive or pH measurement is simply a control parameter, the information gained from the pH measurement can provide insights into the experimental conditions or the behavior of the film in contact with water [26-28].

3. Results and Discussion

3.1. UV spectrum of Simvastatin in pH 7.4 phosphate buffer.

The UV spectrum of Simvastatin in pH 7.4 phosphate buffer is shown in Fig 1.

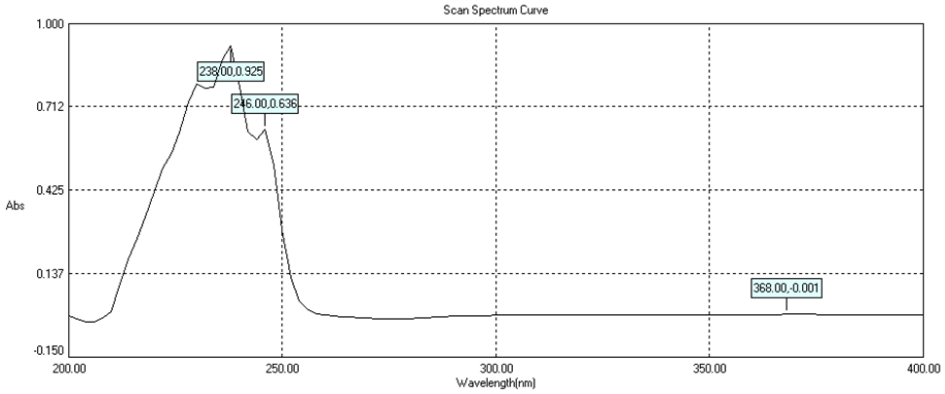

Figure 1. UV spectrum of Simvastatin in pH 7.4 phosphate buffer.

3.2. Fourier transform infrared analysis.

The FTIR analysis of the drug was carried out for compound identification. The powdered drug was placed carefully over the sample holder for scanning. The FTIR spectrum for the pure drug is shown in Fig 2.

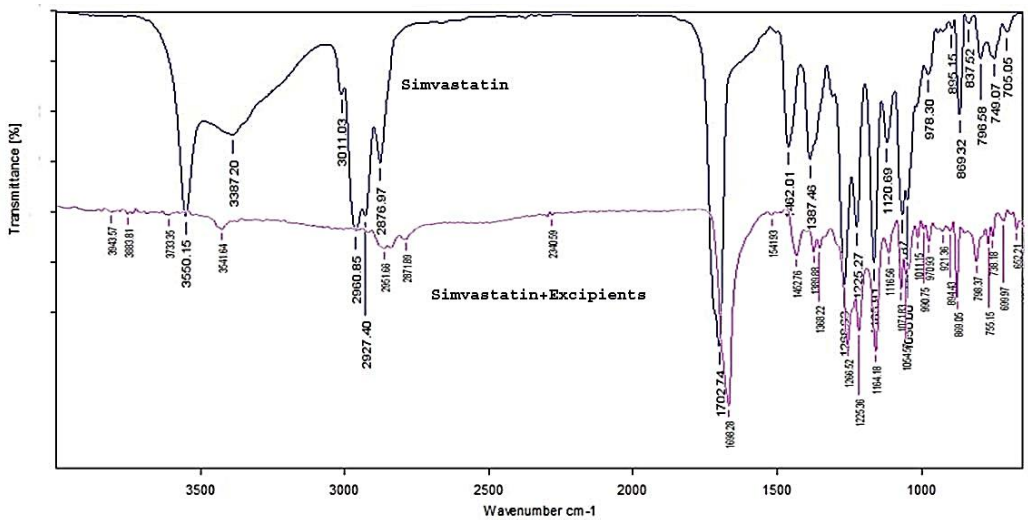

Figure 2. FTIR spectrum of Simvastatin and with excipients.

3.3. Solubility.

The solubility study of the drug sample revealed its solubility characteristics in different solvents. The drug sample was found to be freely soluble in water and dichloromethane, indicating that the drug can readily dissolve in these solvents. On the other hand, the drug sample was sparingly soluble in ethanol, implying that it dissolves to a lesser extent in ethanol

than water and dichloromethane. Solubility studies of Simvastatin in different media are seen in Table 2.

Table 2. Solubility studies of Simvastatin in different media (Mean ± S.D, n=3).

Medium Composition (Ethanol: Distilled water (%V/V)	Solubility (µg/ml) (n=3)
20:80	0.22±0.01
30:70	0.34±0.08
40:60	0.57±0.06
50:50	0.76±0.11

3.4. Evaluation of transdermal patches.

3.4.1. Physical appearance.

The formulated patches exhibited favorable physical characteristics, as they were found to be smooth and flexible.

3.4.2. Thickness.

The thickness of different formulations was measured and found to be within the range of 0.31±0.01 to 0.37±0.02mm (table 1). The table displays the various formulations (Form 1, Form 2, Form 3, and Form 4) and their corresponding thickness values. The thickness measurements indicate the physical dimension of the formulations, providing insight into their overall size or depth. The given range (0.31 to 0.37mm) suggests that the formulations exhibit similar thicknesses, with minor variations between them.

3.4.3. Weight variation and flatness.

The weight variation was measured for different formulations, and the results showed a range of 0.29 to 5.01% in weight variation. The specific values of weight variation for each formulation are presented in Table 1. The given range (0.29 to 5.01%) indicates that there is variability in weight among the formulations, with some formulations experiencing minimal weight variation (0.29% in Form 1) and others exhibiting higher weight variations (5.01% in Form 4).

The provided information measured the strip lengths before and after a longitudinal cut for different formulations. The results indicate no variation in the strip lengths before and after the cut for any formulations (Table 1). This finding suggests that the formulations exhibit 100% flatness and 0% constriction. In other words, they maintain an even surface when applied to the skin.

3.4.4.Drug content.

In the provided information, drug content measurements were conducted for different formulations. The results indicate that the drug content ranges from 87% to 98% (Table 1). The 87% to 98% range signifies variability in the drug content among the formulations. Formulation 1 has the lowest drug content at 87%, while Formulation 4 has the highest at 98%.

3.4.5. Folding endurance.

In the provided information, the folding endurance of different formulations was measured, and the results indicate a range of 253±3 to 289±2 for the folding endurance values. Table 1 presents the specific folding endurance values for each formulation. The range of 250

to 290 suggests that the formulations exhibit varying levels of folding endurance. Formulation 1 has the lowest folding endurance at 253±3, while Formulation 4 has the highest folding endurance at 289±2.

3.4.6. Surface pH.

The surface pH of different formulations was measured, and the results indicate a range of 6.1 to 7.1 for the surface pH values. This suggests that the formulations exhibit slightly acidic to neutral pH levels on their surfaces. The range of 6.15±2 to 7.13±2 suggests that the formulations have surface pH levels that are somewhat acidic to nearly neutral (Table 3).

These characteristics suggest that the prepared patches were made with consistent weight, thickness, and drug content. They exhibited good flexibility (folding endurance) and were closer to neutral regarding pH.

Table 3. Evaluation tests of simvastatin transdermal patches.

Formulation	%weight variation	Thickness (mm)	Folding endurance	Surface pH SD	Drug content
F1	0.29±0.02	0.31±0.01	253±3	6.15±1.22	89.26±3.48
F2	1.36±0.03	0.33±0.02	259±7	6.52±0.08	87.21±2.15
F3	1.89±0.01	0.36±0.01	273±6	6.71±0.11	93.31±9.02
F4	2.53±0.05	0.32±0.02	262±5	6.91±0.37	91.22±6.36
F5	2.97±0.04	0.34±0.03	281±4	6.22±0.17	88.85±2.13
F6	3.71±0.08	0.37±0.02	279±8	6.42±0.84	94.01±5.28
F7	4.23±0.03	0.35±0.02	283±6	6.53±0.36	98.39±2.89
F8	4.85±0.05	0.33±0.01	264±5	7.13±0.232	96.55±4.52
F9	5.01±0.02	0.34±0.01	289±2	6.38±0.85	92.91±3.25

Values in mean±SD (n=3)

3.4.7. Moisture content and moisture uptake.

The moisture content of the prepared films fell within the specified limits of 2.13±0.3 to 4.76±0.6, and the moisture uptake was found to be 3.00±0.37 to 9.00±0.23 indicating that the moisture content in the patches was consistent and stable. Maintaining appropriate moisture levels is crucial for ensuring the stability and flexibility of the prepared patches (Table 4).

Table 4. Moisture content and Moisture uptake of Simvastatin patches.

Formulation code	Moisture content (%)	Moisture uptake (%)
F1	3.24±0.24	3.00±0.37
F2	2.35±0.61	3.35±0.23
F3	2.61±0.45	4.09±0.58
F4	3.96±0.59	6.90±0.65
F5	3.24±0.70	5.10±0.24
F6	4.49±0.66	8.30±0.83
F7	2.13±0.38	7.19±0.34
F8	4.76±0.65	7.61±0.48
F9	2.97±0.74	9.00±0.23

Values in mean±SD (n=3)

3.4.8. *In-vitro* permeation study.

The cumulative percentage of the drug released in 72h varied among different formulations of transdermal films. The percentage of drugs released ranked in the following order: F6>F5>F4>F3>F2>F1. Formulation F6 exhibited the highest cumulative drug release of 85.7% within 72-h, indicating a more efficient drug release profile than the other formulations. The percentage of drug release for different formulations is shown in Figure 3.

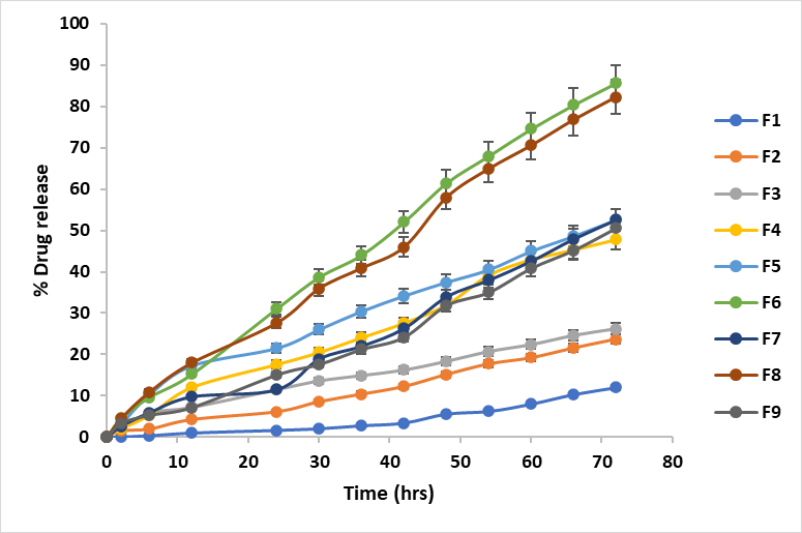

Figure 3. Cumulative % drug release.

The pH 7.4 phosphate buffer at 236 nm was used for the 72-h *in vitro* drug diffusion tests. Tables 4 and 5 reflect the findings of this research. At the end of the 72nd h, formulation F6 had the maximum drug release of all the studied formulations. This implies that when compared to the other formulations, F6 delivered the medication slowly over a longer period. This result suggests that formulation F6 is considered optimal for achieving a prolonged release of the medication. F6 is a good option for applications that need regulated and extended medication administration because of its slower release rate and longer duration of drug release (Fig.4).

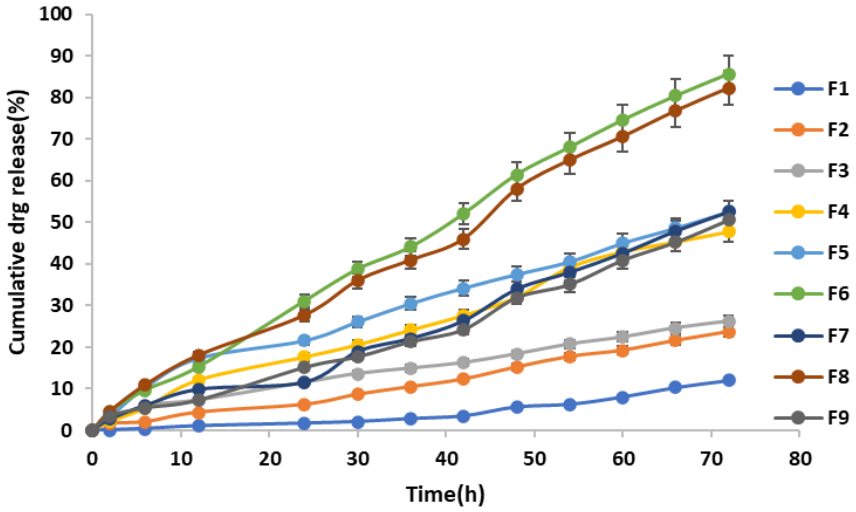

Figure 4. *In vitro* drug permeation charts.

3.4.9. Optimization of simvastatin-loaded transdermal patch formulation using CCD.

The dependent and independent variables in this study were as per Table 5.

Table 5. Composition and characterization of simvastatin transdermal patch formulations.

Formulation code	Independent variables		Dependent variables	
	A:EC (mg) (X_1)	B: OBEC (mg) (X_2)	Folding endurance (Y_1)	DP@24h (Y_2)
1	300	300	267	43.40
2	600	300	261	24.58
3	300	400	293	41.32
4	600	400	288	26.96
5	237.868	350	279	46.00

Formulation code	Independent variables		Dependent variables	
6	662.132	350	273	24.12
7	450	279.289	256	33.00
8	450	420.711	296	32.30
9	450	350	263	35.98

3.4.10. ANOVA for quadratic model.

The ANOVA details for response 1 were as per Table 6.

Table 6. ANOVA details for the Folding Endurance of the patches.

Source	Sum of Squares	F-value	p-value	Statistical significance
Model	1713.38	186.67	0.0006	significant
A-EC	47.46	25.85	0.0147	
B-OBSM	1500.66	817.46	< 0.0001	
AB	0.2500	0.1362	0.7366	
A^2	135.01	73.55	0.0033	
B^2	135.01	73.55	0.0033	

The contour and 3D plots of responses are shown in the Fig.5.

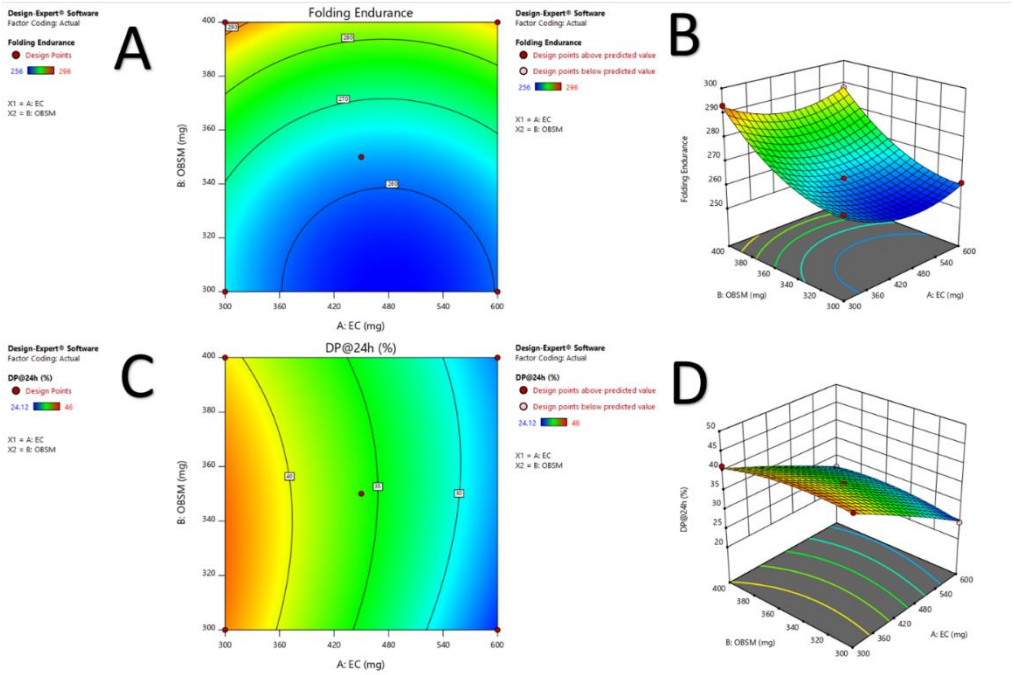

Figure 5. Contour plots of responses showing the interactive effects of the amount of lipid and amount of ethanol on folding endurance (Y_1) and drug permeation@ 24h (Y_2).

Based on the information provided, the study involved the preparation of SDP (presumably referring to solid dispersion preparations) using a rotatable CCD (central composite design) around a fixed point. The study considered two independent variables: ethyl cellulose concentration (mg) and OBSM (mg), represented as X_1 and X_2, respectively.
The range of each independent variable is likely provided in Table 5, which is not included in the given information.

The dependent variables, or the factors being measured, were folding endurance (Y_1) and DP@24h (Y_2). Folding endurance represents the ability of the SDP to withstand repeated folding without breaking, indicating its flexibility. DP@24h refers to the dissolution performance or drug release rate of the SDP within 24 h.

The specific values, ranges, and relationships between the independent and dependent variables would require access to the complete data, including Table 5, to provide more detailed information or insights.

To provide a more detailed analysis or interpretation, it would be helpful to have access to the actual values and contours from the RSM plots (Fig.5) or any additional information from Table 5.

The regression equations obtained for Y_1 and Y_2 are as follows:

Folding Endurance $=+263.00-2.44A+13.70B+0.2500AB+6.81A^2+6.81B^2$

DP@24h $=+35.98-8.02A-0.0862B+1.11AB-0.4075A^2-1.61B^2$

4. Discussion

The UV spectrum of Simvastatin in pH 7.4 phosphate buffer shows an absorption maximum of 238nms and an absorption maximum of 238nm, indicating the drug's purity. This suggests that the sample of Simvastatin used in the study was free from impurities or contaminants that could interfere with the UV absorption measurement.

The characteristic peaks and stretches obtained in the FTIR spectrum of Simvastatin and its drug combination were found undisturbed, indicating the compatibility of Simvastatin with the excipients used. FTIR spectroscopy is commonly used to analyze a sample's chemical bonds and functional groups. The fact that the characteristic peaks and stretches of Simvastatin remained unchanged in the presence of excipients suggests that there were no significant chemical interactions or disruptions in the molecular structure of Simvastatin due to the excipients.

Solubility studies are essential in pharmaceutical formulation and drug delivery systems to determine the ability of a drug to dissolve in different solvents. The solubility characteristics of a drug influence its formulation and the selection of appropriate solvents for dissolution and delivery. By studying the solubility of Simvastatin in various solvents, researchers can gain insights into its behavior and potential interactions in different formulations. This knowledge is crucial for formulating the drug into different dosage forms and optimizing its dissolution and delivery characteristics.

The transparent or clear appearance of the patches indicates that they were free from any visible particulate matter or turbidity. This clarity suggests the absence of impurities or suspended materials within the patches, ensuring their quality and purity.

The smooth surface of the patches is desirable for transdermal patches as it ensures comfortable application and adherence to the skin. A smooth surface reduces the likelihood of irritation or discomfort during use and enhances the overall user experience.

The uniformity in physical appearance observed in the patches suggests consistent formulation and distribution of ingredients throughout the patch. This uniformity is essential for ensuring consistent drug delivery and efficacy. It indicates that the patches were manufactured with precision and attention to detail, resulting in reliable and predictable performance.

The flexibility of the patches allows them to conform easily to the skin's contours and accommodate movement without causing discomfort. Flexibility is a crucial characteristic of transdermal patches, as it ensures proper adhesion and patient comfort during use.

The absence of air bubbles in the patches indicates that the formulation and application process was performed effectively. The entrapment of air bubbles can interfere with drug

release and affect the contact between the patch and the skin. The absence of air bubbles ensures optimal performance and reliable drug delivery.

The uniformity in thickness of the patches is vital for assessing the consistency and suitability of the formulations for specific applications or requirements. The measured thickness values provide a quantitative understanding of the physical characteristics of the patches, aiding in quality control and ensuring their functionality.

Weight variation measurements help assess the consistency and quality of formulations. The measured weight variation values provide insights into the variability in the weights of different patches, which can impact their effectiveness and performance. These measurements are crucial in ensuring the uniformity and stability of the formulations during production and use.

Measuring the drug content is essential in pharmaceutical analysis to ensure the consistency and potency of the formulations. The measured drug content values provide a quantitative understanding of the quantity of the active drug present in each formulation. These measurements aid in evaluating the quality and efficacy of the formulations, ensuring they meet the required standards and specifications. The desired drug content can vary depending on specific formulation requirements, therapeutic goals, and regulatory guidelines.

The consistent strip lengths of the formulations indicate that they have been designed and manufactured to maintain their shape and integrity during application. This is important for ensuring proper adhesion and comfort during use, especially in applications where a flat surface is desired. The data in Table 1 provide evidence of the formulations' ability to maintain an even surface and lack constriction when applied to the skin, supporting their suitability for various applications.

Folding endurance measurements assess the durability and flexibility of the formulations. Higher folding endurance values indicate better resistance to folding and the ability to withstand repeated handling or bending without damage. The folding endurance data in Table 1 serve as references for evaluating the materials' robustness and suitability for specific applications. These measurements are essential in pharmaceutical and packaging industries, where materials need to endure folding or bending without compromising their integrity or functionality. The measured folding endurance values contribute to the evaluation and quality control of the formulations, ensuring their reliability and performance in practical applications.

The uniform weight of the patches indicates consistent manufacturing processes, where all patches have a similar weight. The low weight variation among the patches, less than 5%, further confirms the consistency in the manufacturing process. This consistency in weight and weight variation is crucial for ensuring the uniformity and stability of the formulations during production and use, which can impact their effectiveness and performance.

The pH range of the formulations, particularly when close to the pH level of healthy skin, promotes compatibility and reduces the likelihood of irritation or adverse reactions. The measured surface pH values aid in evaluating the formulation's skin-friendliness and potential impact on the skin's natural pH balance. By considering the desired surface pH based on specific application and user requirements, formulators, researchers, and regulatory agencies can ensure that the formulations meet the desired specifications, providing optimal performance and safety when applied to the skin or relevant surfaces.

The uniform thickness and weight of the patches also contribute to the uniformity in drug content. This ensures consistent delivery of the active drug and supports the reliability and performance of the formulations.

The moisture content of the patches falling within the specified limits indicates they have the desired moisture content range. Maintaining consistent moisture levels is essential to ensure the patches' stability, flexibility, and overall quality. Adherence to the specified moisture content limits demonstrates the precision and control exercised during manufacturing. It indicates that the formulation and processing techniques successfully and consistently achieved the desired moisture content range across the prepared patches. This knowledge is valuable for ensuring the patches' stability, functionality, and durability during storage, handling, and application.

The reported Model F-value of 186.67 suggests that the overall model is statistically significant, as the probability of obtaining such a large F-value by chance is extremely low (0.06%). Their corresponding p-values can evaluate the importance of model terms. Terms with p-values less than 0.05 are considered statistically significant, while those with p-values greater than 0.1 are considered insignificant. Model reduction, which involves removing non-significant terms, can simplify the model and potentially improve its overall performance.

The Adeq Precision ratio of 35.017 indicates a high signal-to-noise ratio, meaning the model can adequately capture and explain the variation in the response variable. This suggests that the model provides a robust understanding of how the factors influence the response and can be relied upon for navigating the design space.

In a balanced design, the standard errors of the model coefficients should be similar. Lower standard errors indicate more precise estimates, which is generally desirable. A balanced design ensures that each factor level has an equal number of observations, helping to reduce variability.

The Variance Inflation Factor (VIF) measures multicollinearity, which assesses the correlation between predictor variables in the model. VIF values above 10 are generally considered a cause for concern, indicating the presence of multicollinearity. Values above 100 suggest a severe issue of multicollinearity, which can lead to poorly estimated coefficients.

The R-squared (R^2) value represents the proportion of variance in the response variable explained by the model. While higher R^2 values are desirable, very high values may indicate a high correlation between the model terms, which can lead to problems such as overfitting and poor generalization of new data.

If the design has multilinear constraints, multicollinearity may be more pronounced, leading to inflated VIFs and R^2 values that are less informative. In such cases, prediction-based metrics like Fraction of Design Space (FDS) statistics are recommended.

Power is not an appropriate tool for evaluating response surface designs. Instead, prediction-based metrics like FDS should be used to assess the design's performance. The FDS graph provides valuable information about the design's predictive capabilities.

When selecting a model, it is essential to include only the expected significant terms. Including unnecessary or irrelevant terms can lead to overfitting and reduced model performance. To ensure a valid lack of fit test, it is recommended to have at least 3 degrees of freedom for lack of fit and 4 degrees of freedom for pure error.

Response surface methodology (RSM) contour surface plots are graphical representations that show the correlation between the dependent variables (Y_1 and Y_2) and the independent variables (X_1 and X_2). By observing the variations in the dependent variables while varying the independent variables, these plots provide insights into the relationship between them. Contour surface plots can help identify optimal regions or conditions that yield desirable responses for the dependent variables.

5. Conclusions

Based on the information provided, transdermal patches of Simvastatin were prepared using *Ocimum bacilicum* seeds mucilage (OBSM) to enhance the patch properties. The results indicate that formulation F5 exhibited favorable characteristic properties and showed promising in vitro drug diffusion. Additionally, OBSM played an effective role in film formation and patch fabrication. Formulation F5 demonstrated favorable characteristic properties, suggesting that it exhibited desired attributes such as good physical integrity, flexibility, and adhesion. These properties are crucial for transdermal patches as they ensure proper handling, application, and comfort for the user.

Furthermore, the in vitro drug diffusion results indicate that formulation F5 showed effective drug release and permeation through the skin. This suggests that the patch delivered Simvastatin efficiently and effectively through the skin into the bloodstream. The use of OBSM in preparing the patches played an important role in film form. Mucilage is a gel-like substance that can provide viscosity, adhesiveness, and film-forming properties. It is often used as a natural binder or thickening agent in pharmaceutical formulations. The effective role of OBSM in film formation suggests it contributed to forming a cohesive and continuous film in the patch. This is essential for ensuring the structural integrity and stability of the patch during storage and application. Overall, the results indicate that formulation F5, prepared with the aid of OBSM, exhibited favorable characteristic properties and demonstrated effective in vitro drug diffusion. This highlights the potential of OBSM in enhancing the film-forming properties and overall performance of transdermal patches containing Simvastatin.

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None.

Conflicts of Interest

None.

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