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Research Article

FORMULATION AND EVALUATION OF POLYHERBAL CREAM CONTAINING *Cinnamomum zeylanicum* BLUME, *Glycyrrhiza glabra* L AND *Azadirachta indica* A. JUSS EXTRACTS TO TOPICAL USE

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ABSTRACT

Alcoholic extracts of medicinal plants *Cinnamomum zeylanicum* Blume, *Glycyrrhiza glabra* L, and *Azadirachta indica* A. Juss were subjected to the evaluation of antioxidant properties and combined for the cream formulation. The antioxidant property was determined by using the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) assay and inhibition of lipid peroxidase assays. The cream formulation was designed using Minitab software and a central composite design was used to study the effect of dependent variables, steric acid and cetyl alcohol on the response variables such as, viscosity, pH, and spreadability. The phytochemical screening of extracts showed the presence of tannin, phenol, flavonoids, saponins, and alkaloids. Antioxidant properties of the extracts and their relative composition were found variable. Composition F3 (*C. zeylanicum* Blume: *G. glabra* L: *A. indica* A. Juss; 01: 02: 01) possessed the highest antioxidant capacity compared to other ratios. The cream prepared from this composition was found stable for pH, viscosity as well as antioxidant activity under normal condition (25 ºC) and accelerated condition (40 ºC). The cream with DPPH scavenging activity of 93.86 % at 15 µg/mL (IC_{50} 8.58±0.30) and lipid peroxidase assay 90.93 % at 200 µg/mL (IC_{50} 72.30±0.60) with pH 5.50 was found with a non-Newtonian positive thixotropic flow property. Parameters like pH, viscosity, and spreadability of the cream were within the acceptance range, and found stable and permeable.

Keywords: Antioxidant, Botanicals, Formulation, Polyherbal Cream, Quality

INTRODUCTION

Application of topical formulations with plant extracts included can help minimize oxidative stress in the skin and thereby delays skin aging by reducing the wrinkles, protecting against UV radiation, and prevent degradation of collagen. Herbal cosmetics products have been claimed for their efficacy and intrinsic acceptability and devoid of the side effects commonly seen in synthetic products. Currently, the use of extracts in formulations is common, due to consumers' concerns about synthetic ingredients/chemical substances (Masih & Singh, 2012). Several studies have shown the medicinal plants as the valuable alternative herbs for cosmetic purposes due to therapeutic properties complied with Ayurveda. The secondary metabolites of plant present in the skincare products support the strength, integrity and texture of the skin, while moisturize and maintain the elasticity of the skin by providing photoprotection and reducing collagen degradation (Kumar *et al.*, 2016a; Kumar *et al*., 2016b). Thus, the presence of herbal ingredients in skincare formulation helps reduce the production of free radicals in the skin and maintain for a long time. Active ingredients delayskin aging by reducing the wrinkles, protect against UV radiation by antioxidant property (Rousseaux & Schachter, 2003). A plethora of research have claimed that, skincare products get therapeutic benefit by the addition of plant-based active ingredients such as alpha-hydroxy acid, retinoic acid, ascorbic acid, and coenzyme Q10 (Knott *et al.*, 2015).

The extracts used to manufacture numerous cosmetics, produced from *Glycyrrhiza algebra* L (Bradley, 1992; Visavadiya *et al*., 2009; Ju *et al.*, 1989; Cronin & Draelos, 2010; Ashawant *et al*., 2008), *Azadirachta indica* A. Juss (Arivazhagan *et al.*, 2000; Kareru *et al*., 2010; Ngo *et al.*, 2017; Maurya *et al*., 2014, Zeenat et al., 2018) and *Cinnamomum zeylanicum* Blume, (Bisset, 1994; Vangalapati *et al.*, 2012; Ratz-Lyko *et al.*, 2012; Mancini-Filho, 1998; Nabavi *et al.*, 2015) are evaluated for their therapeutic benefits. The possibility of obtaining specific therapeutic effects from a complex mixture of natural extracts is currently considered a key element of modern herbalism and skincare (Marks, 1997; Koo & Desai, 2003). This approach was designed to develop a novel herbal formulation with the basic composition of antioxidant-rich herbal extract for skincare products.

MATERIALS AND METHODS

Materials

The plants, *G. glabra* L, *A. indica* A. Juss, and *C. zeylanicum* Blume were collected in September 2016 from the local market of Kathmandu Nepal, identified by Department of Pharmacy, Kathmandu University, and stored as an herbarium specimen (HR 022, HR023 and HR024, respectively) in the Department of Pharmacy,

Kathmandu University, Dhulikhel, Nepal. DPPH was purchased from Sigma-Aldrich. Cetyl alcohol, and stearic acid were purchased from Godrej Industries, India. Ethanol and other solvents used in the experiment were HPLC grade.

Preparation of extract

The powdered leaf samples were extracted in ethanol using a Soxhlet apparatus for 24 hours. The extracts were filtered, then concentrated to dryness under a controlled temperature in rotavapor (Buchi R215, Switzerland), and preserved in a refrigerator.

Phytochemical Screening

The plant extracts were assessed for the existence of the phytochemical classes as described by Trease and Evans (2002), and Harborne (1973).

Herbal Formulation

Based on phytochemical screening, different compositions were prepared to obtain the best antioxidant combinations of herbs (Table 1). The plant composition was made as per the previously described method (Krishnan *et al.*, 2017) by blending the individual plant to obtain an optimized antioxidant combination of such herbs.

Table 1. Composition of herbs to optimize the antioxidant property for cream formulation

Plants	Composition 1	Composition 2	Composition 3	Composition 4
C. zeylanicum Blume	1	2	1	1
G. glabra L	1	1	2	1
A. indica A. Juss	1	1	1	2

Antioxidant activity test of extracts

The reference of ascorbic acid and the plant extract solutions (100, 50, 25, 20, 12.5, 10, 6.25, 5, 2.5 ppm) were prepared in ethanol. Diphenylpicrylhydrazyl (DPPH) 100 µg/mL (5.0 mL) and methanol (2.0 mL) were added into 1.0 mL of each extract sample solution. Methanol and DPPH solution was made as blank. The mixture was shaken and incubated at room temperature for 30 minutes. The antioxidant activity was determined by measuring the absorbance of each sample by UV-Vis spectrophotometer (Shimadzu UV 1800, Japan) with an optimum wavelength of 514 nm using equation (1). All readings were taken in triplicate. The ratio possesses the highest antioxidant activity that was selected for the formulation of the herbal cream by loading in the cream base (Bradley, 1992; Sharma & Bhat, 2009).

$$\text{DPPH scavenging activity (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100 \quad (1)$$

Where, $A_{control}$ is absorbance of DPPH solution without sample, and A_{sample} is absorbance of sample.

Cream preparation

The cream was prepared by mixing the three types of plant extract in the base formula following the previously described method with slight modification (Gyawali *et al*., 2016). The base was prepared by adding a non-polar phase (steric acid and cetyl alcohol) to the polar phase (water, triethanolamine, glycerine) with rapid stirring to avoid separation of an oil phase and water phase (Table 2). Both polar and non-polar phases were heated to 75 °C and blended slowly. Steric acid and cetyl alcohol were used as an independent variable while spreadability, pH, and viscosity as dependent variables. A mathematical relationship for measured dependent and independent variables was developed using statistical software Minitab. Three output variables (responses) such as viscosity, pH, and spreadability were evaluated.

Antioxidant activity of formulated cream

DPPH Scavenging Activity: A total of one gm of formulated cream and cream base was dissolved in 25 mL of ethanol separately, stirred for 10 min, and filtered. A total of 5 mL of filtrate was diluted to different concentrations (15, 10, 7.5, 5, 2.5 ppm) and then evaluated for DPPH scavenging activity (Sharma & Bhat, 2009).

Lipid peroxidation activity: Lipid peroxidation inhibition of CE in egg yolk extract was performed according to the previous method with minor modifications (Rajneesh *et al*., 2008). A total of 100 mL egg yolk homogenate was prepared in a 1000 mL 1.15 % KCl solution. A total of 0.5 mL of yolk homogenate was added with 0.10 mL of the extract of different concentrations by making the final volume of 1.0 mL with distilled water.

Thereafter, 0.05 mL of $FeSO_4$ (0.07 M) was added and the mixture was incubated at 37 °C for 30 min. Then, 1.5 mL of acetic acid was added followed by 1.5 mL of thiobarbituric acid (0.06 M) in sodium dodecyl sulfate. The resulting mixture was vortex mixed and heated at 95 °C for 1 hour. After cooling, 5 mL of butanol was added and the mixture was centrifuged at 3000 rpm for 10 min. The absorbance of the organic upper layer was measured at 532 nm against blank as control and the percentage inhibition was calculated with the formula, as depicted in equation (2).

$$\text{Inhibition of lipid peroxidation}\,(\%) = (1 - \frac{A_{sample}}{A_{control}}) \times 100 \quad (2)$$

Where, $A_{control}$ is absorbance without sample, and A_{sample} is absorbance with sample.

Table 2. Cream formulation using different chemicals and extract

Formulation	Composition of Formulation (% w/w)						
	Steric acid	Cetyl alcohol	TEA	Glycerine	Sodium benzoate	Extract	Water
F 1	10.50	3.50	1.2	8	0.02	1	75.78
F 2	10.50	2.00	1.2	8	0.02	1	77.28
F 3	10.50	3.50	1.2	8	0.02	1	75.78
F 4	10.50	3.50	1.2	8	0.02	1	75.78
F 5	10.50	3.50	1.2	8	0.02	1	75.78
F 6	10.50	5.00	1.2	8	0.02	1	74.28
F 7	20.00	3.50	1.2	8	0.02	1	66.28
F 8	3.78	2.43	1.2	8	0.02	1	83.57
F 9	10.50	3.50	1.2	8	0.02	1	75.78
F 10	0.00	2.43	1.2	8	0.02	1	87.35
F 11	1.00	3.50	1.2	8	0.02	1	85.28
F 12	3.78	4.56	1.2	8	0.02	1	81.44
F13	17.21	4.57	1.2	8	0.02	1	68.00
Optimized	11.50	2.48	1.2	8	0.02	1	75.62

Optimization of formulation base

The formulation was optimized using a response optimizer in Minitab software. The excipients used as variables were stearic acid and cetyl alcohol. Desirability function was calculated for pH (Y1), viscosity (Y2), and spreadability (Y3) using the software. Based on the ratio obtained from the software final optimized formulation was developed.

Evaluation of pharmaceutical parameters of cream

pH

Cream pH was measured with a digital pH meter (Jaya Sri Lab Instruments, Hyderabad, India). A total of 10 % solution of cream was prepared in distilled water and the solution was immersed in the pH meter.

Viscosity

Viscosity was evaluated in Brookfield viscometer using the LV-64 spindle. The rotation rate was adjusted to 25 rpm. The formulated cream was directly immersed into the spindle and the viscosity was measured, as described elsewhere (Kumar *et al.*, 2016b).

Spreadability

The spreadability of cream was determined by the parallel plate method. Two glass slides of 20/20 cm were selected. About one gm of the cream formulation was placed over one of the slides. The other slide was placed upon the top of the cream such that the cream was sandwiched between the slides and 125 gm weight was placed upon the upper slide so that cream between the two slides was pressed uniformly to form a thin layer. The weight was removed and the spread diameter was measured (Garg *et al.*, 2002).

Sensitivity

A portion of cream was applied on the forearms of 6 volunteers and left for 20 min. After 20 min any kind of irritation if occurred was noted (Draize *et al.*, 1944).

Washability

A portion of cream was applied over the skin of the hand and allowed to flow under the force of flowing tap water for 10 min. The time when the cream completely removed was noted.

Appearance

The color, odor, and homogeneity of the cream were visually determined.

Type of emulsion test

Dye solubility and dilution tests were conducted to determine the type of emulsion formed. In this test, an emulsion was mixed with a water-soluble dye (amaranth) and observed under the microscope. Continuous phase appearing red was considered as the emulsion is o/w type while scattered globules appearing red and continuous phase colorless were considered as w/o type. In the

dilution method, to find out the oil in water emulsion, it was diluted with an aqueous solvent whereas to find out the water in oil emulsion, it was diluted with an oily liquid.

Permeability of cream

In-vitro permeation study was conducted using Franz diffusion cell (Electrolab India Pvt Ltd, India). The cellophane membrane was used to separate the donor compartment and the receiver compartment. The donor compartment was applied with 0.3 gm of cream sample and the receiver compartment was filled with phosphate buffer solution (pH 7.40). The temperature of the diffusion medium was thermostatically controlled at 32 ± 1° C by surrounding water in jacket and the medium was stirred by magnetic stirrer at 100 rpm. The sample (1 mL) was withdrawn as per predetermined (30 min, 60 min, 120 min, 180 min, 240 min) intervals and replaced by an equal volume of fresh fluid (Inoue *et al.*, 2014). The sample withdrawn was studied for their percentage DPPH scavenging activity with phosphate buffer solution as blank. The activity was converted to percentage release using the formula, as given in equation (3):

$$\text{Percentage release} = \left(\frac{\%\ \text{activity of sample}}{\%\ \text{activity of cream}}\right) \times 100 \qquad (3)$$

Stability test

To assess the formulation stability, the cream was filled in a bottle and kept at 25±2 °C (room temperature) and 40±2 °C for three months in a hot air oven. They were studied for properties like pH, viscosity, spreadability, and antioxidant activity (Mishra *et al.*, 2014).

RESULTS AND DISCUSSION

Phytochemical screening

The chemical grouping was performed and Table 3 shows that the nature of secondary metabolites is variable within the plants. However, phenolic compounds responsible for the antioxidant property are common.

Table 3. Phytochemical classes present in plant extracts

Phytoconstituents	Test	*C. zeylanicum*	*G. glabra*	*A. indica*
Glycosides	Keller-Killani test	-	+	+
Alkaloids	Dragendroff's test	-	-	+
Flavonoids	Lead acetate test	+	+	+
Saponins	Froth test	+	+	+
Tannins	Ferric chloride test	+	+	+
Phenolic compounds	Ferric sulfate test	+	+	+
Terpenoids	Salkowski's test	+	+	+

The phytochemical screening of extract from *G. glabra* L, *A. indica* A. Juss, and *C. zeylanicum* Blume showed the presence of tannin, phenol, flavonoids, saponins, and alkaloids. Most ingested flavonoids are extensively degraded to various phenolic acids, some of which still possess a radical-scavenging ability. The absorbed flavonoids display an *in-vivo* antioxidant activity, which is evident from an increase in the plasma antioxidant status (Mancini-Filho *et al.*, 1998; Cheng *et al.*, 2012).

Antioxidant properties

The antioxidant assays measured the relative antioxidant ability of the extracts to scavenge the free radicals produced in the reagents. Antioxidant properties of the extracts and their relative composition varied. Composition F3 (*C. zeylanicum* Blume: *G. glabra* L: *A. indica* A. Juss; 01: 02: 01) possessed the highest antioxidant capacity compared to other ratios (Figs. 1 and 2). The polyherbal antioxidant preparation containing extracts of *G. glabra* L, *A. indica* A. Juss, and *C. zeylanicum* was shown to exhibit excellent antioxidant properties. Composition F3 was considered as the optimized phytochemicals and further evaluated for IC_{50}, which shows potential with a pattern similar to ascorbic acid (Fig. 3).

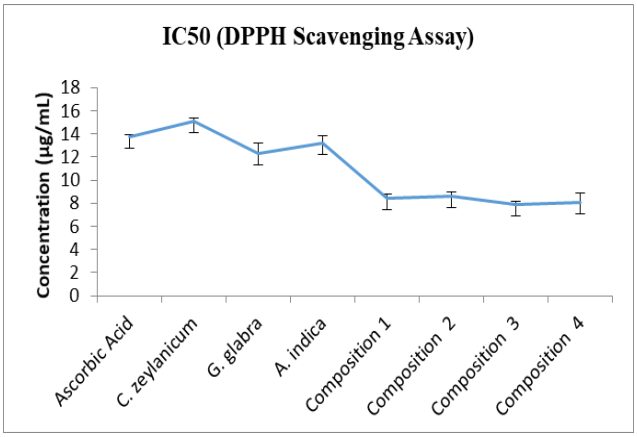

Fig. 1. Antioxidant properties (IC_{50}) of extracts and their combinations by DPPH assay

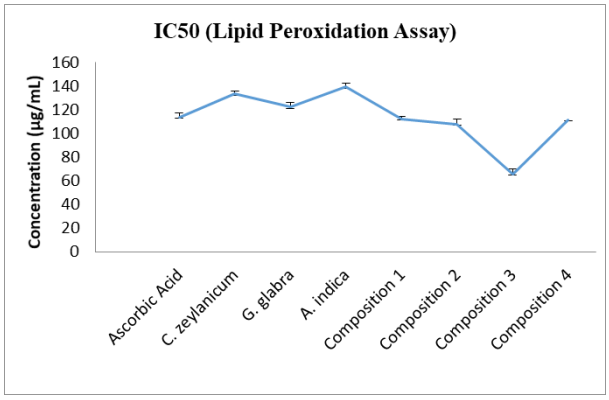

Fig. 2. Antioxidant properties (IC_{50}) of extracts and their combinations by lipid peroxidation assay

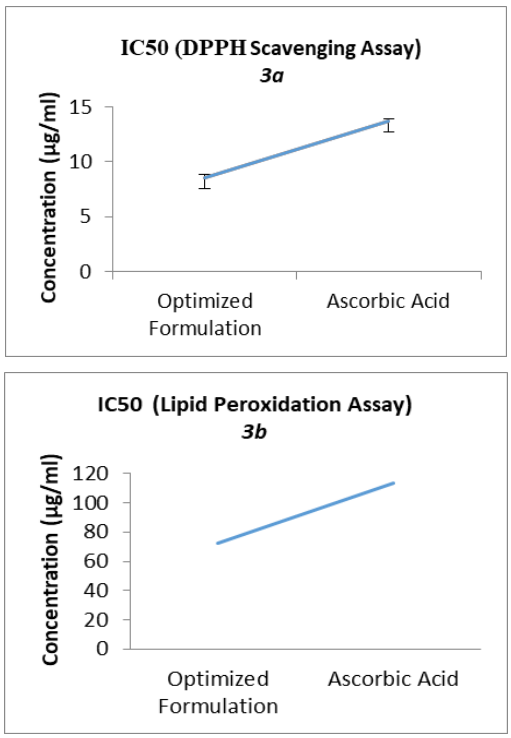

Fig. 3. Antioxidant IC_{50} of optimized formulation by DPPH assay (3a) and lipid peroxidation assay (3b)

In a previous study, *G. glabrous* was responsible for powerful antioxidant activity, similar to our observation of 12.28 µg/mL, and identical result in the DPPH assay with IC_{50} value of 28.3µg/mL was reported (Visavadiya *et al.*, 2009). Inhibition of lipid peroxidation was 21 % at 50 ppm which was similar to our study (Franceschelli *et al.*, 2011). Some studies on *C. zeylanicum* were related to present findings (Lee *et al.*, 2002; Mancini-Filho *et al.*, 1998; Kiranmai *et al.*, 2011; Deka *et al.*, 2013). A recent study showed IC_{50} of *C. Zeylanicum* to be 15.08 µg/ml which was very identical (15.08 µg/mL) to this findings (Mancini-Filho *et al.*, 1998; Cheng *et al.*, 2012). Recent research also showed that from overlapping or complementary effects, the complex mixture of phytochemicals in the selected herbs provides a better protective effect on health than single phyto-constituent (Eberhardt *et al.*, 2000). Our result is supported by previous findings that, *A. indica* leaf possesses an antioxidant property (Arivazhagan *et al.*, 2000).

Effect on the viscosity of the cream

It was observed that cetyl alcohol has harmful whereas the stearic acid has a positive effect on the viscosity. An increase in the concentration of cetyl alcohol decreased viscosity, but increase in the concentration of Stearic acid increased the viscosity (Fig. 4). The model proposed the following polynomial equation (4) for viscosity:

Viscosity=1388+179 steric Acid+212 cetyl alcohol+23.38 steric Acid*steric acid-94 cetyl alcohol*cetyl alcohol +230.8 steric acid*cetyl alcohol (4)

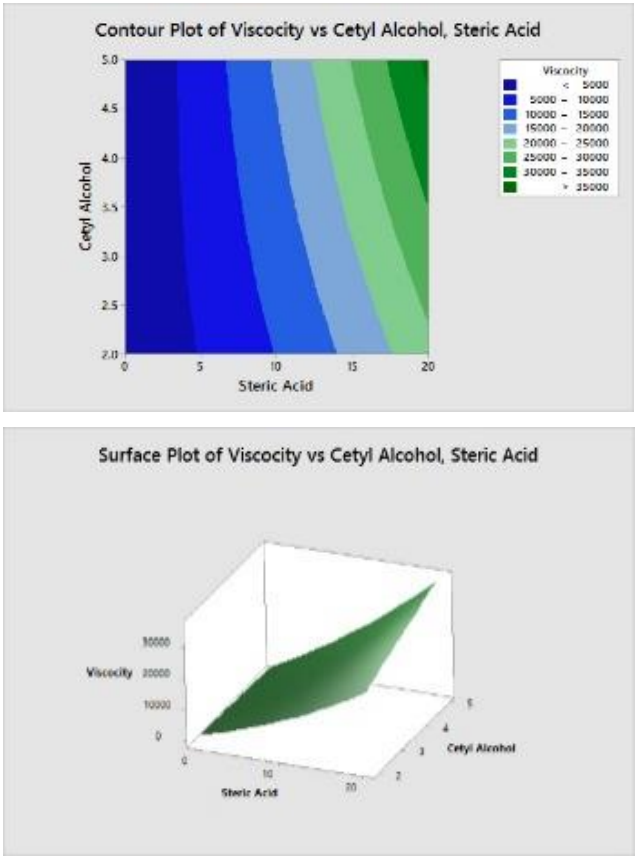

Fig. 4. Contour plot and response surface plot elucidating the relationship between the viscosity and independent variables

Effect on pH of cream

The pH of the cream was within the limit which indicated that the lotion is stable and safe to use for skin. The pH of cream influences stability. The stability of lotion increased with an increase in the viscosity of the medium (Fig. 5). The model proposed the following polynomial equation (5) for pH:

pH=6.38+ 0.241 Steric acid- 0.12 cetyl alcohol 0.02326 steric acid*steric acid-0.011 cetyl alcohol*cetyl alcohol-0.0099 steric acid*cetyl alcohol (5)

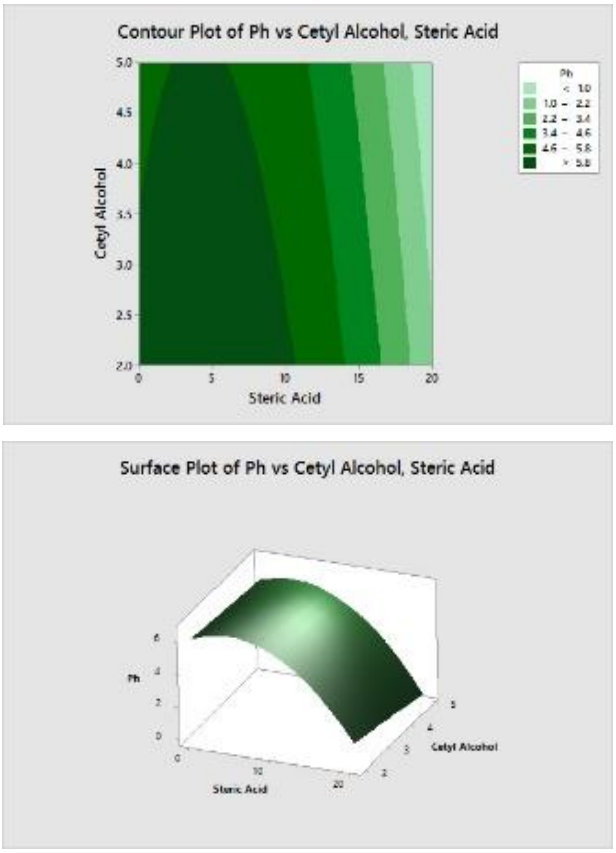

Fig. 5. Counter plot and response surface plot elucidating the relationship between pH and independent variables

Effect on spreadability of cream

Cetyl alcohol has a positive effect so an increase in the concentration of cetyl alcohol increased the spreadability of cream. In contrast, as the concentration of stearic acid increased the spreadability of the lotion decreased. The positive coefficient value of cetyl alcohol indicated the increase in spreadability as the concentration of stearic acid increased (Figs. 6 and 7). The model proposed following polynomial equation (6) for spreadability of cream.

Spread ability = 18.41- 0.689 stearic acid- 0.88 cetyl alcohol - 0.01028 steric acid*steric acid - 0.300 cetyl alcohol*cetyl alcohol+0.1646 steric acid*cetyl alcohol (6)

A plethora of research on a pharmaceutical cream proposed that semisolid preparations containing one or more medicinal agents dissolved or dispersed in either water-in-oil (w/o) emulsion or oil-in-water (o/w) emulsion or in another type of water-washable base. The stability was relatively good in amphiphilic creams of various unstable extracts (Eros *et al.*, 1994).

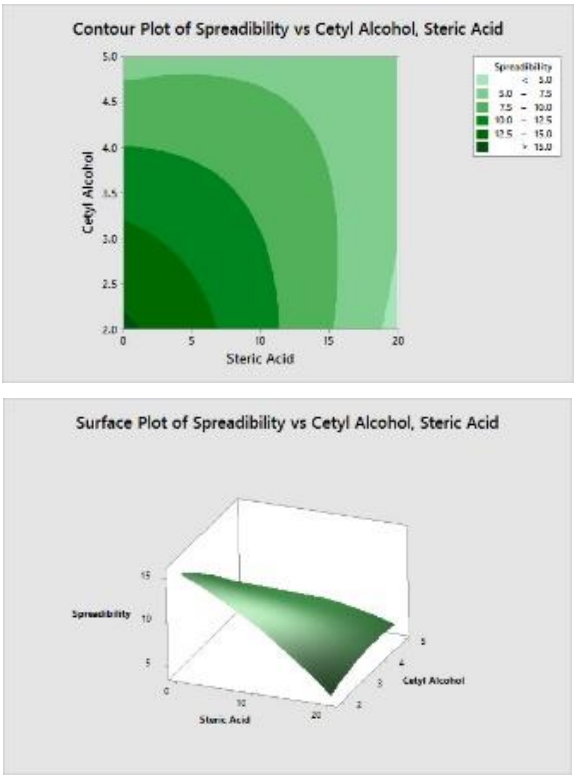

Fig. 6. Counter plot and response surface plot elucidating the relationship between pH and independent variables

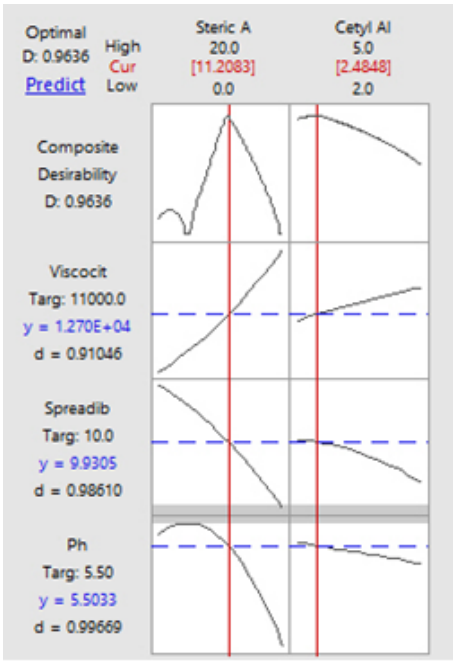

Fig. 7. Response optimization plot

Optimization of the base formula of the cream

The pH range suitable for a hand cream is 4 to 7 and the desired range for spreadability is between 7 and 13 cm.

The viscosity should be such that the cream can be easily spread over the skin surface. The pH, viscosity and spreadability parameters were within the limit and suitable for application over the skin (Table 4).

Table 4. Physical parameters of formulated cream

Sample	pH	Viscosity (cP)	Spread ability (gm*cm/sec)	Sensitivity	Wash ability time (min)
F1	5.50	13812	9.00	No Irritation	5.00
F2	5.70	10520	11.25	No Irritation	6.00
F 3	5.40	14000	10.00	No Irritation	4.75
F 4	5.50	13910	09.00	No Irritation	4.50
F 5	5.50	13800	09.00	No Irritation	5.00
F 6	5.80	16000	07.50	No Irritation	7.50
F 7	1.00	30000	05.00	No Irritation	9.00
F 8	6.00	5399	11.25	No Irritation	4.50
F 9	5.50	13800	10.00	No Irritation	4.75
F 10	8.50	1000	15.00	No Irritation	1.00
F 11	6.00	1413	12.85	No Irritation	2.00
F 12	5.40	6185	6.92	No Irritation	5:45
F13	1.20	28950	6.00	No Irritation	8.00
Optimized	5.50	11500	10.00	No Irritation	5.00

Rheology

It was found that the viscosity decreased as the rotational speed of the viscometer increased suggesting that the greater the shearing, lower the viscosity. Rheogram was drawn by measuring the shear stress by changing the shear rate of each formulation. A comparative study of viscosity and spreadability showed that as the viscosity of the formulations increased, spreadability decreased, and vice versa (Figs. 8 and 9).

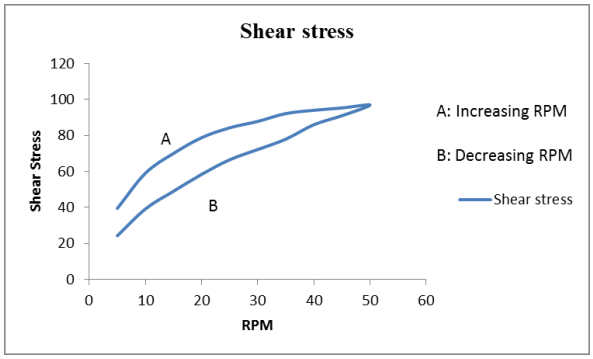

Fig. 8. Rheogram of optimized formulation (shear stress vs shear rate)

From Rheogram, it was found that most of the cream followed positive thixotropy. Among all the creams optimized and checked for accelerated study condition at room temperature, formulation F10 underwent phase separation. Since Stearic acid was not added in F10, it could have resulted in insufficient emulsification and thus the phase was separated (Miller *et al.*, 1997). For the optimized formulation at real-time and accelerated stability analysis for 2 months, the value of pH, viscosity, and spreadability and DPPH scavenging activity were within the required range since no change in activity was observed. This indicated there was no interaction between extract and the excipients.

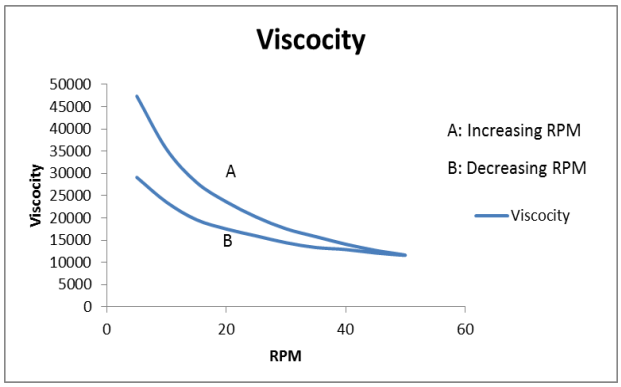

Fig. 9. Rheogram of optimized formulation (viscosity vs shear rate)

The stability

The stability of the final optimized cream was found stable at room temperature and accelerated temperature for at least three months. The value of pH, viscosity, and spreadability were within the required range. There was no major difference in values of pH, viscosity, and spreadability compared to the initial value (Table 5).

Table 5. Stability at room temperature and accelerated temperature of optimized cream

Parameters	Initial value	Room Temperature (25±2 °C)		Accelerated Temperature (40±2 °C)	
		1 month	3 months	1 month	3 months
Viscosity (cP)	11500	11550	11515	11485	11480
pH	5.50	5.60	5.65	5.80	5.70
Spreadability (g.cm/sec)	10.00	9.50	10.35	10.26	10.00
Scavenging Activity (%)	95.76	95.77	95.72	95.76	95.77

Permeation profile

It was found that formulations F1, F2, F3, F5, F8, F9, F11, F12, and the optimized formulations followed the first order permeation kinetics while F6, F7, and F13 followed zero-order kinetics of permeation (Table 6). The zero-order model characterizes a drug delivery system that does not disaggregate, permeation of the active substance being slow, independent of the initial drug concentration.

Table 6. Permeation profile of formulated creams

Formulation	Release (%)				
	0.5 hr.	1 hr.	2 hr.	3 hr.	4 hr.
F1	25.1	45.2	70.15	84.9	91.2
F2	19.5	48.3	73.2	84.7	93.1
F3	22.3	44.6	70.6	84.3	90.2
F4	26.5	42.5	68.2	85.1	91.3
F5	22.3	42.2	72.3	82.1	85.8
F6	14.9	38.2	58.5	77.5	86.3
F7	10.2	23.9	44.2	60.2	83.2
F8	42.1	68.2	81.2	81.1	89.2
F9	22.3	44.6	70.6	84.4	90.1
F11	47.5	72.3	84.4	90.1	91.2
F12	41.5	74.2	85.5	87.7	90.1
F13	13.1	26.7	53.3	68.6	86.3
Opt	27.3	41.2	68.4	76.2	84.1

In contrast, the first-order model best describes a permeation process that is directly proportional to the drug concentration embedded in the vehicle. Assuming a homogeneously dispersed drug in a planar matrix and under perfect sink conditions, Higuchi's mathematical model suggests a pure diffusion permeation mechanism of the active substance from a vehicle, with neither erosion nor swelling of the matrix. The Korsmeyer-Peppas model can be used as a decision parameter between the Higuchi and zero-order models.

Since it is a conventional cream, we expect the first-order release and for an extended-release cream, the release was expected to be zero order. But in formulations F6, F7 and F13, zero-order release was observed. As per the characteristics of cream, it possessed high viscosity and the literature suggested a reciprocal correlation between the viscosity of ointments and the quantity of the released drugs (Erös *et al.,* 1994). Thus the initial permeation decreased and followed a constant rate of release independent of concentration.

It was found that formulation F1, F2, F3, F5, F8, F9, F11, F12, and the optimized formulations followed First order permeation kinetics while F6, F7, and F13 followed Zero-order kinetics of permeation. Assuming a homogeneously dispersed drug in a planar matrix and under perfect sink conditions, Higuchi's mathematical model suggests a pure diffusion permeation mechanism of the active substance from a vehicle, with no occurring erosion or swelling of the matrix. The Korsmeyer-Peppas model can be used as a decision parameter between the Higuchi and zero-order models. As per the characteristics of the cream, it possessed higher viscosity and literature suggested a reciprocal correlation between the viscosity of ointments and the quantity of the released drugs (Erös *et al.*, 1994). Thus, the initial permeation decreased and followed a constant rate of release independent of concentration (Table 7).

CONCLUSION

A topical polyherbal cream with a strong antioxidant property was prepared in this research. The formulated cream with a pH of 5.50 has non-Newtonian positive thixotropic flow property. Stearic acid and cetyl alcohol both have a significant effect on viscosity. As the concentration of cetyl alcohol increases, the viscosity of cream increases while an increase in the concentration of stearic acid causes reduced spreadability of the cream. The formulation was optimized and important parameters like pH, viscosity, and spreadability were within the acceptable range, thus a well permeable polyherbal topical cream was developed.

Table 7. Permeation regression coefficient (r^2) of formulated creams

	Zero Order	First Order	Higuchi	Korsemeyer	Peppas
Formulation	r^2	r^2	r^2	N	r^2
F1	0.9836282	0.97197	0.978225	0.621664	0.968983
F2	0.959775	0.96967	0.954638	1.174943	0.980854
F3	0.9760842	0.983196	0.968893	0.912675	0.990197
F4	0.9904598	0.958831	0.985573	0.888278	0.986687
F5	0.9623089	0.99551	0.945252	1.119582	0.989793
F6	0.9814156	0.956221	0.986747	1.226174	0.985231
F7	0.9752888	0.852782	0.986256	1.167626	0.977611
F8	0.8492599	0.937241	0.843212	0.342837	0.923479
F9	0.9757464	0.983671	0.968482	1.872282	0.961578
F11	0.8504964	0.963588	0.856063	1.076501	0.876501
F12	0.7716641	0.922337	0.767371	1.038692	0.989954
F13	0.9969057	0.904023	0.997326	2.225777	0.861114
Opt	0.9859888	0.993712	0.970160	0.631309	0.997160

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