International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 6, 2023

Original Article

THE EFFECT OF VARIATION CONCENTRATION OF TETRAHYDROHEXAGAMAVUNON-5 (THHGV-5) IN EMULGEL PREPARATION ON ACUTE DERMAL IRRITATION EFFECT AND SUN PROTECTING FACTOR (SPF) VALUE

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Received: 04 Mar 2023, Revised and Accepted: 15 Sep 2023

ABSTRACT

Objective: A tropical nation experiences intense daytime solar radiation. The likelihood that this condition will result in skin conditions like skin cancer may increase. The skin can be protected as one strategy for coping with this poor potency. Applying various cosmetic products to the skin can provide protection. Due to the antioxidant activity of certain components, various active ingredient types are used in the formulation of those products. A chemical that was created from the structure of curcumin is one of the examples. This substance is referred to as a curcumin analog. THHGV-5 is an analog of curcumin that has strong antioxidant properties. The purpose of this investigation is to ascertain how different Tetrahydropentagamavunon-5 (THHGV-5) concentrations affect the emulgel's sun-protecting factor (SPF) value and irritancy effect.

Methods: The three different concentrations of THHGV-5 emulgel are 1.50%, 1.75%, and 2.00%. Then, tests are conducted on the physical qualities (organoleptic, pH, adhesion, dispersiility, and viscosity). The UV spectrophotometric method was used to determine the SPF value of THHGV-5 emulgel *in vitro*. Regression analysis was used to examine the SPF values from measurements. The acute dermal irritation method was used to measure the Primary Irritation Index (PII) in real-time. The Indonesian Food and Drug Administration's *In vivo* Non-Clinical Toxicity Test Guidelines are followed by this procedure. PII results were analyzed with Kruskal-Wallis statistical analysis with a 95% confidence level.

Results: SPF and PII values will rise as a result of increasing the THHGV-5 content in the formulae. The concentration of THHGV-5 (1.50%, 1.75%, and 2.00%) causes the increase of the SPF values of the formulas (5.76±1.10, 13.03±1.39, and 15.77±0.22) by moderate, maximum, and ultra protection. PII values obtained are significantly different, with a significance level of ≤ 0.05.

Conclusion: According to the study's findings, emulgel formulas with higher THHGV-5 concentrations would have higher SPF values and irritant effects. Since a tropical country's SPF recommendation is 15, THHGV-5 with a 2.00% concentration will be able to provide enough protection. However, a study of three different THHGV-5 concentrations (1.50%, 1,75%, and 2.00%) revealed that none of the formulae were skin-safe since they can irritate the skin.

Keywords: THHGV-5, Emulgel, SPF, Primary irritation index

DOI: https://dx.doi.org/10.22159/ijap.2023v15i6.47741. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

An area with a tropical climate experiences more sun radiation time than areas with other types of climates. Long-term or excessive exposure to UV radiation from the sun can have photooxidative effects on the skin, including early aging. Wrinkles, skin pigmentation, inflammation, and reduced skin endurance [1] are its distinguishing features. Using sunscreen products is one approach to protect your skin among other options. Products like sunscreen can act as a shield against solar radiation. Therefore, the skin is not harmed by the radiation impacts.

One class of substance that can protect skin from UV damage is an antioxidant. By lowering levels of oxidative stress and the quantity of malondialdehyde (MDA), the compound curcumin, which is derived from Curcuma Longa L., exhibits antioxidant action. Additionally, it raises TAC, or total antioxidant capacity [2]. Antioxidant properties of compounds resulting from structural modifications to curcumin are currently being investigated. This is due to the phenolic groups on the structure of curcumin analog molecules, which are in charge of their antioxidant action. In comparison to hexagamavunon-5 (HGV-5) and vitamin E, the curcumin analog tetrahydrohexagamavunone-5 (THHGV-5) shows higher antioxidant activity. A variation of HGV-5 is called THHGV-5. Tetrahydropentagamavunon-0 (THPGV-0), another analog of curcumin, has also been used in the formulation of emulgel and lotion [3]. THPGV-0 and THHGV-5 share a similar structure.

According to the DPPH method, THHGV-5, HGV-5, and vitamin E had antioxidant values of 68.95 M, 150.44 M, and 226.80 M (IC50), respectively. THHGV-5, HGV-5, and vitamin E had IC50 values of 20.30 M, 35.10 M, and 76.80 M, respectively, using the ferric ion method. The IC_{50} value for the DPPH method and the ferric ion method both indicate that THHGV-5 has a higher potential for antioxidant activity than HGV-5 and Vitamin E [4].

THHGV-5 compound was created into an emulgel recipe and further refined by assessing its SPF rating and potential for acute dermal irritation effect. The THHGV-5 formulation used the Emulgel formulae form. This is as a result of its superior qualities to the gel formula form. Emulgel enables the production of hydrophobic active substances in the oil phase. Granules of this will be distributed into the water phase or the other way around. In comparison to alternative topical preparation types, Emulgel also has greater stability features. Emulgel can be prepared in less time and with less expensive materials [5].

SPF testing was done in this study to assess THHGV-5 emulgel's suitability as a sunscreen product. With the aid of UV spectrophotometric analysis, the SPF value was ascertained *in vivo* [6]. On the other hand, topical medication typically can irritate the skin. In light of this, a toxicity test is required.

The experiment was conducted in accordance with Indonesian Food and Drug Administration (BPOM) Regulation No. 10 of 2022 regarding Guidelines for *In vivo* Non-Clinical Toxicological Tests, Development of New Medicines, Traditional Medicines, Cosmetics, Health Supplements, and Food [7].

The SPF test and acute dermal irritation test study at the various variations of THHGV-5 concentrations are supported by the

background presented above. The purpose of this study is to evaluate the effectiveness of THHGV-5 emulgel formulae as a sunscreen or its capacity to shield skin from UV rays.

MATERIALS AND METHODS

Chemicals and reagents

Tetrahydrohexagamavunon-5 (THHGV-5) (fig. 1), an analog of tetrahydro curcumin and curcumin, was the active component used in this study. Using a palladium carbon (Pd/C) 10% catalyst, the hydrogen reaction is used to synthesize this compound [8]. The Curcumin Research Center (CRC), Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia, provided this substance.

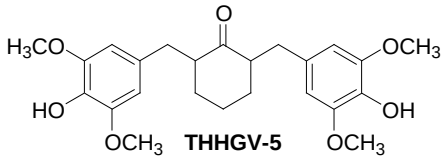

Fig. 1: The structure of THHGV-5

Oleic acid (Bratachem), liquid paraffin (Bratachem), Tween 80 (Bratachem), propylene glycol (Bratachem), carbopol 940 (Bratachem), triethanolamine (Bratachem), DMDM hydantoin (Bratachem), and distilled water (Bratachem) are the ingredients used to make THHGV-5 emulgel. Ethanol p. a. (Merck) is used in the *in vitro* determination of SPF.

Preparation of the THHGV-5 emulgel

Preparation of the emulsion

Oleic acid was combined with liquid paraffin to create the oil phase. THHGV-5 was dissolved in Tween 80 using a sonicator, added to the oil phase, and mixed for 15 min with a magnetic stirrer. Propylene glycol and distilled water were combined then stirred for 15 min with a magnetic stirrer to create the water phase. Following a thorough mixing of the oil and water phases, heating is carried out on each phase separately to a temperature of 60 to 70 °C. Following the heating procedure, both phases are homogenized by being blended with an ultraturax [9].

Preparation of gelling agent

The gelling agent was created by mixing carbopol with distilled water TEA, and letting it sit for an entire night. After one night, DMDM hydantoin was added after the gelling agent had been stirred for 15 min at a speed of 300 rpm with a stirrer [9].

Preparation of emulgel

For 15 min, the emulsion and gelling agent were thoroughly blended by stirring at a speed of 400 rpm.

Determination of SPF value *in vitro*

SPF THHGV-5 solution

By reading the UV-Vis spectrophotometer (*in vitro*) and applying the Mansur equation, the SPF value of the THHGV-5 solution was calculated [6]. One gram (1000 mg) of the THHGV-5 compound was used to make the primary solution. It was then placed in a 50 ml volumetric flask and slowly dissolved in ethanol. The primary solution was subjected to sonication for five minutes in order to make it clear. From a primary solution in ethanol, a series of concentrations were made, with concentrations of 2.00%, 1.75%, 1.50%, 1.25%, 1.00%, 0.50%, 0.40%, 0.20%, and 0.10%. Using a UV-Vis spectrophotometer, the absorption value was measured between 290 and 320 nm at 5 nm intervals, three times per interval. The blank for reading the absorption value was ethanol p. a. [6].

SPF THHGV-5 emulgel

Through the use of the Mansur equation and the reading of a UV-Vis spectrophotometer (*in vitro*), the SPF value of THHGV-5 emulgel was determined [9]. THHGV-5 compound was weighed at 100 mg or 0.1 g, added to a 10 ml volumetric flask, and thoroughly dissolved with ethanol. Five minutes of sonication were used to make the sample clear. Using a UV-Vis spectrophotometer, the absorption value was measured three times at 5 nm intervals between wavelengths 290 and 320. The blank for reading the absorption value was ethanol p. a. [6].

Mansur equation

The following equation illustrates how the Mansur equation was used to determine the SPF value at reading wavelengths between 290 and 320 nm.

$$SPF = CF\ x \sum_{290}^{320} EE\ (\lambda) x\ I\ (\lambda) x\ Absorbansi\ (\lambda)$$

Table 1 shows that EE x I value is a fixed value based on the wavelength (λ) used, whereas CF (correction factor) is stated with a value of 10.

Table 1: Relation of λ and EE x I [10]

Wavelength (nm)	EE x I
290	0.0150
295	0.0817
300	0.2874
305	0.3278
310	0.1864
315	0.0839
320	0.0180
Total	1

Categorization of SPF Protection

Table 2 provides evidence of sunscreen's skin-protective abilities.

Table 2: SPF protection ability [11]

SPF value	Protection ability
2–4	Minimal
4–6	Moderate
6–8	Extra
8–15	Maximal
>15	Ultra

Acute dermal irritation test

According to Ethical Clearance No. 00060/04/lPPT/XII/2019, the test was conducted.

Preparation of test animal and test sample

Three adult, healthy, female New Zealand albino rabbits weighing±2 kg are used as test subjects. Prior to testing, test animals must acclimate for about 5 d in individual cages in the experiment room. An area of the animal's hair at the test site that is no smaller than 10 x 15 cm, or no less than 10% of the body surface area, must be shaved in advance, at least 24 h prior to the test's execution. Shaving begins halfway down the body on each side and moves from the shoulder area to the waist area [7].

Acute dermal irritation response test of THHGV-5 Emulgel

The test samples included the THHGV-5 emulgel base formula and variations with concentrations of 2.00%, 1.75%, and 1.50%. A back area of the test animal measuring approximately 6 cm^2 (2x3 cm^2) will be exposed to test samples weighing up to 0.5 g before being covered in gauze and non-irritating plaster. The test sample's residue was immediately cleaned with distilled water after the four hours of exposure and checked for erythema or udema. Following the removal of the plaster, assessments of observation and behavior were made at 1, 24, 48, and 72 h. additionally, it is necessary to record the body weight of test animals. Observation was conducted

until the 14th d to observe reversibility but if the skin condition returned to normal then the test stopped immediately [7].

Determination of acute dermal irritation response scores of THHGV-5 emulgel

The primary irritation index (PII) was created using an equation in accordance with the Indonesian FDA acute dermal irritation toxicity test and categorization of irritation response in accordance with table 4 after the acute dermal irritation response test scores were calculated based on the assessment regulation that can be seen in table 3.

$$Primary\ Irritation\ Index = \frac{A - B}{C}$$

Annotation:

A: Erythema and udema score totals at 24, 48, and 72 sample observation points divided by the number of observations.

B: Total erythema and udema score of control observation points at 24, 48, and 72 divided by the number of observations

C: Number of observations.

RESULTS

Formulation and physical properties test of THHGV-5 Emulgel

THHGV-5 emulgel formula

Based on the formula for the Clarithomycin emulgel, the THHGV-5 emulgel was created [12]. Rezi (2019) [9] improved this formula by substituting THHGV-5 compounds for clarithromycin, as shown in table 5. As shown in table 6, the THHGV-5 emulgel's physical properties, including pH, spreadability, adhesion, and viscosity, were also tested.

Test to the SPF of THHGV-5 solution and THHGV-5 Emulgel

SPF of THHGV-5 solution

The UV spectrophotometric method was used to evaluate the SPF values of the THHGV-5 solution *in vitro* at a wavelength of 290-320 nm (UVB absorption). Table 6 displays the SPF values for the THHGV-5 solution.

The regression equation depicted in fig. 2 allows one to observe the relationship between THHGV-5 concentration and SPF value. Based on Kruskal-Wallis test analysis with a 95% confidence level (sig. value 0.05), SPF values of THHGV-5 solution also significantly change between concentrations.

SPF THHGV-5 emulgel

The UV spectrophotometric method was used to assess the SPF values of THHGV-5 emulgel *in vitro* at a wavelength of 290-320 nm (UVB absorption). Table 7 lists the SPF values for THHGV-5 emulgel.

The regression equation depicted in fig. 3 allows one to observe the relationship between THHGV-5 concentration and SPF value. According to the Kruskal-Wallis test analysis with a 95% confidence level, the SPF values of THHGV-5 emulgel differ significantly depending on concentration (sig. value 0.05).

Table 3: Reaction assessment on skin [6]

Erythema formation	**Score**
No erythema	0
Erythema is very small (almost indistinguishable)	1
Erythema is visible	2
Erythema is moderate to severe	3
Erythema is severe (red meat) to the formation of *eschar,* which inhibits erythema assessment	4
Udema formation	**Score**
No udema	0
Udema is very small (almost indistinguishable)	1
Udema is small (area boundary visible)	2
Udema is moderate (area increase of about 1 mm)	3
Udema is severe (area increase more than 1 mm and widened beyond the exposure area)	4

Table 4: Categorization of irritation response at rabbit [6]

Average score	**Response category**
0,0–0,4	negligible
0,5–1,9	slight
2,0–4,9	moderate
5,0–8,0	Severe

Table 5: THHGV-5 Emulgel formula

Materials		**(g)**
THHGV-5	Base	0.0000
	Formula A	1.5000
	Formula B	1.7500
	Formula C	2.0000
Oleic acid		2.0000
Liquid Paraffin		4.0000
Span 80		0.0000
Tween 80		1.5000
Propylene glycol		5.0000
Carbopol 940		0.7500
Triethanolamine		q. s
DMDM Hydantoin		0.5000
Aquadest		Ad 100.00

Table 6: SPF values of THHGV-5 solution

The concentration of THHGV-5 solution (g/ml)	SPF of THHGV-5 solution*
1.50%	24.99±0.03
1.75%	29.77±0.13
2.00%	50.50±0.25

*Number of experiments: Data were replicated 3 times for each formula; SPF value of THHGV-5 solution 1.50%: 24.99±0.03, 1.75%: 29.77±0.13, 2.00%: 50.50±0.25

Table 7: SPF values of THHGV-5 Emulgel

Concentration of THHGV-5 Emulgel (g/ml)	SPF of THHGV-5 Emulgel*
Basis	3.38±0.04
Formula A (1.50 %)	5.76±1.10
Formula B (1.75 %)	13.03±1.39
Formula C (2.00 %)	15.77±0.22

*Number of experiments: Data were replicated 3 times for each formula; SPF value of Formula A: 5.76±1.10, formula B: 13.03±1.39, Formula C: 15.77±0.22

Evaluation of the acute dermal irritation of THHGV-5 emulgel

Three adult, healthy New Zealand albino female rabbits were employed as test subjects. The bunnies weighed less than 2 kg and were 8 to 9 mo old. Five locations on the rabbits' backs served as the testing grounds for the sample. THHGV-5 emulgel formula A was used in sample 1, THHGV-5 emulgel formula B in sample 2, THHGV-5 emulgel formula C in sample 3, emulgel base in sample 4, and no exposure (control) was used in sample 5. Fig. 4 depicts the acute dermal irritation test's pattern. Table 9 displays the results of the test for acute dermal irritation.

The results of the Kruskal-Wallis test were used to do a statistical analysis on the Primary Irritation Index (PPI). According to the analysis, there are significant differences (sig. value 0.05) between the control and base emulgel groups using formulas A, B, and C. The base emulgel group and the control group do not vary significantly (sig. value>0.05).

Additionally, the body weight of the rabbit was monitored. This shows whether the rabbits are under stress or experiencing discomfort during the exam. Table 8 displays the weights for rabbits I, II, and III. By using the Kruskall-Wallis test, a statistical analysis of the body weight of rabbits was achieved. According to the analysis, there was no discernible variation in the weight of the rabbits during the test (sig. value).

Table 8: Rabbit weight before and after exposure

Rabbit	D-0 (kg)	D-1 (kg)	D-2 (kg)	D-3 (kg)
I	2,0	2,0	2,0	2,0
II	1,9	1,9	1,9	2,1
III	2,1	2,1	2,1	2,1

Table 9: Physical properties pH, spreadability, adhesion, and viscosity THHGV-5 emulgel

Formula	pH*	Spreadability (cm)*	Adhesion (seconds)*	Viscosity (dPas)*
Base	5.09±0.16	4.23±0.55	9.40±1.37	148.9±11.9
Formula A (1.50%)	5.08±0.34	4.00±0.05	19.11±0.92	192.4±27.4
Formula B (1.75%)	5.05±0.32	4.02±0.26	26.09±1.58	193.2±23.9
Formula C (2.00%)	5.40±0.10	3.96±0.03	32. 64±1.90	175.7±7.8

*Number of experiments: Data were replicated 3 times for each formula; Physical Properties of THHGV-5 Emulgel Formula A (1.50%): pH = 5.08±0.34, Spreadibility = 4.00±0.05 cm, Adhesion = 19.11±0.92 seconds, Viscosity = 192.4±27.4 dPas, Formula B (1.75%): pH = 5.05±0.32, Spreadibility = 4.02±0.26 cm, Adhesion = 26.09±1.58 seconds, Viscosity = 193.2±23.9 dPas, Formula C (2.00%): pH = 5.40±0.10, Spreadibility = 3.96±0.03 cm, Adhesion = 32. 64±1.90 seconds, Viscosity = 175.7±7.8 dPas

Table 10: Primary irritation index THHGV-5 emulgel

Exposure	Primary irritation index	Category (ISO 10993-10, 2002)
Control	0.00	Negligible Irritant
Base	0.00	Negligible Irritant
Formula A	0.42	Slight Irritant
Formula B	0.50	Slight Irritant
Formula C	0.67	Slight Irritant

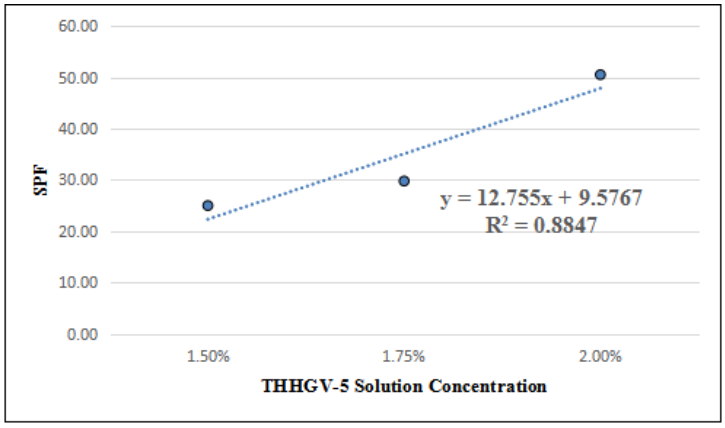

Fig. 2: Regression and correlation graph of THHGV-5 solution concentration against the SPF value

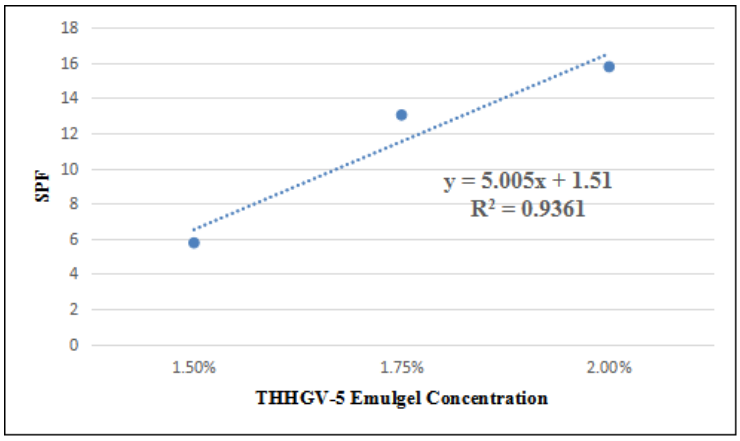

Fig. 3: Regression and correlation graph of THHGV-5 emulgel concentration against the SPF value

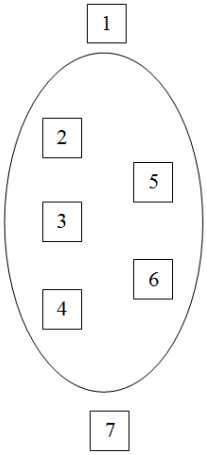

Fig. 4: Back area pattern of test animal

Annotation:

1. Head
2. Exposure of THHGV-5 Emugel 1.5%
3. Exposure of THHGV-5 Emugel 1.75%
4. Exposure of THHGV-5 Emugel 2%
5. Exposure of Emugel Base
6. Without Exposure (Control)
7. Tail

DISCUSSION

The THHGV-5 emulgel formula's physical characteristics were examined initially. The THHGV-5 emulgel's organoleptic characteristics include odorlessness, white color, semi-solid form, and good homogeneity (the preparation has no discernible granules). According to table 9, the THHGV-5 emulgel is designed with a pH that is appropriate for human skin in the range of 4.5 to 6.5 [13], spreadability that is suitable for the semi-stiff category on semi-solid preparations in the range of 3 to 5 cm [14], an adhesion value greater than 4 seconds for all formulas [15], and a viscosity that is within the range of 50 to 1000 dPas [16].

THHGV-5 solution and emulgel SPF values were determined *in vitro* using a UV spectrophotometric technique at a wavelength of 290–320 nm (UVB absorption). THHGV-5 solution's SPF values at concentrations of 1.5%, 1.75%, and 2% are all higher than 15. According to Wilkinson and Moore [11], these THHGV-5 concentrations of 1.5%, 1.75%, and 2% can offer ultra-protection on the skin. The concentration of THHGV-5 solution significantly affects the SPF values that are determined from the R-value of 0.9406. The THHGV-5 solution's coefficient of determination (R2) is 0.8848, indicating that concentrations have an influence on the increase in SPF value of 88.48% and other factors have an influence of 11.52%. Based on the Kruskal-Wallis test analysis with a 95% confidence level (sig. value 0.05), SPF values of THHGV-5 solution also significantly change between concentrations. This demonstrated that elevating the concentration can raise the SPF rating.

According to Wilkinson and Moore [11], the SPF rating of emulgel base (SPF 3.38) offers very minimal skin protection. The skin is moderately, maximally, and ultra-protected by the SPF value of THHGV-5 emulgel at concentrations of 1.50% (SPF 5.76), 1.75% (SPF 13.03), and 2.00% (SPF 15.77), respectively. THHGV-5 concentration significantly influences the SPF value that is determined by the R-value of 0.9676. The THHGV-5 solution's coefficient of determination (R2) is 0.9362, indicating that concentrations had an influence on the increase in SPF value by 93.62% and that other factors had an influence of 6.38%. According to the Kruskal-Wallis test analysis with a 95% confidence level, the SPF values of THHGV-5 emulgel differ significantly depending on concentration (sig. value 0.05). This demonstrated that elevating the concentration can raise the SPF rating.

The SPF value for the sunscreen product that is advised for tropical regions is 15 [17]. While the concentrations of 1.50% and 1.75% do not have a suitable value according to the specified SPF value, the SPF value of THHGV-5 emulgel with a concentration of 2.00% does. However, THHGV-5 emulgel can offer moderate, maximal, and ultra-protection against UVB radiation at concentrations of 1.50%, 1.75%, and 2.00%, respectively.

THHGV-5 has a connected hydroxyl group to an aromatic group in its structure, which can shield skin from UVB radiation exposure. This group can absorb UVA and UVB rays while also lessening the radiation's intensity when it hits the skin. As a result, UVA and UVB radiation will not harm the skin [1]. The number of hydroxyl groups in the emulgel formula and SPF values will grow as THHGV-5 emulgel concentrations are increased.

Numerous medications are administered topically [18] and come in a variety of dose formats [19]. One of the formulations utilized for topical administration is emulgel [20]. Topical medications typically have a weakness that causes skin irritation when used. To ascertain the possible harm that a topical product, in this case THHGV-5 emulgel, might cause to the skin, an acute dermal irritancy test is performed. The control and emulgel base have a PPI of 0.00, which, according to ISO 10993-10 is considered a minimal irritant (table 10). According to ISO 10993-10, Formula A (1%), B (1.75%), and C (2%) have PPI values of 0.42, 0.50, and 0.67, which are considered to be minor irritants. This shown that the emulgel formulation on formulations A, B, and C is not regarded as skin-safe. Erythema and udema were not brought on by exposure to the control or the

emulgel base formula. While all rabbits are developing erythema without udema in response to formulations A, B, and C. Rabbit I is reversible after three exposures to the formula in 24 h. Rabbit II is reversible after three exposures to the formula in 48 h. On formulas A and B, Rabbit III is reversible in 24 h; on formula C, it takes 48 h.

The Kruskal-Wallis test was used to get the statistics for the PPI study. According to the analysis, the base emulgel group with formulas A, B, and C differ significantly from the control group (sig. value 0.05). The base emulgel group and the control group do not vary significantly (sig. value>0.05). This demonstrates that rabbit skin won't become irritated by the basic emulgel. The 1.5%, 1.75%, and 2% concentrations of THHGV-5 emulgel formula irritate the skin of rabbits. The body weight of the rabbits was also monitored to determine whether or not they experienced stress or pain during the test. Table 10 displays the weights of rabbits I, II, and III. Utilizing statistics, the Kruskall-Wallis test can be used to determine the body weight of rabbits. According to the analysis that was done, there was no discernible difference in the weight of the rabbits during the test. (Sig-value>0.05). Because it did not result in a weight shift that differed noticeably, this demonstrates that the discomfort is still at a low level.

CONCLUSION

In general, it can be deduced that as the amount of THHGV-5 in the emulgel composition increases, so does the SPF rating. The THHGV-5 emulgel formula's suggested SPF value for tropical regions is 2%, which is a suitable concentration. However, the 1.5%, 1.75%, and 2% concentrations of THHGV-5 emulgel formula are not recommended for usage since they may irritate the skin.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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