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Formulation Development and Evaluation of Anti acne Tazarotene & Hydroquinone Cream using novel excipients Rice bran wax

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Abstract

Besides delivering drug to the body, a drug delivery system aims to improve patient compliance, patient acceptance. The dosage formsavailable for the delivery of topical agents include ointment, paste, CREAM, moisturizing cream and powder. However, cream is more preferabledue to their properties. Present research work is attempted to develop gel by using rice bran wax. Rice bran wax is the vegetable waxextracted from rice bran oil. The oil generally contains 2–6% wax. However it is assumed that on an average it contains 3% wax.Physicochemical tests such as globule size, evaluation of the intrinsic viscosity and homogeneity of cream products, have been traditionallyused to provide reasonable evidence of consistent product performance. However, for the purposes of these studies, the final cream productswere characterized for their clarity, pH, viscosity, spread ability, skin irritation test and in vitro diffusion studies using standard procedure. All the results match with official specifications.

Key Words: Rice Bran wax, Anti acne,Transdermal drug delivery system.

Introduction

Waxes (animal and plants) are esters of high molecular weight monohydroxy alcohols and high molecular weight carboxylic acids. They are chemically different from fats and oils, from hydrocarbon or paraffin waxes, and from synthetic polyether waxes such as carbowax1. During thepast few decades a number of non conventional vegetable oils have been accepted as good quality edible oils in India and in other countries. Since India is one of the principle producers of rice in the world enormous stress is laid upon the extraction of oil from rice bran. Rice bran is the brownlayer between the rice and outer husk of the paddy. The bran is obtained as the by-product in rice milling. Rice bran contains around 15-20% of oil, which can be economically obtained only by solvent extraction process. Rice bran oil is now gaining importance as one of the edible oils in India because of its nutritional property. Crude rice bran wax is dark brown in color and has its own typical physical andchemical composition. The literature survey reveals that rice bran wax has been used in cosmetics and toiletries. Unfortunately the details of this literature are not available. Rice bran wax is also utilized as an ingredient for coating candy and chewing gums. But the utilization of rice bran wax in pharmaceuticals is meager or hardly there is any report inspite of large production.

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Therefore the rice bran wax utilization in pharmaceuticals is worth investigating. Keeping in view the potential availability of rice, its contents such as oils and wax an attempt is made to utilize rice bran wax as pharmaceutical aid. Recent work indicates that rice bran wax is mainly an ester of lignoceric acid and myricyl alcohol. The hard nontacky wax separately recovered is reported to be chiefly melissyl cerotate and melts at about 80-85°. Research had showed that the properties of the refined and bleached wax are similar to those of presently imported carnauba wax 2.

Present study attempts to find if rice bran wax is useful as gel base. The Cream base is prepared by using rice bran waxand evaluated for their clarity, pH, viscosity, spreadability,skin irritation test and in vitro diffusion studies using standard procedure.

Material and Methods

Tazarotene and Hydroquinone of pharmaceutical grade were obtained as gift sample from Euphoria ealthcare Pvt. Ltd. Mumbai. Rice bran wax obtained from Triveni Interchem Pvt Ltd., Vapi, Gujarat, India. All other reagents and chemicals used were of analytical reagent grade.

Formulation development of cream

Preparation of aqueous phase

The o/w type cream was prepared by hot melt method in which water phase was consist all water soluble material such as triethenolamine, glycerin, drug and sorbitol. These were mixed in a beaker and heated till it attained a temperature of about 70 °C.

Preparation of oil phase

Oil phase was prepared by incorporating and mixing of rice brane wax, glycerol monostearate, cetostearyl alcohol, stearic acid, lanolin and liquid paraffin followed by heating at 70 °C to prepare a homogenous solution of lipid.

Preparation of cream

The both phase were maintained at 70°C and aqueous phase was transferred gradually to the oil phase at the same temperature i.e. 70°C. The mixture was stirred manually with a glass rod until homogeneous mixture is form. Then temperature of the mixturewas allowed to cool to 50°C with continuous stirring manually, and a separate solution of tazarotene, hydroquinone, methyl and propyl paraben in propylene glycol was added. The Mixture was stirred until obtained a smooth consistency of cream. Cream was packed into 25 g capcity wide mouth jars and stored at room temperature (25°C) until required for further analysis.

Ingredients (g)	**Oil Phase**								
	CS1	**CS2**	**CS3**	**CS4**	**CS5**	**CS6**	**CS7**	**CS8**	**CS9**
Tazarotene	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Hydroquinone	3	3	3	3	3	3	3	3	3
Rice Bran Wax	2.5	5	7.5	10	12.5	15	17.5	20	20
Stearic Acid	15	15	15	15	15	15	15	15	15
Lanolin	2	2	2	2	2	2	2	2	2
Liquid Paraffin	5	5	5	5	5	5	5	5	5
Cetostearyl Alcohol	2	2	2	2	2	2	2	2	2

Glyceryl Monostearate	3	3	3	3	3	3	3	3	3
	Aqueous Phase								
Triethanolamine	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Glycerin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Sorbitol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol	5	5	5	5	5	5	5	5	5
Methyl paraben	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water (qs to)	100	100	100	100	100	100	100	100	100

Characterization of developed formulation

Cream was evaluated for their organoleptic characteristics, washability, spreadability, pH, viscosity, drug content, in vitro drug diffusion studies, stability study, in vitro skin irritation test, and antimicrobial efficacy test. All studies were carried out in triplicate and average values have been reported.

Organoleptic characteristics: The Psychorheological characteristics were studied for topical cream formulations like colour, odor & texture.

Washability: Formulations were applied on the skin and then observed for it removal after washing with water.

Spreadability: This test is done for cream and not for CREAM. An important criterion for creams is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the cream readily spreads on application to skin. The therapeutic efficacy of a formulation also depends on its spreading value.

A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time taken to slip a movable slides from another fixed slide placed in a frame with formulation under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability. Two glass slides of standard dimensions (6×2) were selected. The cream formulation (2.5g) whose spreadability had to be determined was placed over one of the slides. The second slide which was tied to a string with support of pulley and having hanging panel in another end of thread was placed over the slide. 100 grams of weight was placed up on the upper slide so that the cream formulation between the two slides was traced uniformly to form a thin layer.

The weight was removed and the time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight (200g) was noted. The experiment was repeated and the average of 6 such determinations was calculated for each cream formulation.

$$Spreadability = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)
m = weight tied to the upper slide (200 grams)
l= length of glass slide (6cms).
t = time taken is seconds.

Determination of pH: PH of formulation was determined by digital pH meter. Electrode of pH meter was dipped in to the formulation until constant reading obtained. The measurements of pH of each formulation were replicated three times.

Viscosity: Viscosity of all the cream formulations was measured in triplicate using spindle number 6 of Brookfield viscometer (RVT 230, USA) without spindle guard at 100rpm for 5 minutes in 30ml beaker at room temperature and values were averaged. For CREAM formulation spindle number 2 was used in place of 6. Other parameters were kept same as cream.

Following formula was used to calculate the viscosity.

Viscosity (cps) = Spindle reading X Factor for spindle at 100 rpm.

Drug Content: 0.1g of topical formulation was added in a 10ml volumetric flask and sonicated with pH 7.4 phosphate buffer for 15 minutes which was then filtered through number 42 whatman filter paper and one ml of the above filtrate was then mixed with phosphate buffer to make 10ml then the drug content was estimated spectrophotometrically at at 351.0 nm for Tazarotene and at 288.0 nm for hydroquinone; all the spectrophotometric analysis was carried out three times and the results were averaged.

In-vitro drug release studies

Preparation of cellophane membrane for the diffusion studies:

The cellophane membrane of approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in phosphate buffer pH 7.4 for 24 hours, before used for diffusion studies and was mounted on the diffusion cell for further studies.

Drug Diffusion Studies:

The in-vitro diffusion of drug from the different cream preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100mm height. The diffusion cell membrane was placed with one gram of the formulation and was tied securely to one open end of the tube, the other end was kept remain open.. The cell was inverted and immersed slightly in 250 ml of beaker containing freshly prepared phosphate buffer pH 7.4, as a receptor media and the system was maintained for 2 hrs at 37± 0.5o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of 15, 30,45, 60, 90, 120 min and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the phosphate buffer pH 7.4 and analyzed by UV-Vis spectrophotometer at 351.0 nm for Tazarotene and at 288.0 nm for hydroquinone. Phosphate buffer was used as blank.

Data analysis via drug release kinetics study

The data of in-vitro release of formulations was applied on different drug release kinetic model to determine release kinetic profile.,

1. Cumulative of drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining to be absorbed versus time (First order model)
3. Cumulative amount of drug release versus square root of time (Higuchi model)
4. Log cumulative drug released versus log time (Korsmeyer-Peppas model)

Stability Study: Stability of optimizedformulation was evaluated by keeping the prepared formulation up to 6 months, at 25°C ± 2°C/60% ± 5% RH and 40°C ± 2°C/75% ± 5% RH in stability chamber; samples were withdrawn on 1st day, 30th day, 90th day and 180th day and analysed for organoleptic characteristics, washability, spreadability, pH, viscosity, and drug content by the methods as described previously in this section.

***In vitro* skin irritation study:** Probability of skin irritation due to optimized formulations was assessed by exposing the goat hairless skin to the prepared formulation. The piece of freshly excised goat skin was placed on Franz diffusion cell and allowed to treat with 1 mL of optimized formulation for 1hr followed by washing with phosphate buffer. The other two different sets of experiments consist of treatment for 1 hr with toxin Isopropyl alcohol and phosphate buffer pH 7.4 as a positive and negative control respectively, followed by washing with phosphate buffer of pH 7.4 for comparative analysis. After 1 h of application pieces of skin were removed from the diffusion cell and were stained by hematoxylin and eosin and examined with an optical microscope. Photomicrographs of the prepared slides weretaken under a future ewinjoel projection microscope (MEM 1300) with 40 X magnifications

***In vitro* Antimicrobial Study:** Zone inhibition study using standard cup plate method was used to compare the in-vitro antimicrobial effectiveness

of optimized formulation over conventional cream. Propionibacterium acne (Microbial Type Culture Collection and Gene Bank, Chandigarh, number 433), Staphylococcus epidermidis (MTCC number 3160), and Cutibacterium acnes (MTCC number 3384) were used as test organism as they are frequently implicated as invasive bacteria in acne; 3 Petri plates of approximately 90 mm internal diameter (for 3 different micro-organisms) were filled with 30 ml of previously autoclaved nutrient agar medium, after congealing, the media was inoculated with 0.1 ml of culture containing overnight inoculums of test organism and then 3 wells of 12mm diameter were punched using sterile borer in each petri plate.

First well was filled with optimized formulation, next with conventional cream and last with placebo optimized formulation; these petri plates were kept at place for 4 hours at room temperature as a period of pre-incubation diffusion and then incubated at 37°C for 24 hours, afterward zones of inhibition were measured with vernier caliper; each assay in this experiment was carried out in triplicate.

Results and Discussion

Characterization of developed formulation

Organoleptic charecteristics

Physical characteristics of all the formulations are presented in following tables

Table: Evaluation of cream

Washability

All the formulations were washable with water which confirms their easy removal from the skin after application.

Spreadability

Spreadability of cream was observed between 109.48 ± 5.57 and 41.65± 3.49. Spreadability of CREAM was observed between 129.41 ± 5.71. Optimized cream (batch CS8) showed the spreadability of 41.78 ± 3.54 and optimized CREAM (batch L8) showed the spreadability of 62.59 ± 2.25.

Determination of pH

pH of both the cream and the gel formulations was measured using pH meter. pH meter was calibrated each time before use. pH of all the cream and gel formulations was around 6. pH of optimized cream (CS8) was 6.11 ± 0.06 and pH of optimized CREAM (L8) was 6.12± 0.07.

Viscosity

At start 7 number spindle was used at 20 rpm for the determination of viscosity of cream but dial reading obtained was below 10 and ideally dial reading should be between 10 to 100 so speed of spindle rotation was increased from 20 to 100rpm in order to check out the possibility of increasing the dial reading, but still it was below 10, then spindle no 6 was used instead of 7 at 100 rpm which had given required results so then viscosities of all the cream formulation was determined using spindle no 6 at 100rpm. Dial reading for CREAMs using spindle number 2 at 100 rpm was above 10 so CREAMs were evaluated for viscosity using spindle number 2 at 100rpm. Viscosity of optimized cream (CS8) was 4650 ± 50 and viscosity of optimized CREAM(L8) was 3500 ± 100.

Drug Content

Drug content of all the cream and CREAM formulations was found around 99%, indicating the minimum loss of drug during manufacturing.

In-vitro drug release studies.

Release of drug from cellophane membrane was observed influenced by the amount of rice bran wax used in the formulation and these results confirmed that drug permeation was more retarded from 8 to 16 hours from cream and 8 to 14 hours from CREAM with the increase in the amount of rice bran wax from 10 to 20 %

Model fitting analysis on the in vitro permeation study data was performed to confirm the drug release mechanism. Zero order, 1st order, Higuchi and Korsmeyer-Peppas equations were applied to the release data and graphs were plotted as shown in the following figure. From these graphs correlation coefficients (r2) were determinedwhich are shown in **table** and from the results, it was conclude that, the drug got permeated from vesicles by a higuchi controlled diffusion mechanism.

Test	Physical Characterization			Washability	pH	Viscosity (cps)	Spread ability g cm/sec	Consistency
	Color	Odor	Texture					
CS_1	Evaluation was not done as formulation was very thin like watery liquid							
CS_2								
CS_3								
CS_4	Pale yellow	Characteristic	Smooth	Washable	6.05±0.04	1600±50	109.48±5.75	Slightly Viscous liquid
CS_5	Pale yellow	Characteristic	Smooth	Washable	6.11±0.03	2750±50	88.67±6.22	Slightly Viscous liquid
CS_6	Pale yellow	Characteristic	Smooth	Washable	6.05±0.05	3500±100	70.50±2.87	Viscous liquid
CS_7	Pale yellow	Characteristic	Smooth	Washable	6.10±0.04	3950±100	63.82±3.43	Viscous liquid
CS_8	Pale yellow	Characteristic	Smooth	Washable	6.11±0.06	4650±50	41.78±3.54	Semisolid
CS_9	Pale yellow	Characteristic	Smooth	Washable	6.11±0.04	4650±50	41.65±3.49	Semisolid

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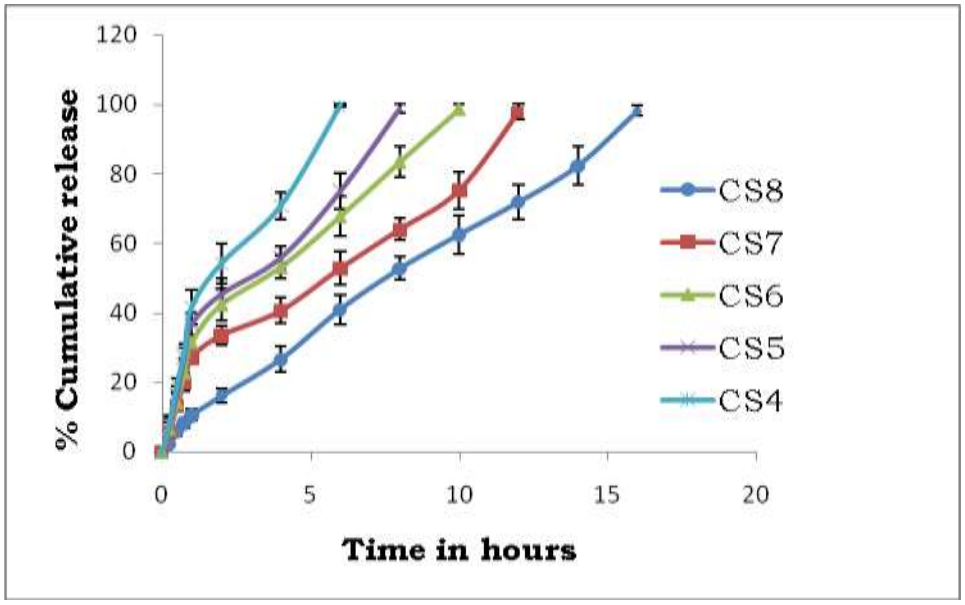

Fig: Zero order release graph of Tazarotene from cream.

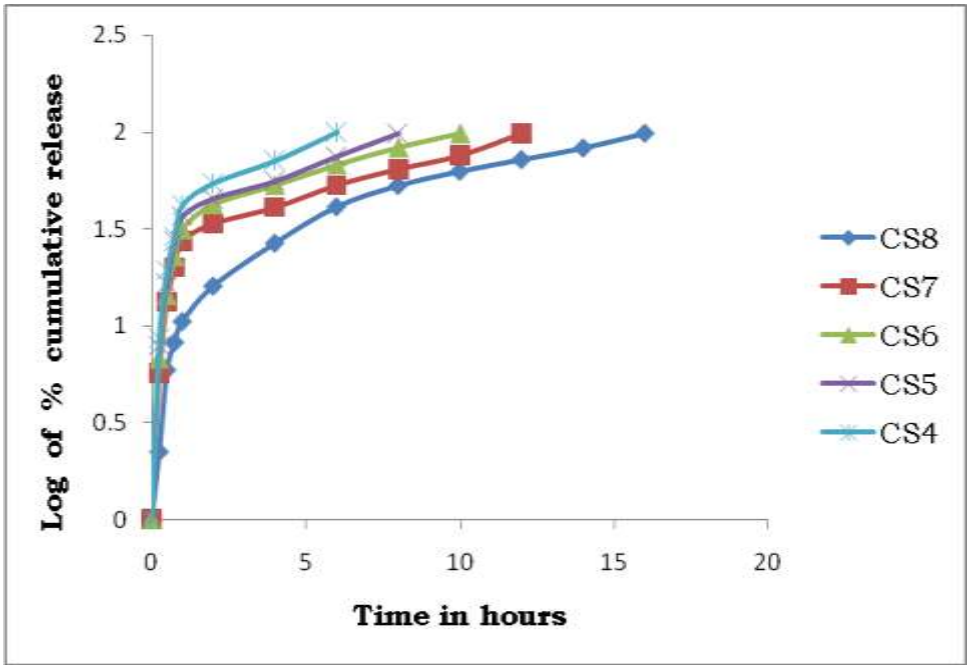

Fig: First order release graph of Tazarotene from cream.

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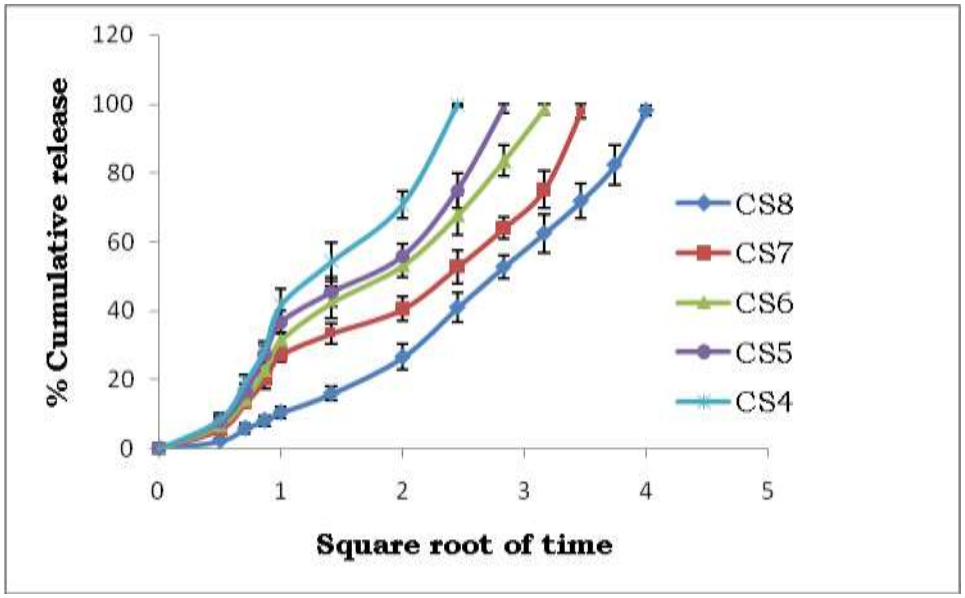

Fig: Higuchi release graph of Tazarotene from cream

Fig: Korsmeyer-peppas release graph of Tazarotene from cream

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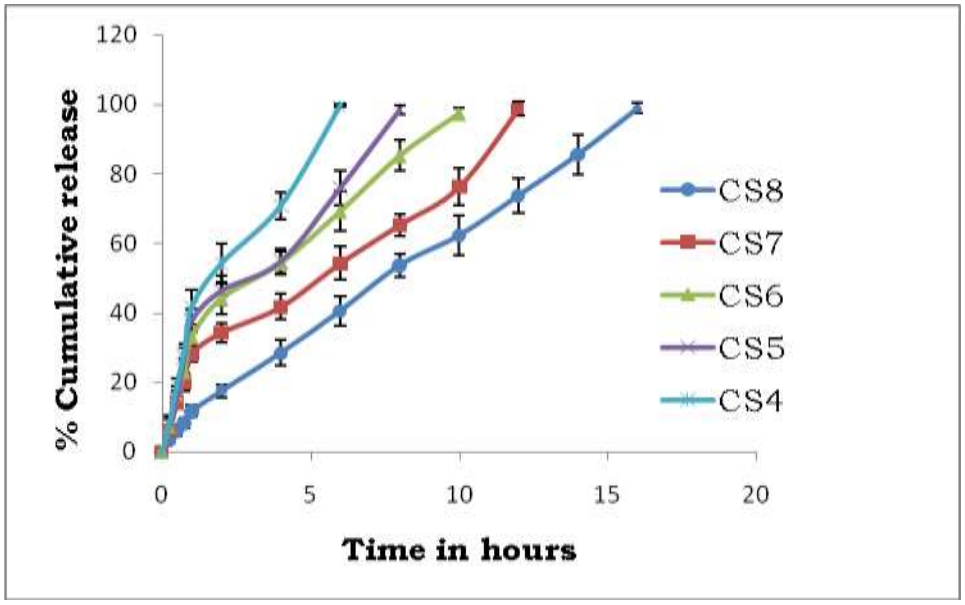

Fig: Zero order release graph of Hydroquinone from cream.

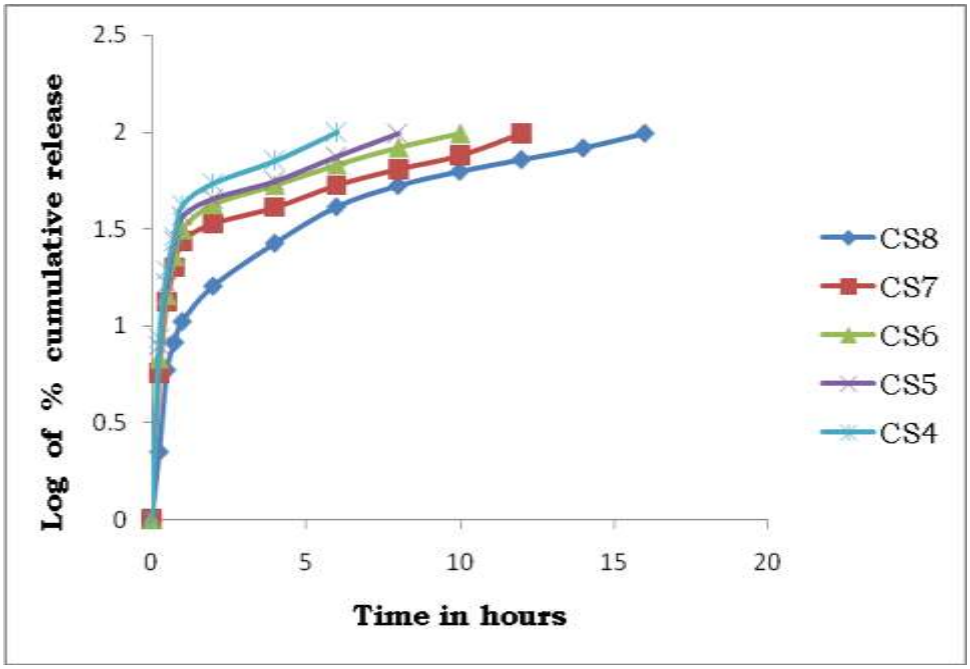

Fig: First order release graph of Hydroquinone from cream.

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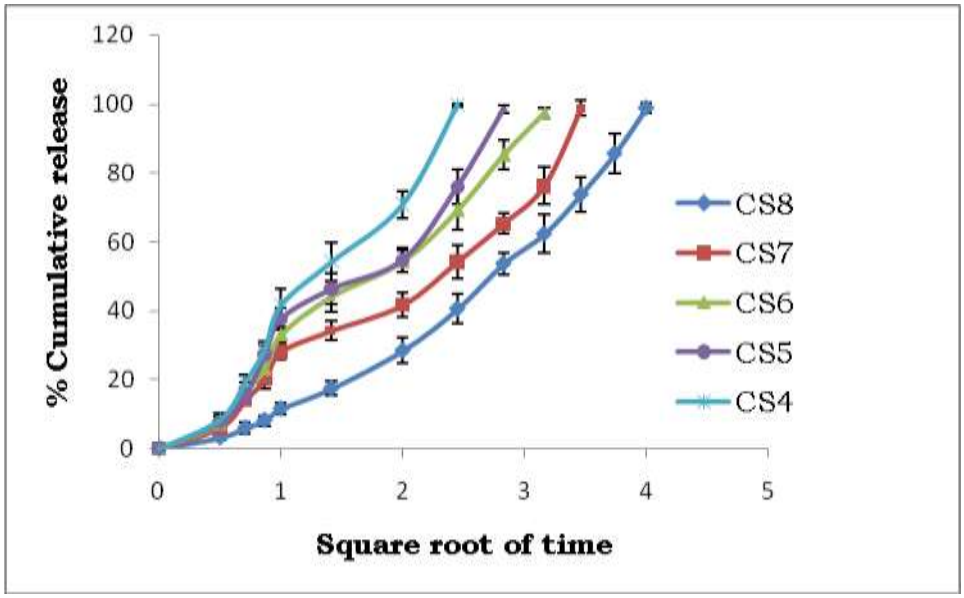


Fig: Higuchi release graph of Hydroquinone from cream.

Fig: Korsmeyer-peppas release graph of Hydroquinone from cream

Optimized cream were found stable with no changes in physical characteristics, washability and pH at all the temperature and humidity conditions used. Viscosity of all formulations was decreased at elevated temperature condition (40°C ± 2°C/75% ± 5% RH)but effect was not drastic. There was a very slight variation in viscosity and spreadability of all the formulations at room temperature (25°C ± 2°C/60% ± 5% RH).

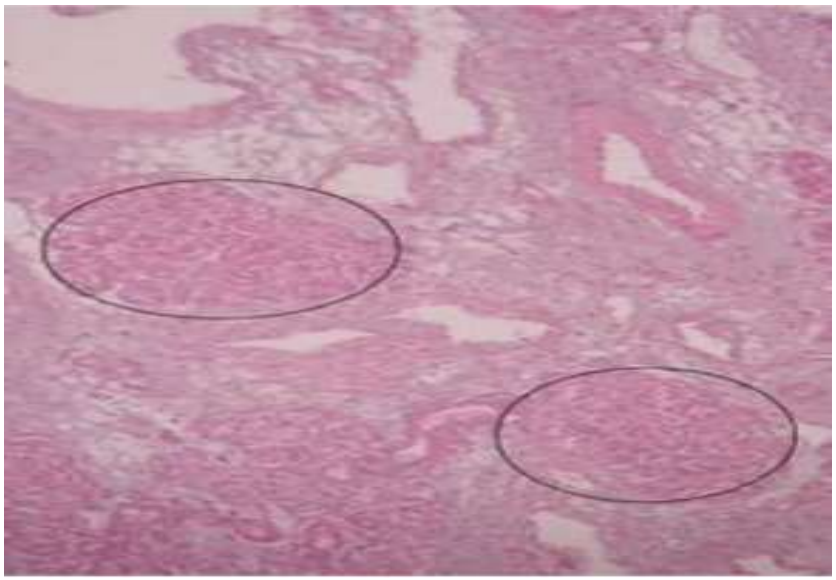
After a period of 6 months, the amounts of drug remained in the optimized cream was 97.58% and 95.31% when stored at 25°C ± 2°C/60% ± 5% RH and 40°C ± 2°C/75% ± 5% RH respectively thus loss of drug at elevated temperature was in acceptable rage of ±5% variation. Thus both optimized cream and CREAM were found stable.

Table: Stability study data of optimized cream *In vitro* skin irritation study

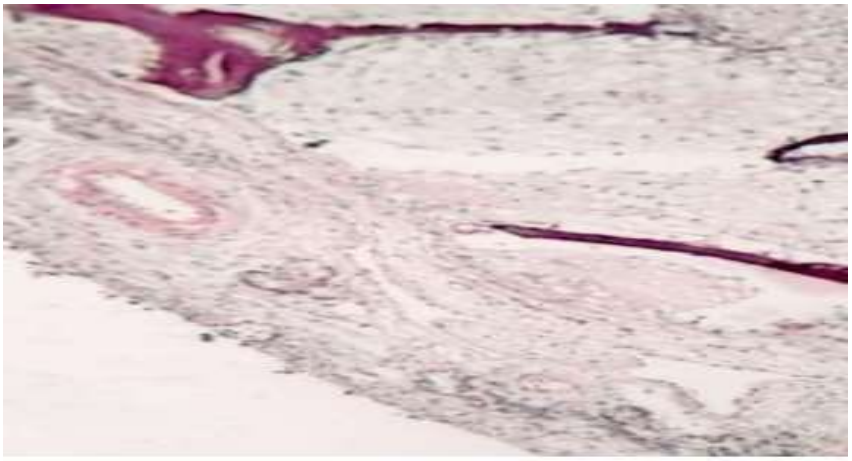
Test	Physical Characterization			Washability	pH	Viscosity (cps)	Spread ability g.cm/sec	Drug content (%)
	Color	Odor	Texture					
Initial	Pale yellow	Characteristic	Smooth	Washable	6.11 ±0.04	4650 ±50	41.65 ±3.49	99.81 ±0.16
25°C ± 2°C/60% ± 5% RH								
1month	Pale yellow	Characteristic	Smooth	Washable	6.10 ±0.04	4600 ±100	42.60 ±1.13	98.06 ±0.23
3months	Pale yellow	Characteristic	Smooth	Washable	6.10 ±0.05	4550 ±50	43.71 ±1.21	97.73 ±0.15
6months	Pale yellow	Characteristic	Smooth	Washable	6.09 ±0.04	4550 ±50	43.74 ±1.25	97.58 ±0.13
40°C ± 2°C/75% ± 5% RH								
1month	Pale yellow	Characteristic	Smooth	Washable	6.05 ±0.03	4450 ±50	46.16 ±1.02	96.66 ±0.16
3months	Pale yellow	Characteristic	Smooth	Washable	6.05 ±0.02	4400 ±50	47.17 ±1.12	96.54 ±0.17
6months	Pale yellow	Characteristic	Smooth	Washable	6.04 ±0.03	4400 ±50	47.23 ±1.24	95.31 ±0.14

(CS_8)

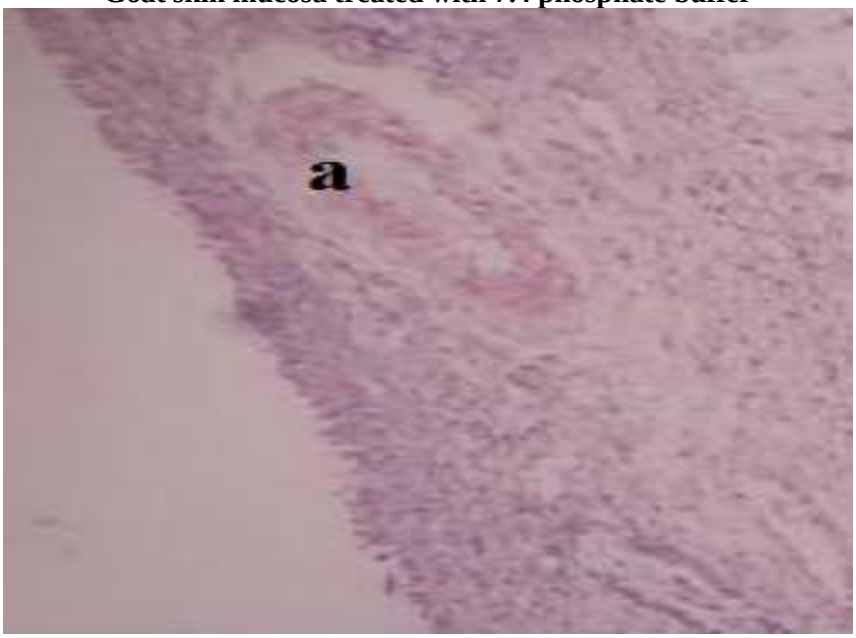
Upon comparing skin irritation potential it was observed that goat skin treated with isopropyl alcohol as a positive control, showed inflammation and cell damage, whereas skin treated with 7.4 phosphate buffer and formulation were found to be intact.



Goat skin treated with isopropyl alcohol, wherein circle indicates inflammation and cell damages.



Goat skin mucosa treated with 7.4 phosphate buffer



Goat skin mucosa treated with optimized a) cream

***In vitro* Antimicrobial Study:**

The inhibitory activity of formulation was determined against *Propionibacterium acne*, *Staphylococcus epidermidis*, and *Cutibacterium acnes.*Distinct zones of inhibitions were obtained for optimized formulation and conventional formulation whereas placebo formulation had not shown any zone of inhibition. Results of this study are shown in following tables; since the zone of inhibition of optimized CREAM against all strains of bacteria used is greater than optimized cream and conventionalcream, we can infer that the antibacterial activity of optimized CREAM is superior to the optimized cream and conventional formulation.

Table: The inhibition zones of optimized cream.

Microorganism	**Optimized cream (mm)**	**Marketed cream (mm)**
Propionibacterium acne	18±1.0	16±1.0
Staphylococcus epidermidis	18±0.5	17±0.5
Cutibacterium acnes	15±0.5	14±0.5

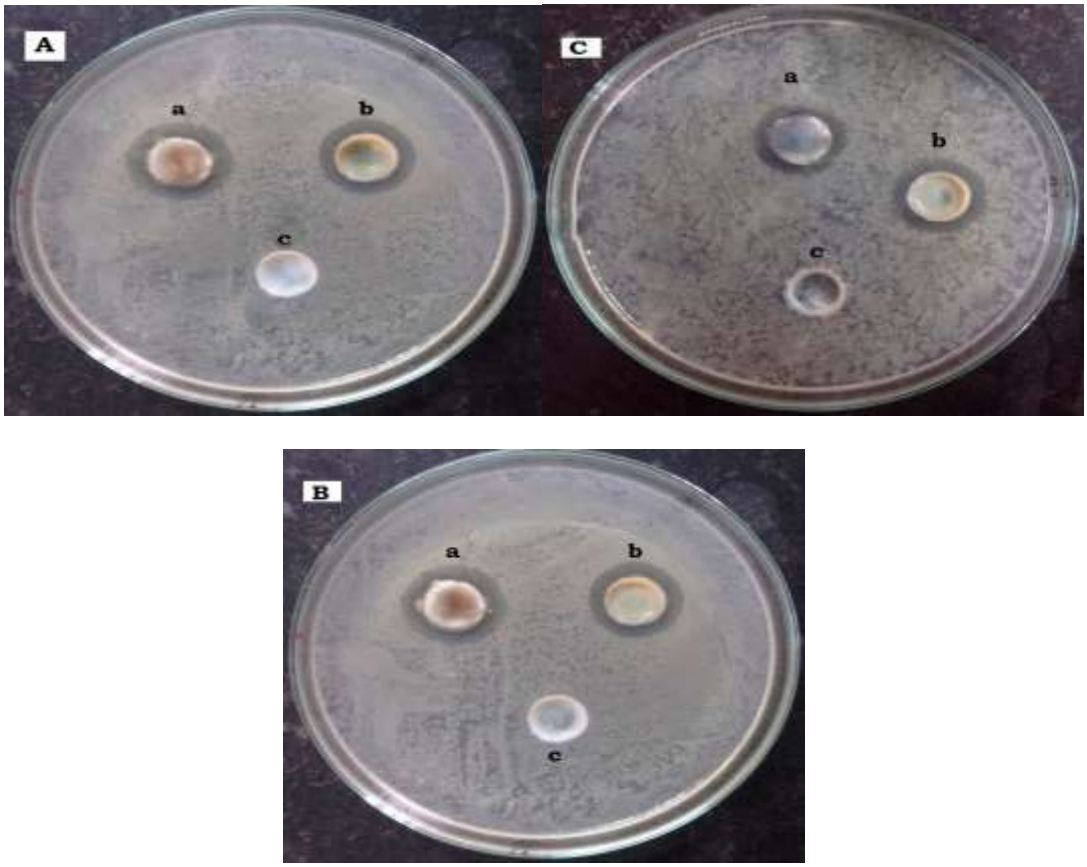


Fig: In vitro antimicrobial zone comparison of a) optimized cream b) marketed cream and c) pseudo cream, against A) Propionibacterium acne, B) Staphylococcus epidermidis, and C) Cutibacterium acnes

evaluation, stability study, *in vitro* skin irritation study, and *in vitro* anti-microbial study.

Conclusion

In this study an attempt was made to develop the sustained release formulations of Tazarotene and Hydroquinone for acne treatment. The experimental work was divided into preformulation studies, formulation development,

Preformulation study was carried outto verify that the drug does not react with the excipients and affect the shelf life of dosage form. It was done by exposing the mixture of drug and excipients to 40°C ± 2°C/75% ± 5% RH for one month which

did not show any incompatibilities. Cream was developed using vanishing cream base and evaluated for organoleptic properties, spredability, washability, viscosity, pH, drug content, and*in vitro* release study. Optimized formulation was evaluated for *in vitro* skin irritation study, *in vitro* antimicrobial study, and stability study. *In vitro* antimicrobial study was carried out to check *in vitro* effectiveness of optimized creamand CREAM in comparison with marketed formulation and it was revealed that optimized formulation shows better antimicrobial activity against acne pathogens compared to marketed formulation. *In vitro* skin irritation study revealed that the optimized formulation is safe to use.

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