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FORMULATION AND EVALUATION OF TRANSDERMAL CREAM OF CURCUMIN PREPARED USING NOVEL ABSORPTION BASES AND PERMEABILITY ENHANCER

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ABSTRACT

In present study, leading objective is to prepare and evaluate transdermal cream of curcumin by using three absorption bases namely Shata dhutaghrita, mauhaoil and shea butter along with α -bisabolol as permeability enhancer. Total six batches were prepared (F0-F5) and estimated for physical form, drug content, pH, Spreadability, *In vitro* diffusion and *ex-vivo* permeability studies in association with marketed formulation. Study showed that creams were bright yellow in color. *In vitro* release analysis reveals that the F5 batch had higher drug release than the marketed formulation. Therefore, F5 batch is an optimized batch. The *ex vivo* permeability showed that F5 formulation is more permeable than marketed formulation. The release kinetic data shows that the exponent value of F5 batch is greater than 0.9 which reveals that release kinetic of F5 batch follows supercase II transport drug release mechanism.

KEYWORDS:

Curcumin, Shata dhutaghrita, Mauha oil, Shea butter, α -bisabolol.

INTRODUCTION

Turmeric is made from rhizomes of Zingiberaceae plant *Curcuma longa*. Curcuminoids, which comprise 77 % curcumin and two related chemicals, 17% demethoxycurcumin and 6% bisdemethoxycurcumin, have been credited with much of the pharmacological activity of turmeric¹. The most significant component of turmeric that is involved in biological activity is curcumin. Milobedska et al. provided the first description of yellow-coloured polyphenolic substance known as curcumin². It is known as diferuloylmethane or bis-unsaturated diketone in its chemical form¹. From cancer to Alzheimer's disease, it is used to treat a variety of illnesses. Even when taken at very large doses, it was shown to be safe¹. Chemically named as diferuloylmethane, curcumin has molecular weight of 368.37 g/mol and is polyphenol molecule that occurs naturally. The aryl rings are properly linked to a diketone moiety and include two ortho-methoxy phenolic OH groups. The melting point of curcumin is 183 °C. Two of the more common tautomeric forms of curcumin are the 1,3-diketo form and the 1,3-dienol form (Fig.1).

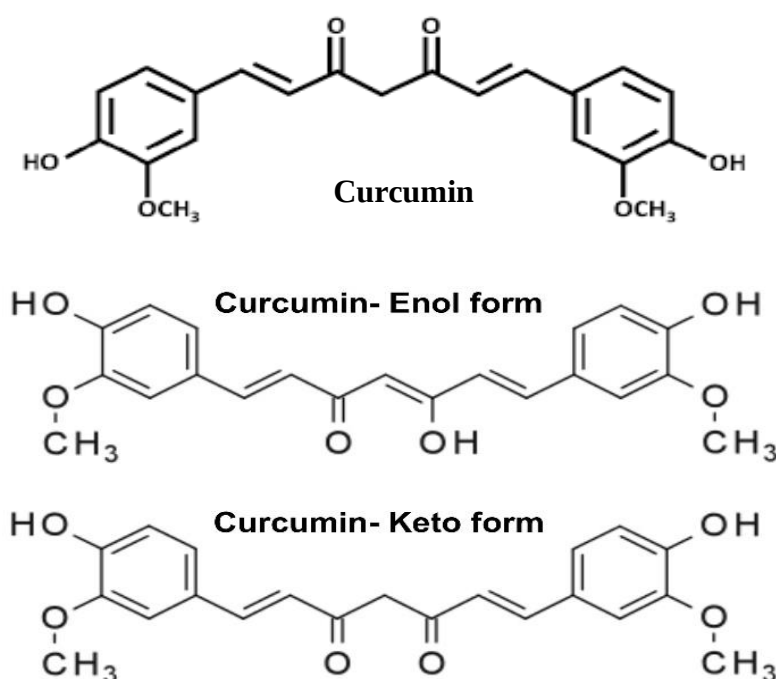


Figure 1: Chemical Structure of Curcumin with Its Derivatives

Physicochemical characteristics, biological processes, and anti-oxidant actions of curcumin are all strongly influenced by the amount of keto-enol forms present². Although enol arrangement is stable in solid phase or solution, their relative concentrations can change depending on temperature, solvent polarity, pH, and substitution of aromatic rings³.

Solutions with a pH greater than 8, the enol form is more common; in acidic to neutral conditions, with a pH of 3, the keto form is more common and is an effective free radical scavenger³. While basic circumstances can enhance curcumin's solubility, its hydrophobic nature makes it poorly soluble in water and hydrophilic solutions. Organic solvents like alcohol, methanol, isopropanol, acetone, and DMSO have a higher solubility of curcumin than hexane, cyclohexane, tetrahydrofuran, and dioxane, which have an intermediate solubility³.

Curcumin is a hydrophobic compound, so having very poor solubility and low permeability, so it categorized as a BCS class IV drug molecule¹. Therefore, there is need of research to improve its solubility, permeability and hence bioavailability. There have been numerous attempts to raise the solubility, stability, and permeability of curcumin in order to increase its bioavailability.

Despite having positive pharmacodynamics, curcumin has poor pharmacokinetics, which results in very low bioavailability because of extremely low solubility and low permeability. Additionally, it has a quick metabolism and systemic elimination. Curcumin has a very poor solubility in water (11 ng mL^{-1}), especially at physiological and acidic pH levels. It breaks down easily when exposed to strong light, high temperatures, or oxidizing conditions. It hydrolyzes quickly in alkaline solutions⁴. Because it is poorly soluble in water and has a high barrier to diffusion, curcumin is considered a BCS class IV drug molecule⁵. To boost curcumin's bioavailability, numerous efforts have been completed to rise its absorption, solubility and stability. It is also possible that Curcumin taken orally has a high first-pass metabolism. Therefore, several attempts were made to employ curcumin in another way, like on the skin or in the buccal cavity. For local and systemic medicinal purposes, transdermal administration (skin route) presents an alluring alternative to oral delivery. Transdermal drug delivery is regarded as a practical method for administering medications because it can escape first-pass metabolism. The skin barrier from the stratum corneum, however, is a significant barrier to transdermal medication administration. The top layer of skin makes it difficult for most medications to penetrate through⁶.

Various methodology has been attempted to improve curcumin penetration through the skin to get better results on curcumin as a drug.

Nikunjana et. al. observed anti-inflammatory belongings of curcumin delivered topically in gel form. Gels were made using carbopol 934P and hydroxypropylcellulose as polymer and using menthol as penetration enhancer. *In vitro* studies on the transdermal penetration of curcumin from a drug reservoir system consisting of carbopol and hydroxy propyl cellulose gel showed that menthol enhanced penetration of curcumin⁸.

Melak Mohammed Al-Busaid et. al prepared curcumin moisturizing conditioner cream by using the wet gum technique. The cream was a striking brilliant yellow color and had a very smooth texture and having cream pH to be around 4.5. Culturing the herbal cream with Muller Hinton agar medium allowed to check for the presence of microorganisms. After being incubated at 37°C for 24 hours, there was no evidence of harmful microbial development and the results were comparable to the control. After stability testing, it was evident from the results that the cream had remained stable⁹.

Vandana D. et al. developed a topical gel using curcumin to combat fungal skin infections. With a viscosity of 6500.3 cps and a drug diffusion rate of 97.5% *in vitro* for 8 hours. The improved formulation exhibited zero-order release kinetics. Research on the anti-fungal properties of curcumin gel by *in vitro* study revealed that it effectively inhibits the growth of *Candida albicans* and *Escherichia coli*, with a renaturation potency of 76% ($p=0.0507$). The resultant product showed as promising antifungal agent; it was a stable topical gel with improved *in vitro* diffusion¹⁰.

Among various methodology have been researched and developed, the most common approach is application of penetration enhancer. So, in this research we were used natural terpenes i.e. sesquiterpene alcohol as penetration enhancer. We focus on to improve permeability, stability of curcumin to enhance bioavailability which help to increase therapeutic efficacy of curcumin as well as to prepare cost effective formulation by formulating transdermal cream of curcumin using three absorption bases (Shata dhautaghrita, shea butter and mahua oil) along with α -bisabolol as permeability enhancer.

For the present study, shatadhutaghrita was reported to be on absorption base because it acts like a Yogavahi (carries the drug with it) and help the drug to penetrate deep into tissues¹¹. Shata dhautaghrita made according to traditional Ayurvedic methods. A hundred is shata, wash is dhauta, and Indian cow's ghee is ghrita. The ghee from Desi cows is washed using water by spinning by using copper vessel which involves mixing water and ghee that kept in a copper pod by trituration. The water remains after washing need to be decanted allowing ghee to be remain on the copper pod. After 100 spins, each round is finished, hence 100 rounds are needed to make shatadhauta ghrita¹¹.

Shea butter contains sixteen different types of fatty acids like oleic, stearic, palmitic, linoleic, and arachidic acid. Shea butter is a wonderful component that can soothe irritability, relieve dry skin, and stop cell deterioration. Shea butter can melt or liquefy at body temperature, which is a significant additional benefit. Allergy sufferers who use shea butter are safe. Shea butter aids in moisture retention, leaving the skin soft and smooth. Because of the high concentration

of anti-inflammatory and antioxidant chemicals in it, it might help to keep the skin supple¹². Mahua oil was discovered to be readily available, inexpensive, non-toxic, biodegradable, and comparable in qualities to synthetic excipients. It was also found to be chemically inert and non-toxic. To the best of our knowledge, however, and based on the information found after examining numerous databases, the use of mahua oil as an emulsifier in the formulation of any w/o based cream has not yet been researched¹³.

The sesquiterpene alcohol α -bisabolol was utilized as permeability enhancer. It is a key component of essential oil of chamomile and is found in numerous healthiness products¹⁴.

MATERIALS AND METHODS

Curcumin (96%) was supplied gift sample by Biogen Extract Pvt. Ltd., Bangalore. TBHQ was supplied as gift sample by Aarnee International Pvt. Ltd, Ahmedabad. Span 80(MONEMUL-80Hi) was supplied as gift sample by Mohini Organic Pvt. Ltd, Mumbai. Shea butter purchased from Mangalam AgroCitSprayAroma Sciences, Nagpur. Mauha oil purchased from Dagadutaili, Nashik. α - Bisabolol was purchased from Sigma Aldrich, Mumbai and Dialysis membrane-70 (LA 393) purchased from Dolphin Pharmacy Instruments Pvt. Ltd. Mumbai. Cetyl Alcohol, Tween 80, Methyl Paraben, Propyl Paraben, Butylated hydroxy toluene (BHT), Methanol-AR Grade were procured from Modern Science, Nashik.

Pre-formulation study

I) Drug Characterization:

A. Organoleptic Properties of Curcumin

- a) **Color:** A small quantity of curcumin was taken in butter paper and viewed in well illuminated place.
- b) **Odor:** Very less quantity of APIs was smelled to get odor.
- c) **Appearance:** Appearance was detected by visual appearance

B. Melting Point:

The melting point is the first sign that the sample is pure. Open capillary method was used to find the melting point of curcumin. Curcumin was filled in the glass capillary whose one end was previously closed by using flame. After that, the capillary was dipped into the liquid paraffin that was inside the melting point device. The liquid paraffin of melting point apparatus was heated and melting point range was recorded.

C. Determination of $\lambda_{\max}$ by UV Spectrophotometer

UV-Vis Spectra of curcumin drug was observed at 200-800 nm on UV Spectrophotometer (Chemito, Spectrascan UV-2700). The $\lambda_{\max}$ of solution of curcumin drug (9.6 $\mu\text{g/mL}$) was determined in Methanol.

Calibration Curve of Curcumin in Methanol

• Standard Stock Solution

10mg curcumin drug (96% w/w) dissolve in methanol AR grade. The solution was put into a volumetric flask of 10 mL, and methanol AR grade was used to make up the rest of the volume to produce stock solution A.

Working Stock Solution

1 mL of Stock-A was taken out with a pipette and transferred it into 10 mL of volumetric flask and mixed with methanol AR grade to make the volume up to 10 mL. A series of curcumin

dilutions were made from working stock solution of $96\mu\text{g mL}^{-1}$ by pipetting out 1 mL, 0.8 mL, 0.6 mL, 0.4 mL, and 0.2 mL, respectively into separate 10 mL volumetric flasks and diluting up to 10 mL with methanol to produce the concentrations ranging from 1.92 to $9.6\mu\text{g mL}^{-1}$. Absorbance of ready solution was measured at 420 nm. Calibration curve was created through plotting graph among concentrations versus absorbance.

D. Fourier Transform Infrared Spectroscopy (FT-IR)

A Shimadzu 8400 FT-IR analyzer was used to record infrared spectrum of pure curcumin. For the sample, the KBr disc method was used (2.0 mg sample in 100 mg KBr). It was then tested in transmission mode. The spectrum was measured using a range of frequencies from 4000 to 400 cm^{-1} . After that, the peaks found in the spectrum were compared to curcumin structure that relevant functional groups of curcumin.

E. Drug-Excipient Compatibility Study

Curcumin drug and other excipients were weighed accurately. The drug excipient compatibility study was conducted by taking Drug-Excipient in 1:1 % w/w ratio for test and control samples. The mixtures were then transferred to previously clean and dried vials. Vials were sealed using rubber closure and aluminum crimp. The control samples were kept at room temperature outside the humidity cum photo stability chamber, while test samples were kept within humidity cum photo stability chamber maintained at $40 \pm 2^\circ\text{C}$ temperature and $75 \pm 5\%$ RH for a period of 7 days. The samples were then observed visually for change in color, odor and appearance.

F. Drug-Excipient Compatibility Assay

2 mg of drug excipient mixture (equivalent to 0.96 mg of curcumin) of test and control samples of curcumin were taken in 10 mL volumetric flask. The content was dissolved by using methanol AR grade and volume was made up to 10 mL with methanol. From the prepared solution pipette was used to take out 1 mL of the sample in 10 mL volumetric flask. The sample was dilute up to 10 mL by using methanol AR grade. The sample was analyzed at 420 nm and concentration was found out by utilizing a calibration graph.

Preparation of Shata Dhauta Ghrita

The copper vessel was cleaned thoroughly and rinsed with distilled water. 50g previously measured Gir cow ghee was taken in copper vessel. About 50 mL of distilled water was added to Gir cow ghee, and mixture was mixed with some pressure by using hand copper agitator. The things that were in the metal vessel were left to settle. Care was taken not to lose any of the ghee while carefully pouring water out of the copper pot. The above steps were repeated after adding 50 mL of fresh distilled water to cow ghee that had already been cleaned. To get

shatadhautaghrita, this process was done one hundred times (1round = 100 rotations). Glyceryl monostearate (0.15% w/v) was mixed into the ready-made shatadhautaghrita to make it more uniform. The prepared homogenized shatadhautaghritawas collected and stored in plastic container at ambient temperature for further work.

Characterization of Shata Dhauta Ghrita:

The organoleptic characters of shatadhautaghrita like appearance, color, odor, texture and pH were observed and compared with Gir cow ghee.

FORMULA DESIGN

Creams were prepared by using trituration method. Drug, excipient, and cream base were taken in different amount as per the formula. The formula with ingredients is shown in Table VII and Table VIII

Table VII: Ingredients and Category of Cream

Sr.no	Ingredient	Category
1	Curcumin	Anti-inflammatory
2	Ceyl alcohol	Emulsifier
3	Shea Butter	Absorption base & Skin smoothing
4	Mauha oil	Absorption base& <i>Moisturizer</i>
5	Span 80	Emulsifier
6	Shata-Dhauta-Ghrita	Absorption base
7	Tween 80	Emulsifier
8	Tert-butylhydroquinone (TBHQ)	Anti-oxidant
9	Methyl Paraben	Preservative
10	Propyl Paraben	Preservative
11	Butylated hydroxytoluene (BHT)	Anti-oxidant
12	α - Bisabolol	Penetration enhancer

I. Formulation of Curcumin Anti-Inflammatory Cream

The amounts of drug and other materials were measured out according to Table VIII, and the formulation was made in the way shown below.

Table VIII: Composition of Curcumin Transdermal Cream

Ingredients	F0	F1	F2	F3	F4	F5
Curcumin (g)	0.2	0.2	0.2	0.2	0.2	0.2
Shea butter (g)	1	1	1	1	1	1
Mauha oil (g)	1.74	1.74	1.74	1.74	1.74	1.74
Span 80 (g)	0.15	0.15	0.15	0.15	0.15	0.15
Shata- Dhauta- Ghrita (SDG) (g)	6.782	6.7714	6.761	6.75	6.74	6.73
Tween 80 (g)	0.12	0.12	0.12	0.12	0.12	0.12
Butylated Hydroxy Toluene (BHT) (g)	0.002	0.002	0.002	0.002	0.002	0.002
Methyl paraben (g)	0.001	0.001	0.001	0.001	0.001	0.001
Propyl paraben (g)	0.003	0.003	0.003	0.003	0.003	0.003
TBHQ (g)	0.002	0.002	0.002	0.002	0.002	0.002
α - Bisabolol (g)	0	0.0106	0.0213	0.032	0.042	0.053
Total weight (g)	10	10	10	10	10	10

1. All glassware were washed and dried in hot air oven.
2. Given quantities of all ingredients and curcumin drug were weighed.
3. Formulation of transdermal cream of curcumin was prepared using previously cleaned and dried mortar and pestle.
4. Beaker A: - Weighed 1 g of shea butter and allowed to melt by using water bath.
5. Beaker B: - Weighed 1.74g of mauha oil and to it 0.15g span 80 was added by stirring.
6. Beaker C: - Weighed shatadhautaghrita according to formula and to it 0.12g Tween 80 was added by stirring and allowed to melt by using water bath.
7. Weighed cetyl alcohol and curcumin as given in formula in mortar and triturate it well.
8. Add melted shea butter in mortar with continue stirring.
9. Now added solution of beaker B and beaker C in mortar content with continue trituration. Contents were triturated till the homogenized mass is formed.

10. Then methyl paraben, propyl paraben, BHT was added followed by the addition of the TBHQ, along with further addition of alpha bisabolol in mortar content.
11. The mixture was mixed unidirectional to obtain homogenous and uniform cream. The formulated cream was then transferred to a suitable light resistant container, labelled and evaluated for different evaluation parameters.

II. Evaluation of Transdermal Cream of Curcumin:

The produced cream was assessed for pH, spreadability, drug content, *in vitro* drug release and *ex vivo* permeability investigations.

Physical Evaluation

All formulations were observed by visual inspection after cream were set in the container.

a) pH

pH of formulation was measured by digital pH meter, which was previously been calibrated. pH of prepared cream was measured by dipping pH meter in cream formulation. pH of topical cream formulation found to be in between 5.31 to 5.45.

b) Determination of Spreadability

Spreadability apparatus was cleaned and dried. 1 g of preparation was weighed and was placed on the fixed slide. The upper slide connected with the pan through pulley by thread was kept over the fixed slide. 100 g weight is kept on upper slide for uniform spreadability and removal of bubbles from the cream for 2 min. Afterwards weight was gradually added in pan and time was noted down for upper slide to travel half of distance from fixed slide. After that, spreadability was determined by using following formula given below.

$$\text{Spreadability} = \frac{\text{Weight put to upper slide} \times \text{Length of glass slide}}{\text{Time taken to separate two slides (sec)}}$$

$$\text{Spread ability} = \text{Weight put to upper slide} \times L / T$$

c) Determination of Drug Content

Curcumin content in cream was measured by taking 1 g of cream in 100 mL volumetric flask and dissolved by using methanol and making up its volume up to 100 mL. After that, 0.1 mL was pipetted out and diluted up to 10 mL in a volumetric flask. A UV Visible Spectrophotometer was used to measure absorbance at 420 nm. Above same procedure was carried out for determination of drug content of marketed cream i.e., Patanjali beauty cream.

d) *In Vitro* Drug Release and its Comparison With Marketed Formulation

Using a dialysis membrane -70 (LA 393) positioned among donor and receptor compartments of Franz diffusion cell apparatus (Dolphin, Mumbai), an *In vitro* drug release study of 2% curcumin cream was conducted. On the donor side, 1 g of cream was applied. The water jacket

was kept circulating to maintain temperature of Franz diffusion cell at $37 \pm 2^{\circ}\text{C}$. Entire assembly was maintained on magnetic stirrer, and magnetic beads were used to continually stir diffusion fluid (a pH 7.4 solution of phosphate buffer) at a speed of 200 rpm. After 15, 30, 60, 120, 180, 300, and 360 min, 2 mL of sample was removed, and same volume was replenished with new diffusion fluid (phosphate buffer of pH 7.4) to maintain sink condition. Samples were analyzed by spectrophotometer at 420nm and %CDR was calculated.

e) Ex Vivo Permeability Study of Optimized Formulation & Its Comparison With Marketed Formulation

Ex vivo permeation study was performed using ear of pig on six station digital Franz diffusion cell apparatus (Dolphin, Mumbai). The ear of pig was collected from local slaughter house. The ear of pig was cleaned and its hairs were removed. The shaved ear was placed between donor and receptor compartment of Franz diffusion cell. Then 1 g cream of optimized formulation, F0 and marketed formulation (Patanjali beauty cream) was applied on donor side of ear of Pig of Franz Diffusion Cell. Temperature of the cell was maintained constant $37 \pm 2^{\circ}\text{C}$ by circulating water jacket. Complete assembly was kept on magnetic stirring and diffusion fluid (phosphate buffer of pH 7.4) solution was continuously stirred using magnetic beads at 200rpm. 2 mL of sample was withdrawn and same volume was replaced with fresh diffusion fluid (phosphate buffer of pH 7.4) to maintain sink condition. Samples were withdrawn at 15, 30, 60, 120, 180, 300 and 360 min. Samples were analyzed at 420 nm and amount of drug permeated was determined in comparison with marketed formulation.

f) Calculating Flux, Diffusion coefficient and Permeability Coefficient (kp)

Flux (J) is amount of drug crossing semi permeable membrane per unit time. Result was shown in Table XV & table XVI

Formula:

$$J = \frac{V (dc/dt)}{\pi r^2}$$

Where,

J = Flux

V = Volume of fluid in cell

dc/dt = Slope of % release Vs time plot

r = Radius of cell

Diffusion coefficient / Permeability coefficient:

$$K_p = J/C_0$$

Where, K_p = Diffusion coefficient / Permeability coefficient

J = Flux

C_0 =Initial concentration of drug

g) Kinetic Assessment of *InVitro* Release of Drug From Prepared Cream

Release data obtained was assessed into several scientific models like Zero, First order, Hixon crowell model, Higuchi model and Korsmeyer peppas model¹⁵. Results were shown in Table XVII

RESULT AND DISCUSSION

Pre-formulation Study of Drug:

A. Organoleptic Properties:

Table I represents the results obtained for the drug samples organoleptic characters such as color, odor and appearance.

Table I: Organoleptic Properties of Curcumin Drug.

Identification test	Observed result	Reported standard
Color	Bright yellow	Bright yellow
Odor	Pungent	Pungent
Appearance	Amorphous	Amorphous

B. Melting Point of Curcumin

The melting point determined by capillary tube method. The results are shown in Table II & compared with reported standard. Curcumin was observed to have a melting point between 180 and 182 °C, which is extremely close to the 183 °C published standard. Thus, we deduce that curcumin was pure.

Table II: Melting Point of Curcumin

Sample	Observed melting point	Reported melting point
Curcumin	180 °C to 182°C	183°C

C UV-Visible Spectrophotometric Analysis of Curcumin

Absorption Maxima Wavelength ($\lambda_{\max}$) of Curcumin in Methanol:

Curcumin was showing the maximum absorbance at 420 nm in methanol. The Absorption maximawavelength of curcumin in methanol shown in Figure 2.

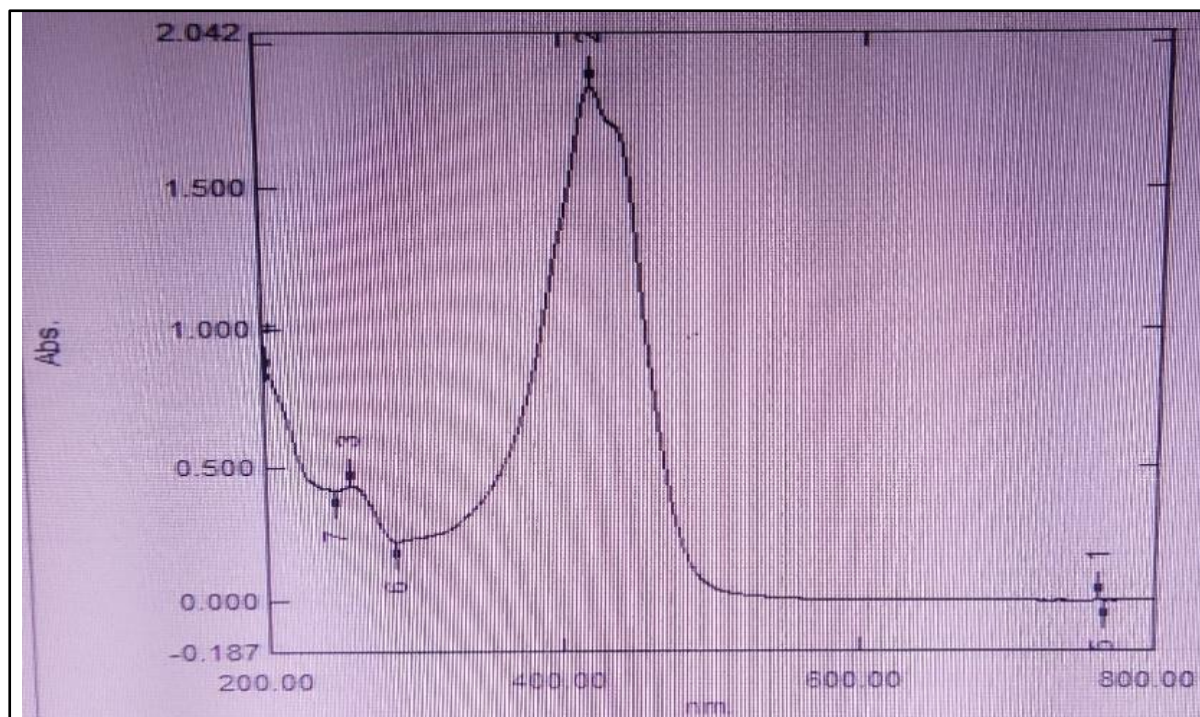


Figure 2: UV-Visible Spectrum of Curcumin in Methanol

Construction of Beer's Lamberts Plot of Curcumin in Methanol:

The Beer's lamberts plot for curcumin in methanol was constructed. The regression coefficient of the lines obtained in methanol was found to be 0.9881 which is shown in Figure3. The linearity in methanol was found in concentration range of 1.92-9.6 μ g/mL.

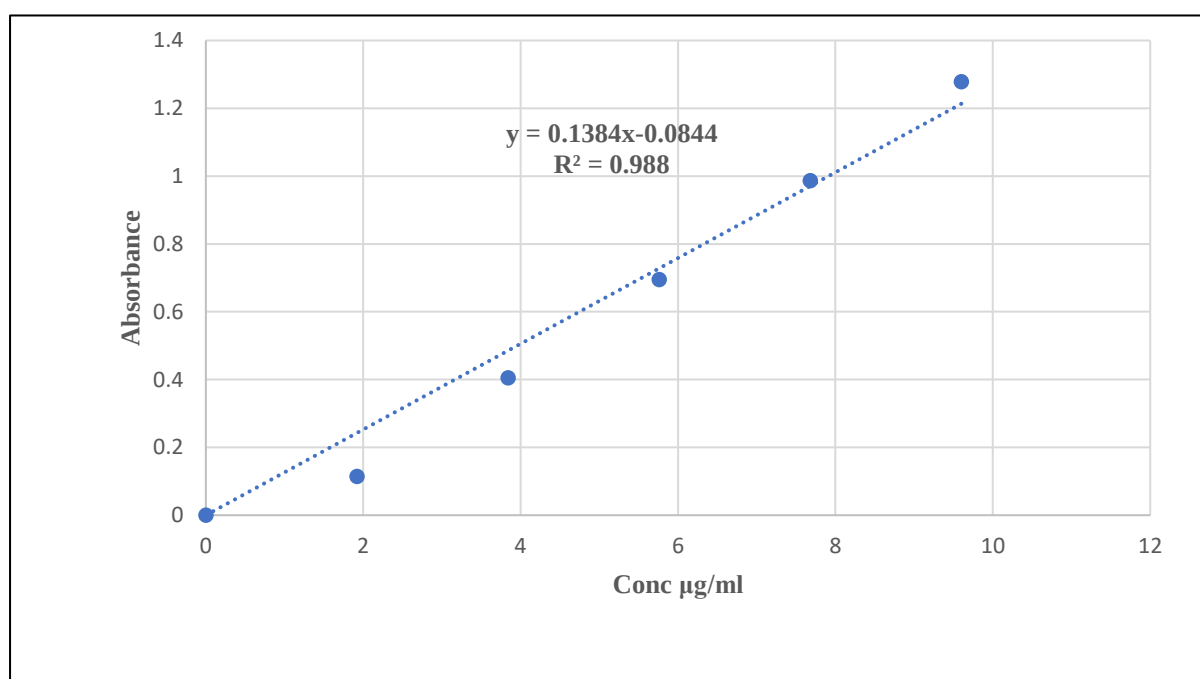


Figure 3.: Calibration Curve of Curcumin in Methanol

D Fourier Transforms Infrared Spectroscopic Study

The FTIR spectra of curcumin showed that it is pure in nature. Outcomes are shown in Table III and Figure 4

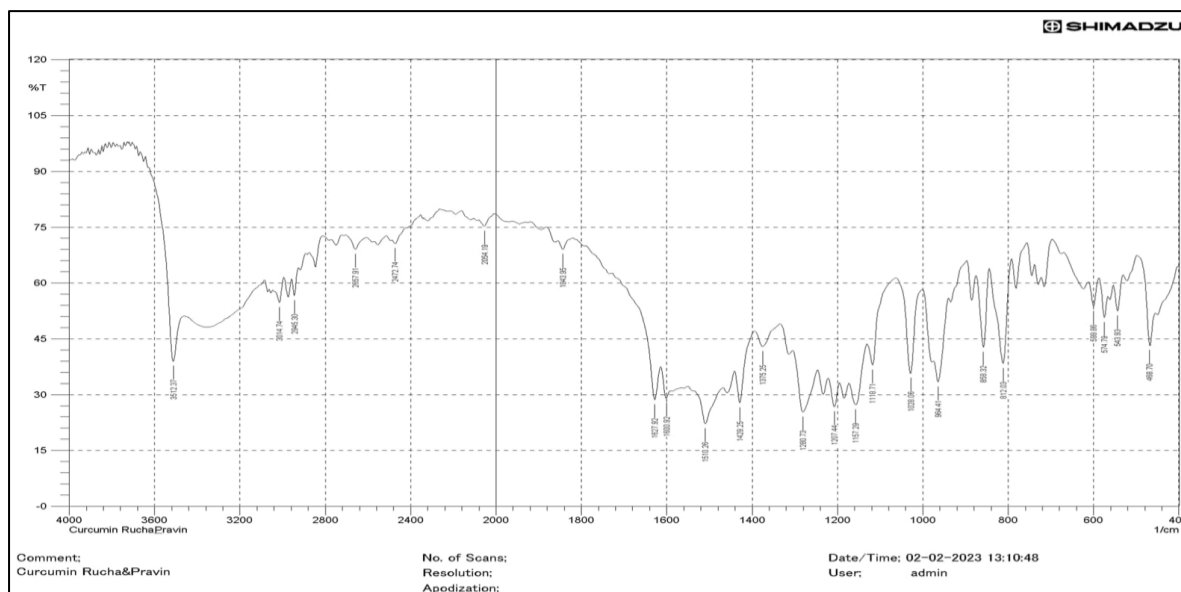


Figure 4: FTIR Spectrum of Pure Drug Curcumin

Table III: Identification of Functional Groups in FTIR Spectra of Drug

Standard ranges cm ⁻¹	Observed ranges cm ⁻¹	Bond	Functional group
3500–3200 (s,b)	3512-3014	O–H stretch, H–bonded	alcohols, phenols
3300–2500 (m)	3014-2945	O–H stretch	carboxylic acids
3000–2850 (m)	3014-2945	C–H stretch	alkanes
2830–2695 (m)	2857- 2472	H–C=O: C–H stretch	aldehydes
1680–1640 (m)	1627	–C=C– stretch	alkenes
1000–650 (s)	964	=C–H bend	alkenes
2860–2800	2850-2800	-OCH	Ether

E Drug-Excipients Compatibility Study

Physical appearance:

Samples were evaluated for color and odor. Outcomes were shown in Table IV.

There was no change in color and odor of curcumin&curcumin-excipient mixture of control & test sample.

Table IV: Result Obtained From Drug-Excipient Compatibility Study of Control Samples and Test Samples

Sr. No	Ingredients	Control samples after 7 days		Test samples after 7 days	
		Color	Odor	Color	Odor
1	Curcumin	Yellow	Characteristics	Yellow	Characteristics
2	Curcumin: α - Bisabolol	Yellow	Characteristics	Yellow	Characteristics
3	Curcumin: Mauha oil	Yellow	Characteristics	Yellow	Characteristics
4	Curcumin: BHT	Yellow	Characteristics	Yellow	Characteristics
5	Curcumin: TBHQ	Yellow	Characteristics	Yellow	Characteristics
6	Curcumin: Methyl paraben	Yellow	Characteristics	Yellow	Characteristics
7	Curcumin: Propyl paraben	Yellow	Characteristics	Yellow	Characteristics
8	Curcumin: SDG	Yellow	Characteristics	Yellow	Characteristics
9	Curcumin: Shea butter	Yellow	Characteristics	Yellow	Characteristics

F Drug-Excipients Compatibility Assay

Control and test samples were evaluated by UV-Visible spectrophotometer to determine % drug content respectively after 7 days. Outcomes were revealed in Table V

In the Drug-Excipients compatibility assay value study of curcumin it was observed that value in samples were more than 90 % and hence it was concluded that curcumin is compatibility with excipients and excipients can be used for formulation of transdermal cream.

Table V: Result Obtained From Assay of Control Samples and Test Samples

Sr. No.	Sample Coding	Assay of control samples	Assay of test samples
1	Curcumin	108%	108%
2	Curcumin: α - Bisabolol	108%	108%
3	Curcumin: Mauha oil	109%	107%
4	Curcumin: BHT	108%	109%
5	Curcumin: TBHQ	109%	109%
6	Curcumin: Methyl paraben	109%	109%
7	Curcumin: Propyl paraben	108%	108%
8	Curcumin: Shata Dhauta-Ghrita	107%	107%
9	Curcumin: Shea butter	108%	107%

G Preformulation Results of Shata DhautaGhrita

Organoleptic Properties:

The physical appearance & pH of prepared shatadhautaghrita was observed in comparison with Gir cow ghee. The results shown in Fig 5 and Table VI

The study shows that shatadhautaghrita was pale green, odorless, tasteless and homogenously smooth in texture and the pH of shatadhautaghritais near to skin pH (4-5.6). Hence, it is suitable for preparation of topical formulation.



Figure5: Prepared of Shata DhautaGhrita in Comparasion With Gir Cow Ghee

Table VI: Results of Identification Test of Shata DhautaGhrita (SDG) and Gir Cow Ghee

Parameter	Gir Cow Ghee	SDG
Color	Golden yellow	Pale – green
Odor	Pleasant	Odorless
Taste	Characteristic	Tasteless
Texture	Granular, Oily	Smooth, non-oily, Homogenous
Physical properties:		
pH	4.7	5.4

H Evaluation Results of Transdermal Cream of Curcumin

a) Physical Appearance:

Prepared creams were evaluated for color, odor & texture. Result shown in Figure6 & Table IX.

The prepared cream was bright yellow in color with characteristic odor and with smooth texture.



Figure6: Prepared Transdermal Curcumin Cream.

Table IX : Observation for Physical Parameter of Cream

Organoleptic Properties	Observations
Color	Bright yellow
Odor	Characteristic
Texture	Smooth

b) pH:

Utilizing the digital pH meter, the pH of cream formulas were found. Table X showed the findings.

The made transdermal cream had a pH range of 5.31 to 5.45, which was compared to Patanjali beauty cream, which is already on the market. It was found that the pH of cream sold in stores was 5.52.

Table X: pH of the Formulations

Batches	pH
F0	5.34 ± 0.026
F1	5.43 ± 0.024
F2	5.45 ± 0.016
F3	5.36 ± 0.020
F4	5.39 ± 0.020
F5	5.31 ± 0.016
Marketed	5.52 ± 0.02

Values represented as mean ± SD, n=3, Where, n = Number of replicates

c) Spreadability:

Spreadability was measured and result shown in Table XI.

Spreadability is time required for formulation to cover distance. A shorter interval specifies improved spreadability. F5 batch showed better spreadability than marketed formulation.

Table XI: Spreadability of Formulated Batches

Sr.no	Batch	Spreadability
1	F0	17.8 $\pm$ 0.3
2	F1	17.4 $\pm$ 0.3
3	F2	18.63 $\pm$ 0.9
4	F3	18.73 $\pm$ 0.3
5	F4	17.89 $\pm$ 1.05
6	F5	16.33 $\pm$ 0.5
7	Marketed Formulation	19.2 $\pm$ 0.4

Values represented as mean $\pm$ SD, n=3, Where, n = Number of replicates

d) Drug Content:

Drug content was measured and shown in Table XII.

Drug content of all prepared cream formulation was in range of 100% - 107% indicating presence of drug without any degradation. While marketed formulation assay value was found to be 27%.

Table XII: Drug Content of Formulated Batches

Sr. No.	Batch	Drug content
1.	F0	106% $\pm$ 0.4
2.	F1	107% $\pm$ 1.6
3.	F2	100% $\pm$ 1.6
4.	F3	101% $\pm$ 1.6
5.	F4	107% $\pm$ 2.4
6.	F5	107% $\pm$ 1.6
7.	Marketed	27% $\pm$ 0.8

Values represented as mean $\pm$ SD, n=3, Where, n = Number of replicates

e) In Vitro Diffusion Studies:

Result of *In vitro* drug release of prepared formulation from F0 to F5 batch, which compared with marketed formulation are shown in Table XIII.

In vitro diffusion study shows that highest % drug release was obtained with F5 batch i.e., 8.404%±0.01 % which higher in compare to marketed formulation value of 1.389%±0.01 % in 6 hrs. Hence, from this study we deduced that F5 batch is optimized batch.

Table XIII: In Vitro Drug Diffusion Studies

Time (min)	% Release						
	F0	F1	F2	F3	F4	F5	Marketed
0	0	0	0	0	0	0	0
15	0.083	0.342±	0.6001±	0.862±	1.125±	1.391±	0.232±
	±0.01	0.009	0.02	0.01	0.04	0.02	0.006
30	0.423±	0.574 ±	0.887 ±	1.254±	1.684±	2.091±	0.304± 0.07
	0.014	0.01	0.01	0.01	0.01	0.02	
60	0.68 ±	0.887 ±	1.232 ±	1.664±	2.233±	2.986±	0.344± 0.01
	0.018	0.01	0.01	0.09	0.02	0.02	
120	0.888±	1.238 ±	1.618±	2.141±	2.807±	3.851±	0.653± 0.01
	0.02	0.02	0.01	0.01	0.01	0.02	
180	1.254±	1.642 ±	2.002 ±	2.613±	3.507±	4.814±	0.838± 0.02
	0.01	0.01	0.01	0.02	0.01	0.01	
240	1.665±	2.002 ±	2.407±	3.108±	4.178±	5.953 ±	1.023 ± 0.01
	0.01	0.16	0.01	0.02	0.009	0.02	
300	2.039±	2.4040 ±	2.815±	3.619±	4.833 ±	7.036 ±	1.2053 ±
	0.01	0.01	0.01	0.01	0.02	0.04	0.02
360	2.475±	2.8141±	3.248±	4.120±	5.6058 ±	8.404±	1.389 ± 0.01
	0.01	0.01	0.01	0.01	0.02	0.01	

Values represented as mean ± SD, n=3, Where, n = Number of replicates

f) Ex Vivo Permeability Study:

Comparative *Ex vivo* permeability study of optimized batch, F0 and marketed formulation was carried out on ear of pig and outcomes were shown in Table XIV.

The study show that % drug permeability by F5 batch was $3.99\% \pm 0.008$ % at 6 hrs in comparison with marketed formulation i.e., $0.782\% \pm 0.003$ % and F0 batch i.e., $0.919\% \pm 0.01$ %

Table XIV: Ex vivo Drug Permeability Study

Time	% Drug permeation		
	F0	F5	Marketed
0	0	0	0
15	0.082 ± 0.01	0.6001 ± 0.01	0.267 ± 0.009
30	0.237 ± 0.01	0.968 ± 0.01	0.368 ± 0.02
60	0.3392 ± 0.01	1.407 ± 0.01	0.449 ± 0.01
120	0.434 ± 0.01	1.829 ± 0.01	0.533 ± 0.01
180	0.544 ± 0.01	2.361 ± 0.008	0.605 ± 0.008
240	0.675 ± 0.08	2.9201 ± 0.008	0.675 ± 0.01
300	0.8006 ± 0.03	3.458 ± 0.01	0.732 ± 0.005
360	0.9191 ± 0.01	3.997 ± 0.008	0.782 ± 0.003

Values represented as mean $\pm$ SD, n=3, Where, n = Number of replicates

g) Flux, Diffusion coefficient, Permeability coefficient:

The result of Flux, Diffusion coefficient and Permeability coefficient was shown in Table XV and Table XVI.

From Table XV it was observed that Flux and Diffusion coefficient of F5 batch is more as compare to F0 and marketed formulation.

From Table XVI it was observed that Flux and Permeability coefficient of F5 batch is more as compared to marketed formulation & F0 batch.

Table XV: Observation of Flux and Diffusion Coefficient

Sr. No.	Batches	Flux (Wb) gm/cm ² /min	Diffusion coefficient
1	F0	0.012 ± 0.01	0.0006 ± 0.01
2	F1	0.013 ± 0.009	0.00065 ± 0.16
3	F2	0.015 ± 0.02	0.00075 ± 0.01
4	F3	0.018 ± 0.01	0.0009 ± 0.02
5	F4	0.025 ± 0.04	0.0012 ± 0.009
6	F5	0.039 ± 0.02	0.0019 ± 0.02
7	Marketed Formulation	0.001 ± 0.01	0.00005 ± 0.02

Values represented as mean ± SD, n=3, Where, n = Number of replicates

Table XVI: Observation of Flux and Permeability Coefficient

Sr. No.	Batches	Flux (Wb) gm/cm ² /min	Permeability Coefficient(m/s)
1	F0	0.0041 ± 0.02	0.000205 ± 0.01
2	F5	0.0191 ± 0.02	0.000955 ± 0.03
3	Marketed Formulation	0.0009 ± 0.008	0.000045 ± 0.01

Values represented as mean ± SD, n=3, Where, n = Number of replicates

h) Kinetic assessment of *In vitro* release of drug from prepared cream:

Many mathematical models were used to suit the released data that had been studied. These models included the Zero order, First order, Hixon-Crowell, Higuchi, and Korsmeyer-Peppas models. Table XVII displayed the results.

Curcumin is integrated into semisolid matrices, as demonstrated by the kinetic data used to *in vitro* diffusion tests, which reveal that optimized batch F5 follows zero order kinetics and Higuchi model, indicating that drug release from formulation F5 is by diffusion. F5 batch's *n* exponent value came out to be 1.0136. F5 batch follows the supercase II transport drug release mechanism, since this value was greater than 0.9.

Table XVII: Regression Coefficient Value of *In-Vitro* Diffusion Studies

Batches	Coefficient of regression R ²					
	Zero Order	First Order	Higuchi model	Hixon model	Korsmeyer Peppas	
					R ²	n
F0	0.9809	0.9623	0.95	0.9625	0.8703	0.3788
F1	0.9949	0.9157	0.9798	0.9162	0.9797	0.3808
F2	0.997	0.7505	0.9908	0.7514	0.979	0.373
F3	0.9946	0.6371	0.9923	0.6381	0.9285	0.4408
F4	0.9948	0.6756	0.9899	0.6772	0.938	0.607
F5	0.9942	0.8529	0.9804	0.855	0.9705	1.0136
Marketed	0.9826	0.7909	0.9767	0.791	0.8729	0.1862

CONCLUSION

Pre-formulation studies namely organoleptic properties, melting point, UV- spectroscopy and FTIR were carried out on curcumin. The studies shows that drug is pure and complies with standards. Drug Excipientscompatibility studies of curcuminwere carried out with various excipients. The study reveals that drug is compatible with excipients. Shata dhutaghrita was prepared and compared with Gir cow ghee. The study shows that shatadhautaghritawas pale green, odorless, tasteless and homogenously smooth in texture and its pH was found to be 5.4 which is near to skin pH. Total six batches of transdermal cream of curcumin were prepared using three absorption bases namely Shata dhutaghrita, mahua oil, shea butter. Prepared cream was evaluated for physical appearance, pH, spreadability, Drug content, *In vitro* diffusion studies and *ex vivo* permeability studies which werecompared with marketed formulation. Study shows that cream was bright yellow in color with smooth texture. Its pH was found to be in range of 5.31-5.4. Spredability of prepared cream is better than marketed formulation.The drug content of cream was found to be in range of 100%-107%, while marketed formulation assay value was found to be 27%. *In vitro* diffusion study shows that highest % drug release was obtained with F5 batch i.e., $8.404\% \pm 0.01\%$ in 6 hrs, which is higher in compare to marketed formulation value of $1.389\% \pm 0.01\%$. Hence, from this study is found that F5 batch is optimized batch. Comparative *Ex vivo* permeability study of optimized batch, F0 and marketed formulation was carried out on ear of pig. The study show thatdrug permeability of F5 batch was $3.997\% \pm 0.008\%$ in 6 hours in comparison with marketed formulation i.e. $0.782\% \pm 0.003\%$ and F0 batch i.e. $0.919\% \pm 0.01\%$. Also, flux, diffusion coefficient and permeability coefficient of F5 batch is more as compared to marketed formulation & F0 batch. Hence, it shows that cream prepared by three absorption bases have higher permeability characteristic as compare to marketed formulation. Curcumin is integrated into semisolid matrices, as demonstrated by the kinetic data used to *in vitro* diffusion tests, which reveal that optimized batch F5 follows zero order kinetics and Higuchi model, indicating that drug release from formulation F5 is by diffusion. F5 batch's n exponent value came out to be 1.0136. F5 batch follows the supercase II transport drug release mechanism, since this value was greater than 0.9.

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REFERENCES

1. Chutima, J. (2013) "Bioavailability enhancement techniques of herbal medicine: A case examples of curcumin," *International Journal of Pharmacy and Pharmaceutical Sciences*, 5, pp. 493–500.
2. Simay, G. (2008) "Biological activity of curcuminoids isolated from curcuma longa, Rec," *Rec. Nat. Prod*, 2, pp. 19–24.
3. Amalraj, A. and Pius, A. (2017) "Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives-A review," *Journal of Traditional and Complementary Medicine*, 7, pp. 205–233.
4. Lee, W. H. et al. (2013) "Curcumin and its derivatives: Their application in neuropharmacology and neuroscience in the 21st century, Curr," *Curr. Neuropharmacol*, 11, pp. 338–378.
5. Tomren, M. A. et al. (2007) "Studies on curcumin and curcuminoids XXXI. Symmetric and asymmetric curcuminoids: stability, activity and complexation with cyclodextrin," *International journal of pharmaceutics*, 338(1–2), pp. 27–34. doi: 10.1016/j.ijpharm.2007.01.013.
6. Wahlang, B., Pawar, Y. B. and Bansal, A. K. (2011) "Identification of permeability-related hurdles in oral delivery of curcumin using the Caco-2 cell model," *European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V*, 77(2), pp. 275–282. doi: 10.1016/j.ejpb.2010.12.006.
7. Radha, K. M., Anoop, K. S. and Jaya, G. A. S. (2006) "Multiple biological activities of curcumin: A short review," *Life Science*, 78, pp. 2081–2087.
8. Nikunjana, A. P., Natvar, J. P. and Rakesh, P. P. (2009) "Formulation and evaluation of curcumingel for topical application," *Pharmaceutical Development and Technology*, 14, pp. 83–92.
9. Melak, M. A., Tanveer, A. and Wegdan, A. (2020) "Development and evaluation of herbal cream containing curcumin from curcuma longa," *Pharmacy & Pharmacology International Journal*, 8, pp. 285–289.
10. Vandana, D. and Shweta, P. (2019) "Formulation and evaluation of topical herbal gel containing inclusion complex of curcumin," *Asian Journal of Pharmaceutical and Clinical Research*, 12, pp. 196–201.
11. Supriya, D. (2009) "Shata dhautaghrita-A case study," *Indian Journal of Traditional Knowledge*, 3, pp. 387–391.

12. Fernande, G. H. *et al.* (2014) "Nutritional composition of shea products and chemical properties of shea butter: A review," *Critical Reviews in Food Science and Nutrition*, 54, pp. 673–686.
13. Ujwala, N. M. *et al.* (2017) "Exploring the role of mahua oil as potent emulsifier in cream formulations," *International Journal of Herbal Medicine*, 5, pp. 93–97.
14. Young, J. S. *et al.* (2014) "Affiliations enantioselective microbial synthesis of the indigenous natural product (–)- α -bisabolol by a sesquiterpene synthase from chamomile (*Matricaria recutita*)," *Biochem Journal*, 463, pp. 239–248.
15. Wael, H. M., Ali, W. and Al-Awady, M. (2018) "Evaluation of In Vitro drug release kinetics and antibacterial activity of Vancomycin HCl - loaded nanogel for topical application," *Journal of Pharmaceutical Sciences and Research*, 1(10), pp. 2747–2756.