Research Article

Design, Optimization And Evaluation Of Polyherbal Cream For The Treatment Of Eczema Using 2^3 Factorial Design

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Abstract

Eczema is the chronic inflammatory skin disease characterised by itchy and dry skin, pruritis small rashes, blisters and infections. Despite the availability of conventional treatments like topical corticosteroids, adverse effects associated with long term use of these conventional treatment has demanded safer and effective alternatives. The aim of the present research is to formulate and optimize the polyherbal topical cream for the management of eczema by using a 2^3 full factorial design approach. Total 8 formulations were prepared by varying the concentration of shea butter, coconut oil and Carbopol and these factors were evaluated at two levels. The responses studied were viscosity, spreadability, and in-vitro drug release. Out of 8 formulations, F7 batch containing 7% sheabutter, 6.5 % coconut oil and 1.5 % Carbopol, was identified as the best formulation as it exhibited desirable viscosity, good spreadability and optimum drug release. F7 exhibited a viscosity of 40,100 cP, spreadability of 18.2 g·cm/s and cumulative in vitro drug release of 94.4% after 7 hours. Stability studies indicated no significant changes over three months. The results indicated that the optimised batch may serve as the promising system for effective management of eczema.

INTRODUCTION

Eczema, a chronic inflammatory skin condition affects millions worldwide, causing significant discomfort and reduced quality of life. It is characterized by dry scaly skin, itchiness, rashes, infection and blisters[1]. The pathogenesis of eczema is multifactorial and involves skin barrier dysfunction, increased transepidermal water loss, immune dysregulation and microbial colonistaion. Conventional treatments like corticosteroids and calcineurin inhibitors offer temporary symptoms relief but on long term use, these are associated with side effects like skin thinning, resistance and life-threatening diseases like cancer, driving interest in alternative therapies[2,3]. Herbal therapies offer a safer and more effective alternative to conventional therapies due to the synergistic effect of phytoconstituents present in plants[4,5]. Various herbs have been recognized for their potent anti-inflammatory, antimicrobial, and antioxidant properties, which can help soothe irritated skin, reduce inflammation, and promote healing[6]. The aim of the present study is to formulate, optimize and evaluate the polyherbal cream containing combination of herbs with potent anti-inflammatory, antimicrobial, and antioxidant properties. To achieve desired anti-inflammatory, antibacterial and immunomodulatory effect, Glycirrhiza glabra[5,6], Azadirachta indica[8,9], Salix alba, Avena sativa and coconut oil have been chosen through deep literature review[10,12,13].

Along with the selection of herbal plants, selection of excipients is also important in topical drug delivery. Despite the therapeutic promise of polyherbal systems, optimization remains a significant challenge due to complex interactions between active constituents and excipients. For formulation, trial-and-error methods are time consuming and are not adequate to study the interaction among actives and excipients. To overcome these limitations, factorial design-based optimization provides a systematic and efficient strategy to evaluate the individual and interactive effects of multiple formulation variables[14].

The effects of concentrations of coconut oil, carbopol, and shea butter on key physicochemical parameters were investigated. The optimized formulation was further evaluated for invitro antibacterial, anti-inflammatory and stability providing a safer and steroid-free herbal alternative for eczema management.

MATERIAL AND METHODS

Hydroalcoholic extracts of Glycyrrhiza glabra (licorice), Azadirachta indica (neem), and Salix alba (white willow bark) were procured from Alkem laboratories and authenticated prior to use. Colloidal oatmeal derived from Avena sativa was obtained from a pharmaceutical-grade supplier. All the chemicals used were of analytical grade.

Experimental design and Optimisation by factorial designing

A 2^3 full factorial design was employed to evaluate the effect of three independent formulation variables on selected response parameters. Design-Expert® software (Version XX) was used to generate the experimental matrix. Three factors Shea butter, Coconut oil and Carbopol were taken as independent variables. Two level (High and Low) for each factor were selected and its effect on Viscosity, spreadability and invitro drug release was analysed. Total 8 formulations were prepared and evaluated for physicochemical properties. The variables with their concentration is shown in Table 1 and 2^3 full factorial design layout is shown in Table 2.

Table 1: Variables and their lower and higher concentrations

Factor	Variable	Low Level (-1)	High Level (+1)
X_1	Shea butter (%)	7.0	8
X_2	Coconut oil (%)	5.5	6.5
X_3	Carbopol (%)	1.0	1.5

Table 2: 2^3 full factorial design layout for polyherbal cream

2^3 Full factorial design layout			
Run	**Shea butter (A)**	**Coconut oil (B)**	**Carbopol (C)**
1	-1 (7.0%)	-1 (5.5%)	-1 (1.0%)
2	+1 (8.0%)	-1 (5.5%)	-1 (1.0%)
3	-1 (7.0%)	+1 (6.5%)	-1 (1.0%)
4	+1 (8.0%)	+1 (6.5%)	-1 (1.0%)
5	-1 (7.0%)	-1 (5.5%)	+1 (1.50%)
6	+1 (8.0%)	-1 (5.5%)	+1 (1.50%)
7	-1 (7.0%)	+1 (6.5%)	+1 (1.50%)
8	+1 (8.0%)	+1 (6.5%)	+1 (1.50%)

Preparation of polyherbal cream [15-17]

All the ingredients were weighed accurately. Oil in water type of emulsion was prepared. In a container, accurately weighed ingredients of Oil phase (Coconut oil, shea butter, and emulsifying wax) were taken and heated to 70 ± 2°C in a water bath. In another container Carbopol 940 was dispersed in distilled water with continuous stirring to avoid lump formation and all the ingredients of water phase (herbal extracts, preservatives,

glycerine) were mixed and heated to 70 ± 2°C. The oil phase was added gradually into the aqueous phase with continuous stirring using a homogeniser. The emulsion was allowed to cool to room temperature and stored in an air tight container. The formulation composition of polyherbal cream is shown in Table 3.

Run	F1	F2	F3	F4	F5	F6	F7	F8
Emulsifying wax	4	4	4	4	4	4	4	4
Glyceryl monostearate (GMS)	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Colloidal oatmeal	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Willow bark extract	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Neem extract	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Licorice extract	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Phenoxyethanol + Ethylhexylglycerin	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Xanthan gum	0.150	0.150	0.150	0.150	0.150	0.150	0.150	0.150
Shea butter (A)	7.0	8.0	7.0	8.0	7.0	8.0	7.0	8.0
Coconut oil (B)	5.5	5.5	6.5	6.5	5.5	5.5	6.5	6.5
Glycerin (C)	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Carbopol 940	1.0	1.0	1.0	1.0	1.5	1.5	1.5	1.5
Distilled water	73.150	72.150	72.150	71.15	76.150	71.650	71.650	70.650

Table 3: Formulation composition of polyherbal cream

EVALUATION OF POLYHERBAL CEAM [15-18]

1. Organoleptic properties

Colour: The colour of the cream was visually observed.

Odor: It was examined by smelling the formulation.

Consistency: The cream was rubbed on hands manually and checked for greasiness and spreadability.

Homogeneity: A thin layer of cream was spread on a glass slide and observed under microscope for the presence of particles or fibers.

2. Type of emulsion

Dye test: The dye methylene blue was mixed with cream and a drop of cream was placed on the slide and covered with cover slip. The cream was observed under microscope for the color in dispersed phase and surrounding medium.

3. pH

pH of the cream was evaluated by using digital pH meter. 1 g of the cream was dissolved in 9 ml of distilled water (1:9 ratio) and stirred for 2 min. The solution was set aside for 5 min. and pH of the solution was determined.

4. Viscosity

Viscosity was determined by using Brookfield viscometer. 100g of cream was taken, mixed thoroughly and then stablilized at room temperature for 30 minutes. Spindle no. 63 was chosen and the speed was set to 100 rpm (torque between 10 to 90). The spindle was dipped in cream and allowed to rotate for 1 to 2 minutes. The viscosity displayed was recorded.

5. Spreadability

Spreadability was measured by using Glass plate method. Two slides were taken and on the bottom slide, 1 g of cream was placed exactly at the centre. The second slide was placed over the applied cream centrally. Standardised weight 100g was applied on the top plate for a minute. After 1 minute the weight was removed carefully and the upper slide was tied with a string and attached to a known weight (20g). The upper slide was allowed to pull by the tied weight. The time required for the upper slide to move a fixed distance was measured.

$$S = \frac{M \times L}{T}$$

Where:

- **S** = Spreadability
- **M** = Weight tied to upper slide (g)
- **L** = Length moved by slide (cm)
- **T** = Time taken (sec)

6. Washability

0.2 g cream was applied on 2 cm^2 area of the skin and rinsed under running water without the application of soap. The ease of washing and any left residue was checked.

8. Phase separation (centrifugation test at defined rpm/time).

Centrifugation tests were performed for the herbal cream immediately after preparation. The herbal cream was centrifuged at 13500 rpm at 25 ºC by placing sample in the tube.

9. In vitro release study

In vitro drug release was determined using franz diffusion cell with a diffusion area of 1 cm^2. Cellulose acetate membrane 0.45 µm was placed between donor and receptor compartment. Phosphate buffer with pH 5.5 was filled in the receptor compartment and the medium was kept inder constant stirring at 600 rpm using magnetic stirrer and the temperature was maintained at 32 ± 0.5 °C to simulate skin surface conditions. Approximately 0.5 g cream was weighed accurately in the donor compartment above the membrane. At predetermined intervals 0.5, 1, 2, 4, 6, and 8 h, 5 ml of the sample was withdrawn and replaced with fresh buffer maintained at same temperature. The sample was analysed for the presence of active constituents using validated HPLC. The cumulative amount of drug released per unit area (µg/cm^2) is plotted against time, and the release kinetics was evaluated by fitting the data to suitable mathematical models such as Higuchi and Korsmeyer–Peppas to describe the release mechanism.

10. In vitro anti-inflammatory activity[19]

The in vitro anti-inflammatory activity of the optimised cream (F7) was evaluated using the protein denaturation method. Bovine serum albumin (1% w/v solution) was prepared in phosphate buffer (pH 6.4). Test sample of different concentrations 10, 20, 30, and 40 and 50 µg/mL were prepared. The 2 ml test samples were added to 0.2 ml of BSA solution and the pH was adjusted to 6.4 using 1N HCl. The samples were incubated for 20 minutes at 37°C and then heated at 70°C for 5 minutes. After cooling, the absorbance was measured at 660 nm using a UV-visible spectrophotometer.

Diclofenac sodium was used as the standard reference drug, while the 0.2 ml (1%) BSA solution added with Phosphate buffer solution (pH 6.4) and 0.02 ml solvent without the test sample served as the control.

$$\% \text{ Inhibition} = \frac{A_c - A_t}{A_c} \times 100$$

11. Antimicrobial studies[20]

The in vitro antimicrobial activity of the cream was evaluated by the agar well diffusion method against positive bacteria and gram-negative bacteria such as Staphylococcus aureus and Escherichia coli. Meuler Hinton Agar was prepared according to clinical laboratory standards. 20 ml of the MHA was poured on the petri plate to maintain the depth of 4 mm and the plates was allowed to dry and solidify. Microorganism was inncoulated on the plate by using a sterile cotton swab. Using a sterile cork borer, 4 wells of uniform diameter (6 mm) were punched into the agar plate aseptically. The wells were labeled for different test samples, standard, reference and control. The cream was extracted with ethanol and a measured quantity of the polyherbal cream extract was introduced into the well labelled as sample using a micropipette. The standard drug (gentamicin) solution was used a positive control and was added into a separate standard well, while the solvent used for dilution served as a negative

control. The plates were incubated at 37°C for 24 hours, after which the antimicrobial activity was determined by measuring the diameter of the zone of inhibition around each well.

12. Irritancy test

A specific area of about 1cm sq. was marked on the dorsal surface of the hand. The cream was applied to the marked area and xthe time was noted. The area was checked for irritation, itching, redness, erythema, edema at regular intervals up to 24 hrs.

RESULT AND DISCUSSION

1. Organoleptic properties

All the batches of formulated cream were evaluated for organoleptic properties like Color, Odor, Homoginiety and Consistency. All the batches showed greenish brown color, characteristic odor and were homogeneous and consistent. The results are shown in table 1.

Table 4.: Organoleptic properties of Polyherbal cream

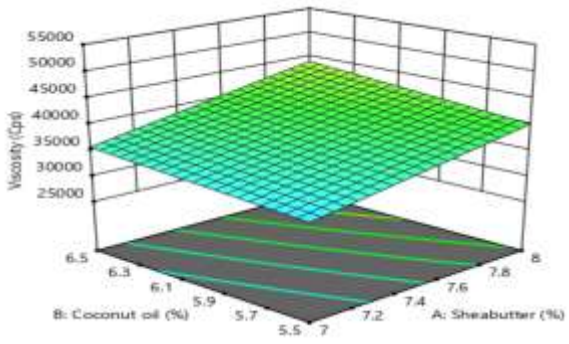
S/ No.	Evaluation Parameters	Observations							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	Color	Greenish brown	Greenish brown	Greenish brown	Greenish brown	Greenish brown	Greenish brown	Greenish brown	Greenish brown
2.	Odor	Characteristics	Characteristics	Characteristics	Characteristics	Characteristics	Characteristics	Characteristics	Characteristics
3.	Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
4.	Consistency	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent

2. Type of emulsion and pH

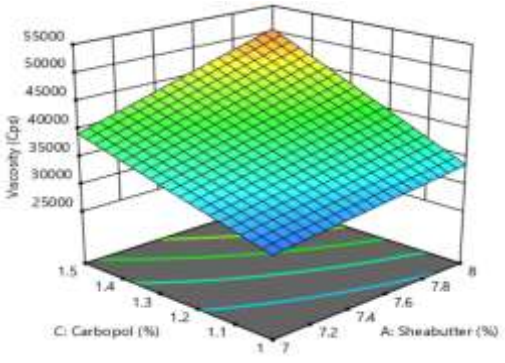
All the batches were found to be oil in water type of emulsion and pH of all batches was found to be in the range of 5.2 to 5.5 which is compatible with pH of the skin.

3. Viscosity

The viscosity range of the formulations was found to be in the range of 22,000 - 54,000 cps, indicating a semi-solid consistency of all the batches. On increasing concentration of Carbopol and sheabutter, viscosity increased. Highest viscosity was observed in F8 which has higher concentrations of sheabutter, coconut oil and Carbopol. Further, on increasing shear rate, the decrease in viscosity was observed indicating the pseudoplastic behaviour of cream. Results are shown in Table 5.



(a)



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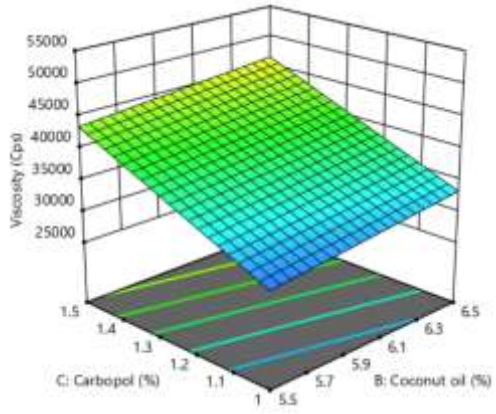
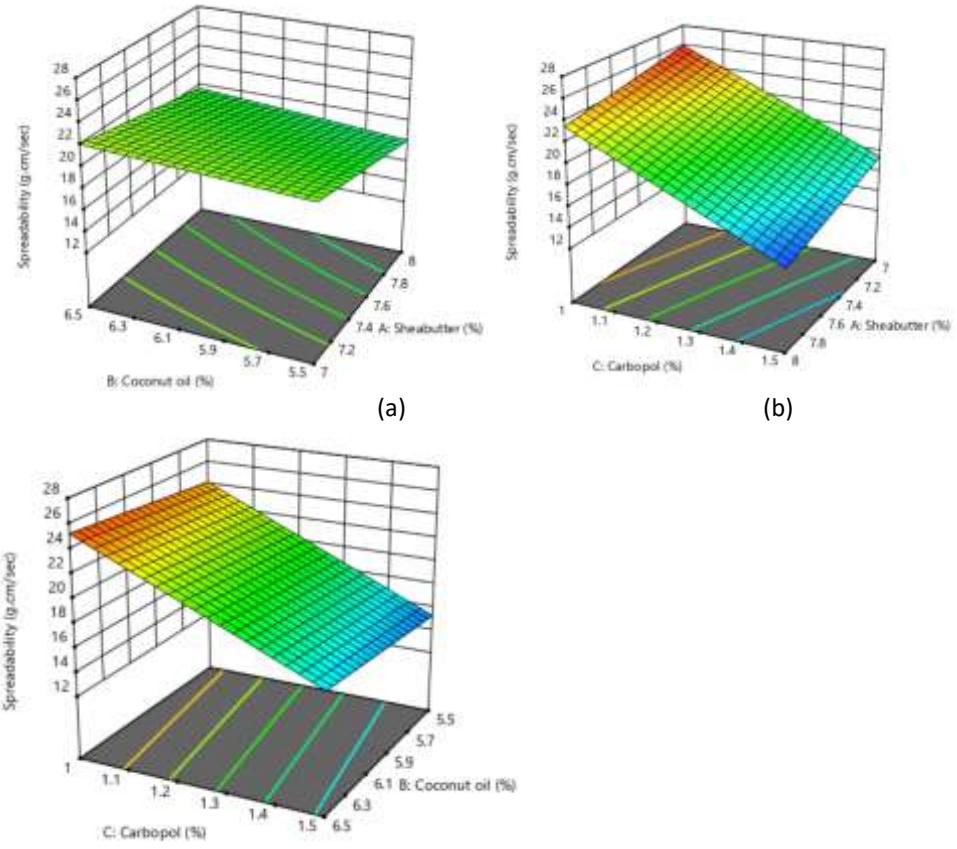


(c)

Figure 1. 3xD response surface plot showing the effect of different factors on the Viscosity of the polyherbal cream formulation. (a): Coconut oil and Sheabutter. (b): Carbopol and Sheabutter, (c): Coconut oil and Carbopol

4. Spreadability[16, 17]

The spreadability of the formulation was found to be in the range of 13 to 26 g.cm/sec. The average time required for the movement of the slide was found to be 6–9 seconds, indicating good spreadability of the cream. Formulation F3 showed maximum spreadability due to lower oil content. The 3D surface plots demonstrate the combined effect of sheabutter, Carbopol and coconut oil on the spreadability of the cream. (Fig.2) The plot demonstrate that on increasing concentration of sheabutter and carbopol, spreadability decrease



(a) (b)

(c)

Figure 2. 3D response surface plot showing the effect of different factors on the spreadability of the polyherbal cream formulation (a): Coconut oil and Sheabutter. (b): Carbopol and Sheabutter, (c): Coconut oil and Carbopol

Table 5: Results for the physicochemical properties of all Formulations (F1 to F8)

Formulation	Emulsion Type	pH	Viscosity (cP)	Spreadability (g·cm/sec)	Invitro drug release	Washability	Irritancy test
F1	O/W	5.4	27600	25.8 ± 0.4	97.1 ± 2.0	Excellent	Nil
F2	O/W	5.3	32000	22.6 ± 0.3	93.8 ± 1.6	Excellent	Nil
F3	O/W	5.5	31300	26.1 ± 0.4	96.1 ± 2.2	Good	Nil
F4	O/W	5.2	35250	24.4 ± 0.3	91.2 ± 1.3	Good	Nil
F5	O/W	5.4	38,500	16.8 ± 0.4	92.3 ± 1.4	Good	Nil
F6	O/W	5.3	48,309	13.78 ± 0.3	88.4 ± 1.4	Moderate	Nil
F7	O/W	5.5	40,100	18.2 ± 0.3	91.9 ± 3.2	Good	Nil
F8	O/W	5.2	52,800	15.1 ± 0.2	85.9 ± 2.5	Moderate	Nil

5. Invitro drug release

The invitro drug release study was performed on all the batches and the results are shown in Table no. 6. All the formulation showed satisfactory release and the maximum release was observed from F1 which may be due to lower viscosity and higher spreadability. After 12 hrs, the cumulative drug release ranged from 86 % to 97 %. It was observed that on increasing the concentration of coconut oil, sheabutter and Carbopol, drug release decreased due to less diffusion through hydrophobic matrix. The effect of different factors on invitro drug release of the polyherbal cream formulation are shown in Fig. 4.

Table 6: Cumulative Drug Release of Polyherbal Cream

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
1	19.1	18.02	20.1	17.6	16.52	16.02	18.22	19.31
2	31.16	29.17	33.3	28.9	27.61	28.6	30.75	31.82
3	42.14	41.01	42.68	39.03	43.12	35.8	46.62	45.09
4	56.8	54.46	57.4	51.04	48.32	45.6	59.33	52.06
5	78.16	75.43	79.16	72.3	71.14	58.8	74.12	70.31
6	87.09	89.15	89.6	86.13	82.5	71.3	89.4	76.32
7	91.51	90.4	92.25	88.14	84.5	74.2	94.4	79.62

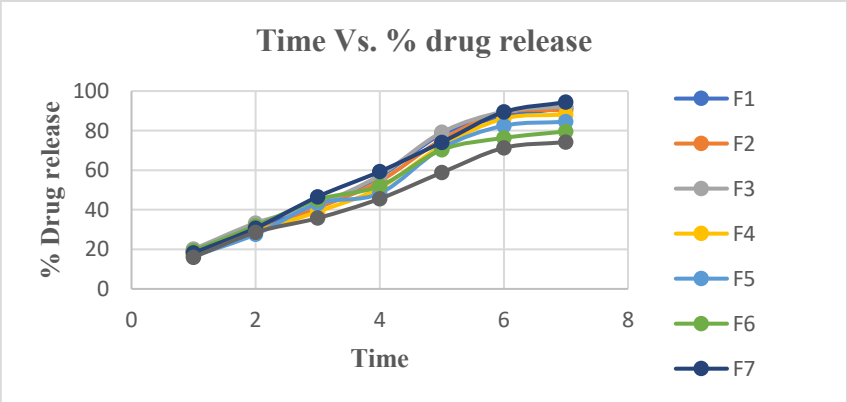
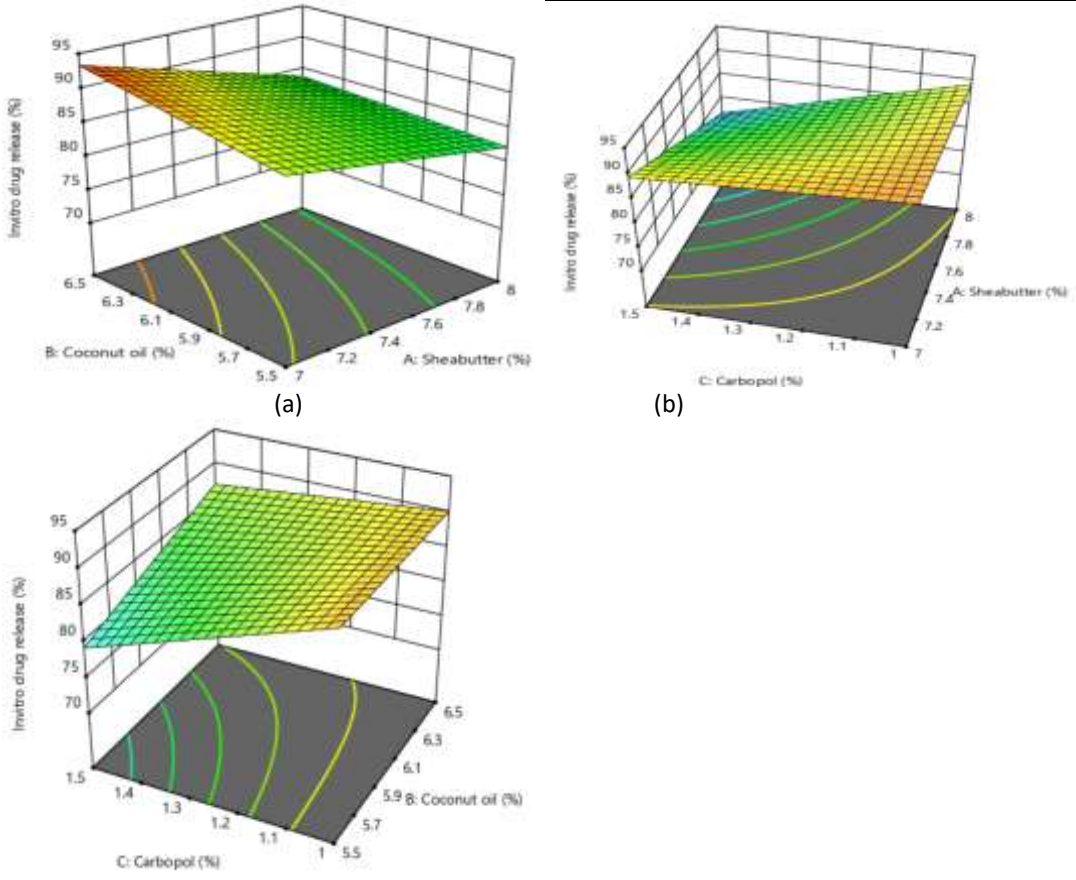


Fig 3. Invitro drug release for Polyherbal cream

Furthermore, the drug release data of the optimized formulation (F7) was fitted into various kinetic models. The Higuchi model was found to be the best fitted model having the highest correlation coefficient $R^2 \approx 0.992$. The results indicated that the drug release was diffusion controlled.

Table 7: Invitro drug release study of optimised batch (F7)

Time (h)	1	2	4	6	8	10	12
Cumulative Release (%)	18.22	30.75	46.62	59.33	74.12	89.4	94.4



(a) (b)

(c)

Figure 4. 3D response surface plot showing the effect of different factors on invitro drug release of the polyherbal cream formulation. (a): Coconut oil and Sheabutter. (b): Carbopol and Sheabutter, (c): Coconut oil and Carbopol

6. Optimisation and selection of best formulation

Based on the evaluation results of viscosity, spreadability and drug release, F7 was selected as the best formulation due to balanced viscosity, good spreadability and sufficient drug release.

Batch	pH	Viscosity	Spreadability	% Drug release at 12 hrs
F7	5.5	40,100	18.2 ± 0.3	94.4

7. Invitro anti-bacterial activity[17]

The invitro antimicrobial study was performed on the base cream and optimised formulation. The antimicrobial efficacy was compared with the standard cream against a gram positive and a gram-negative bacteria. The result of the study is shown in Table 8 and Fig. 5.

Table 8: Antimicrobial studies of optimised formulation

Test Sample	Zone of Inhibition (mm) against S. aureus	Zone of Inhibition (mm) against E. coli
Cream Base (Control)	7.0 ± 0.2	4.0 ± 0.8
Polyherbal Cream	21.2 ± 0.4	18.4 ± 0.6
Standard Drug	28.6 ± 0.7	30.1 ± 0.5

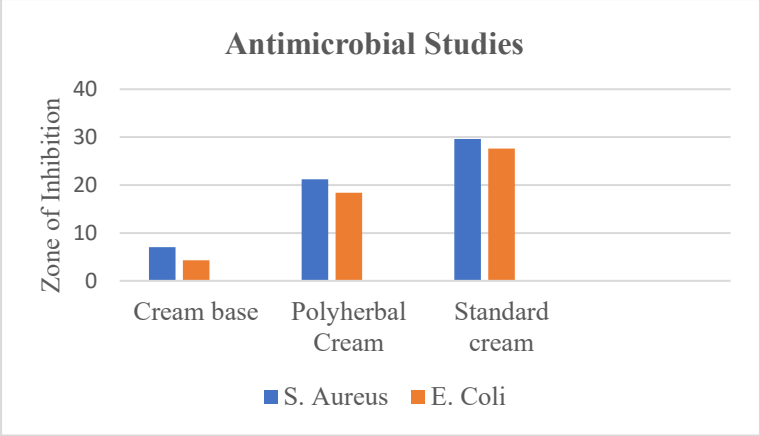


Fig 5. Antimicrobial studies of cream base, polyherbal cream and Standard cream

8. Invitro anti-inflammatory activity[18]

The anti-inflammatory activity of the optimised batch (F7) was evaluated using protein denaturation method. The absorbance of the control was found to be 0.9 and the absorbance of different concentrations of sample solutions and standard solution are shown in Table 9.

The formulation and the standard were evaluated at different concentrations ranging from 50 to 250 (µg/ml) and both the formulation and standard showed concentration dependent inhibition. At lower concentration the F7 batch showed 55.6 % inhibition which was lesser than that of the standard which showed 64.3% of inhibition. Maximum inhibition was seen at the highest concentrations which was 82.7 % and 96.77 % for F7 and Standard diclofenac solution respectively. The anti-inflammatory activity of the formulation was due to the synergistic effect of the phytoconstituents like glycyrrhizin, Azadirachtin which possess potent anti-inflammatory action.

Table 9: Invitro anti-inflammatory studies of optimised batch F7

S. No.	Concentration (µg/mL)	Absorbance (Test)	% Inhibition (Cream)	Absorbance Diclofenac sodium	% Inhibition (Standard – Diclofenac Sodium)
1.	50	0.399	55.6	0.324	64.3
2.	100	0.284	68.4	0.213	76.32
3.	150	0.241	73.2	0.146	83.75
4.	200	0.190	78.8	0.091	90.00
5.	250	0.155	82.7	0.029	96.77
6.	Control	0.9 ± 0.012			

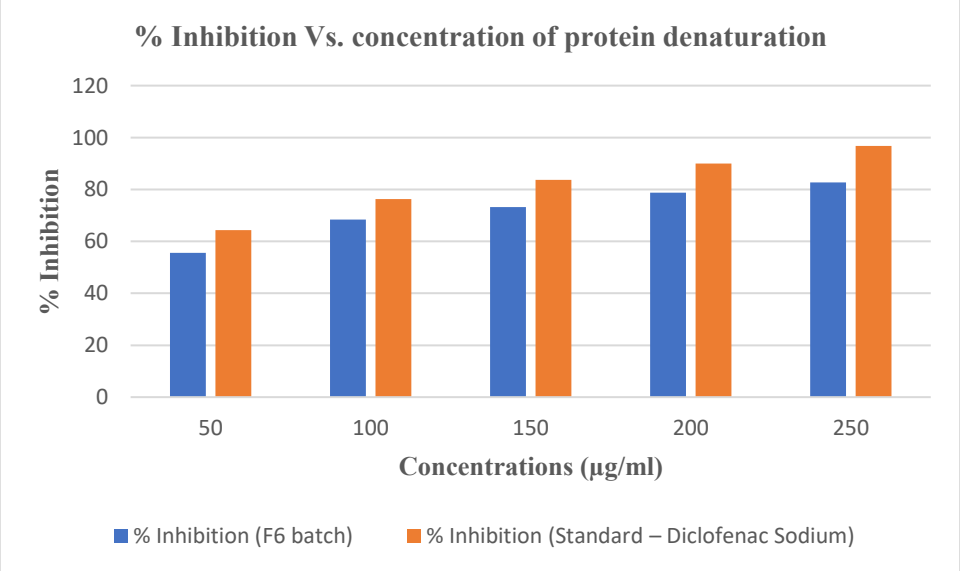


Fig. 6: % Inhibition Vs. concentration of protein denaturation

9. Stability studies

Accelerated stability studies were performed on optimised batch for three months at 40 ± 2°C and 75 ± 5% RH. Various parameters like appearance, pH, viscosity, phase separation and drug content were evaluated after each month. The formulation showed no significant changes in physicochemical properties indicating good stability. Results are shown in table 10.

Table 10: Stability studies of optimised batch

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Smooth, homogeneous	No change	No change	No change
Odor	Characteristic	No change	No change	No change
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous
pH	5.82 ± 0.03	5.80 ± 0.04	5.79 ± 0.03	5.77 ± 0.05
Viscosity (cP)	40100 ± 120	39910 ± 130	39450 ± 115	38420 ± 140
Spreadability (g·cm/s)	22.2 ± 0.3	23.8 ± 0.2	23.7 ± 0.4	23.5 ± 0.3
Phase Separation	Absent	Absent	Absent	Absent

CONCLUSION

In present study, polyherbal cream containing colloidal oat meal, coconut oil and extracts of Licorice, Neem and willow bark was successfully formulated and evaluated. Three factors two level Optimization was applied using Design expert software and total 8 formulations were prepared. Concentrations of sheabutter, coconut oil and Carbopol were taken as independent variables and its effect were analysed on viscosity, spreadability and invitro drug release. Batch F7 containing 7% sheabutter, 6.5 % Coconut oil, and 1.5 % Carbopol was selected as the optimised batch which showed the spreadability of 18.2 g.cm/sec, viscosity of 41000 cps and Invitro drug release of 94.4 % after 7 hours. The batch was smooth, homogeneous, easy to apply, had good washability, indicating both stability and user-friendliness The optimised batch was further evaluated for antibacterial, anti-inflammatory properties and stability. The results demonstrated that the formulation possess efficient antiinflamattory activity and antibacterial properties against gram positive and gram-negative bacteria.

The combination of different herbs provided a synergistic therapeutic effect through antibacterial, anti-inflammatory, skin-soothing, and barrier-restoring mechanisms. Furthermore, the presence of colloidal oatmeal and virgin coconut oil contributed to enhanced skin hydration and protection of the epidermal barrier.

The findings suggested that the developed polyherbal cream can serve a promising natural alternative for the management of eczema and other inflammatory skin disorders and also showed the potential of combining traditional medicinal plants with modern formulation

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