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A facile approach to fabrication and characterization of novel herbal microemulsion-based UV shielding cream

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Abstract

Background: Since many decades, phytoconstituents are well known for their potential therapeutic benefits but the development of herbal products has been limited due to difficulties like collection, isolation, stability and aqueous solubility of the phytoconstituents. The present study focuses on the development of microemulsion-based sunscreen cream formulation containing therapeutically active phytoconstituents like lycopene, β-carotene and curcumin which are reported for both antioxidant and ultraviolet radiation barrier properties. But the major hurdle in the development of the formulation is poor solubility and stability of these 3 components. Microemulsion preparation helps to enhance the solubility and stability of the final product. Screening of oils, surfactants and cosurfactants were done based on solubility studies followed by the construction of pseudo-ternary phase diagrams, sesame oil, span 80 to tween 80 (surfactant) and isopropyl alcohol (co-surfactant) which were selected to stable microemulsion.

Result: Based on a solubility study of components and pseudo-ternary phase diagrams, surfactant to co-surfactant (Smix) with 2:1 ratio and oil to Smix with 2:8 ratio were selected for preparation of the final microemulsion. Results show an average globule size of 208 nm, conductance 0.935 moh/cm, pH 7.1, zeta potential − 17.5 mV, refractive index 1.002, polydispersibility index 0.342, percent transmittance 90.68% and viscosity 82.45 cps. In a drug content study, the presence of lycopene, β-carotene and curcumin was found to be 87.53, 85.08 and 90.65%, respectively. Finally, microemulsion-based sunscreen cream was prepared and evaluated for various parameters like pH, extrudability, spreadability and drug content study. The sun protection factor (SPF) of microemulsion and cream was found to be 36.32 and 37.65, respectively. The stability study data shows better stability of the final formulation.

Conclusion: Formulation of microemulsion-based sunscreen cream may be a better option in the design and development of herbal phytoconstituents.

Keywords: Microemulsion, Surfactant, Lycopene, Curcumin, β-Carotene, Sunscreen cream

Background

Everyone is very conscious about their health, and nowadays, people are even very sensible about looks and external appearance. In short, the world is fond of cosmetics and skin protection against many harmful environmental effects which are on prime importance. One of the harmful factors is the ultra-violet rays coming from the sun. This sunburn may darken the skin and severe consequences may lead to skin damage or cancer. Human exposure to harmful ultraviolet (UV) radiations has very dangerous side effects such as skin melanoma, photoaging, skin pigmentation, sunburn and various painful effects. Ultraviolet radiations increase oxidative stress on skin cells by frequent formation of reactive oxygen species (ROS) leading to initiation and promotion of cancer [1].

There are several products available in the market which are sold by many companies and claiming on the

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basis of skin-protection-factor (SPF). These sunscreen products may be lotion, spray, gel and foam applied topically that absorbs or reflects the ultraviolet radiation. Sun protection factor (SPF) is the measure of the fraction of sunburn coming from the sun.

Ideally, these values of SPF represent the measure of time up to which the product protects the skin from harmful effects of ultraviolet (UV) radiation. Although these products are used widely, regulatory aspects are also taken into consideration during design and development.

The sunscreen preparations are designed and developed to apply topically to prevent the entry of ultraviolet rays directly in the skin by absorbing or reflecting from the skin. There are many synthetic components that are used as sun protection like p-aminobenzoic acid (PABA), phenyl benzimidazole sulfonic acid, cinoxate and oxybenzone and inorganic components like titanium dioxide and zinc oxide. Although innumerable numbers of sunscreen products are available in the market, they have several drawbacks. Some physical sunscreen agents make the preparation opaque and may result in whitish appearance of the skin treated topically with them [2–5].

Sunscreens containing synthetic chemicals may cause side effects, such as erythema, oedema and irritation. Herbal sunscreens are eco-friendly with less or no comedogenic effects. Incorporation of antioxidants could provide additional benefit by scavenging free radicals.

There are many phytoconstituents that have great potential to protect the harmful effects of UV radiation. Natural polyphenols and flavonoids are attractive in this respect, due to their potential activity as photoprotectants and antioxidants [6–10].

Tomatoes contain lycopene, which is the most powerful natural antioxidant. Lycopene has a property to improve the skin's ability to reflect back UV radiations and protect skin from its harmful effect, and β-carotene is the carotenoids present in carrot and emphasizes on the UV protective nature because of the antioxidant potential.

Active chemical constituents of turmeric are curcuminoids, which includes curcumin, desmethoxycurcumin and desmethoxycurcumin. There is some important volatile oil such as turmerone and allenton which help to protect skin from free radical damage; it reduces burning sensation of skin and inflammation, improves the texture of the skin and shows potent UV protective action.

These phytoconstituents include quercetin, lycopene, β-carotene, curcumin and other medicinal herbs like *Embilica officinalis*, *Nelumbo nucifera*, *Moringa oleifera* L, and *Terminalia chebula.* These components can be used to develop sunscreen formulations, but due to certain limitations like their solubility and stability issues, they are restricted [11–13].

The present study focuses on the development of microemulsion of phytoconstituents like lycopene, β-carotene and curcumin. These microemulsion (average globule size of 10–200 μm) are a better option to overcome the issues of solubility and stability of such phytoconstituents. This prepared microemulsion formulation was added to the cream base to develop the final sunscreen formulation with excellent performance of sunburn protection effect.

Microemulsion is isotropic and thermodynamically stable multicomponent fluids composed of water, oil, surfactant and co-surfactant. This unique class of optically clear solutions comprises of the colloidal systems. Microemulsion has transparency, optical isotropy, low viscosity, monophasic, ultra-low interfacial tension, dynamic microstructure and thermodynamic stability. The droplet diameter of microemulsions is generally within the range of 10–200 nm [14].

Pharmaceutical microemulsions contain additional components such as co-surfactant and drugs. The co-surfactant is also amphiphilic with an affinity for both the oil and aqueous phases and partitions to an appreciable extent into the surfactant interfacial monolayer present in the oil-water interface. A wide variety of molecules can function as co-surfactant including non-ionic surfactant, alcohol, alkalotic acids, alkaloids and alkylamines [15–17].

The nanometric size of micelles improved solubilization capacity for lipophilic drug transparency that the property makes the system more suitable for transdermal and topical formulations. Even though microemulsions offer several advantages for topical delivery, it is difficult to stabilize the system because of low viscosity. This problem can be overcome by formulating a microemulsion-based cream [18]. Therefore, the present research work aims at the development of microemulsion containing lycopene, β-carotene and curcumin as an important phytoconstituent possessing both antioxidant and UV radiation protection properties with improved solubility and surface area and stabilization of same by formulating microemulsion-based cream.

Methods

Materials

Crude materials like *Curcuma longa*, *Dacus carota* and *Solanum lycopersicum* are procured from Mahatma Phule Krishi Vidyapeeth, Rahuri, Maharashtra, India. Other supporting materials, tween 80, isopropyl alcohol, sesame oil, glycerine, potassium hydroxide, petroleum jelly, ethanol, chloroform, methanol, dichloromethane and petroleum ether, were procured from Research Fine Chem Pvt. Ltd., Mumbai, India, and were analytical grade.

Methods

Extraction, isolation and pre-formulation study of phytoconstituents

The extraction and isolation of lycopene from *Solanum lycopersicum*, β-carotene from *Dacus carota* and

Table 1 Composition of LCCMBSC

Ingredients	Quantity (g)
Cetostyrl alcohol	0.30
Stearic acid	0.40
Petroleum jelly	0.10
Glycerine	0.40
Potassium hydroxide	0.10
Water	8.5
Methyl paraben	0.02
Polypropyl paraben	0.005
LCCM	1
Rose oil	Q.S

curcumin from *Curcuma longa* were carried out by cold maceration followed by preparative thin-layer chromatography (TLC) [19–21].

Melting point, UV-spectophotometric analysis and FT-IR spectra have confirmed the identification of the above phytoconstituents.

Solubility study

For the preparation of microemulsion, it is most important to check the solubility of the phytoconstituents in either oil, water or surfactant system. Hence, a solubility study was conducted to select suitable components of the microemulsion system. Initially, various oils (sesame oil, olive oil, coconut oil, castor oil, arachis oil), surfactants (span 80, tween 80, polaxamer 407, IPM) and co-surfactants (isopropyl alcohol, n-butanol, polyethylene glycol-400, amyl alcohol, n-propyl alcohol) were procured and solubility of lycopene, β-carotene and curcumin was checked using the shaking flask method in which excess amount of phytoconstituents was added separately to the oils and surfactants. These mixtures were shaken at 37 °C for 48 h to solubilize the components, and after 48 h, samples were investigated for the amount of phytoconstituents using UV spectrophotometer at 440, 460 and 418 nm, respectively [22–24].

Construction of a pseudo-ternary phase diagram

Based on the solubility study, suitable oils, surfactants and co-surfactants were selected for the preparation of the microemulsion system. For the preparation of a stable microemulsion system, initial batches were prepared with the help of a pseudo-ternary phase diagram. Water titration method was implemented, in which double distilled water was added drop-wise using micropipette to previously mix Smix and oils with different ratios (Smix:oils) as 1:1, 2:1, 3:1 and 4:1. Water was added with continuous stirring till turbidity will appear and the amount of added water was noted. Various batches containing Smix:oils at the ratios of 1:1 to 1:9 and 9:1 to 9:8. Finally, a pseudo-ternary phase diagram was constructed with the help of concentration levels of water, oil and Smix to optimize and finalized the stable microemulsion system. Three-component ternary diagrams with each axis representing an oil phase, Smix and water with fix mass ratio were plotted using CHEMIX school software [14, 25, 26].

Selection of a stable microemulsion system

Finally, stable microemulsion systems were selected based on the maximum microemulsion boundary areas detected in the pseudo-ternary phase diagrams and after evaluation of other physical parameters. After the identification of the microemulsion region in the phase diagram, the microemulsion formulations were selected at desired component ratios. Once this blank microemulsion was prepared, the microemulsion containing phytoconstituents was prepared by mixing them (each 1% w/w) into the surfactant or oils in which they were soluble at a higher amount (based on the results of the solubility study). Finally, a clear and stable microemulsion system (W/O type) was obtained using the appropriate amounts of all the components detected in the pseudo-ternary phase diagrams. The microemulsion system containing phytoconstituents was characterized for various physico-chemical properties like globule size analysis, zeta-potential, viscosity, drug content, pH, transmittance and stability study.

Measurement of globule size and zeta potential

The average globule size and zeta potential of phytoconstituents containing microemulsion was evaluated using Malvern Zetasizer (Nano ZS, 90, UK). A small amount of microemulsion sample (0.1 ml) was diluted to 10 ml of doubled distilled water. This diluted sample was tested for globule size and zeta potential using Malvern Zetasizer. Samples were analysed for globule size and zeta potential in triplicate for better accuracy.

Viscosity determination

Viscosity of the microemulsion formulation and sunscreen formulation was measured by using the Brookfield Viscometer (LVDV-II+pro). Appropriate spindles were chosen to measure the viscosity of both the microemulsion and sunscreen cream. All the operating conditions of rpm and torque were set and samples were kept ready to determine the viscosities. Finally, the viscosities were calculated by the following Eq. (1) [27].

$$\text{Viscosity} = \text{Dial reading} \times \text{Factor. For LV at 6 rpm factor is 1M (1000)} \quad (1)$$

Drug content study

Accurately weighed (5 ml) microemulsion containing 1% w/w of lycopene, β-carotene and curcumin was taken in

25 ml capacity volumetric flask and 10 ml ethanol was added to it. The resultant mixture was stirred for 30 min and finally filtered through Whatman filter paper. These filtrates (1 ml) were diluted with 10 ml ethanol and analysed for content study using UV-visible spectrophotometer at 440, 460 and 418 nm for the determination of lycopene, β-carotene and curcumin respectively [18].

Determination of pH and percent transmittance

The prepared microemulsion system was checked for measurement of pH values using digital pH meter (Lab India). Standard buffer systems of pH 4 and 7 were used to determine the pH of microemulsion. Percent transmittance was measured by diluting the microemulsion 100 times and analysed on UV-visible spectrophotometer against distilled water as blank at 640.2 nm.

Stability study

Microemulsion system was tested for physical stability by centrifuging the small amount of sample at 1250 rpm for 5 h and examined for phase separation and other changes, if any. Further, these microemulsion systems were checked for stability issues at various temperature and humidity conditions for 3 months. The microemulsion was subjected to stability study at 4 ± 2 °C, 30 ± 2 °C and 75 ± 5% relative humidity (RH) and 40 °C ± 2.C/ 75 ± 5% (RH) according to ICH guidelines and evaluated for physical and chemical stability [28].

Preparation of sunscreen formulation

Sunscreen cream is o/w emulsion containing aqueous phase as continuous phase and oil phase as dispersed phase. Water phase is prepared by adding a reported amount of distilled water. Accurately weighed all water-soluble components such as glycerine, potassium hydroxide and methyl paraben were dissolved in aqueous phase and resultant mixture allowed to heat up to 80 °C. Oil phase was prepared by mixing ceto-stearyl alcohol, stearic acid, propyl paraben and petroleum jelly together with the mentioned amount of MLCC and heated up to 80 °C. Oil phase was added to aqueous phase at 80 °C with slow and constant stirring for 20 min. As a result, homogenized and uniform emulsion-based cream was formed. The accurately weighed microemulsion was added slowly to the above sunscreen base and incorporated uniformly in mortar and pestle [16] (Table 1).

Determination of sun protection factor (SPF)

The sun protection factor of microemulsion and microemulsion-containing sunscreen cream was determined using the UV-spectrophotometric method. In this method, 1 g of sample was weighed accurately and ethanol was added to make 10 ml of the final volume. The resultant mixture was analysed for absorbance at 290–320 nm and SPF was calculated using following Eq. (2) [29, 30]

$$\begin{aligned} SPF\ spectrophotometric &= CF\,x\,SPF\ \ spectrophotometric \\ &= CFx \\ &= \sum_{290}^{320} EE(\lambda)Abs(\lambda) \end{aligned} \tag{2}$$

where
CF = Correction factor (10)
EE = Erythrogenic effect of radiation with wavelength (λ)

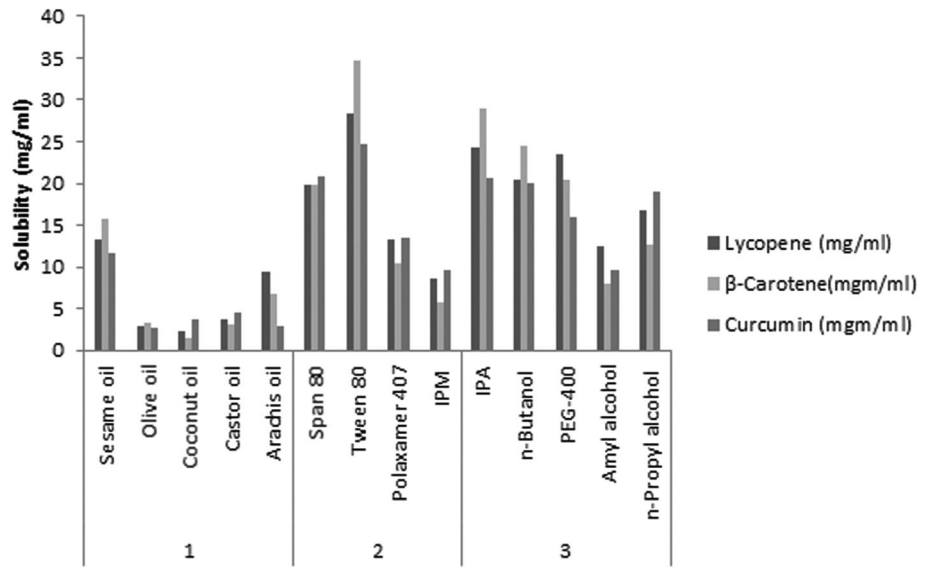

Fig. 1 Solubility of lycopene, β-carotene and curcumin in different oils (1), surfactants (2) and cosurfactants (3)

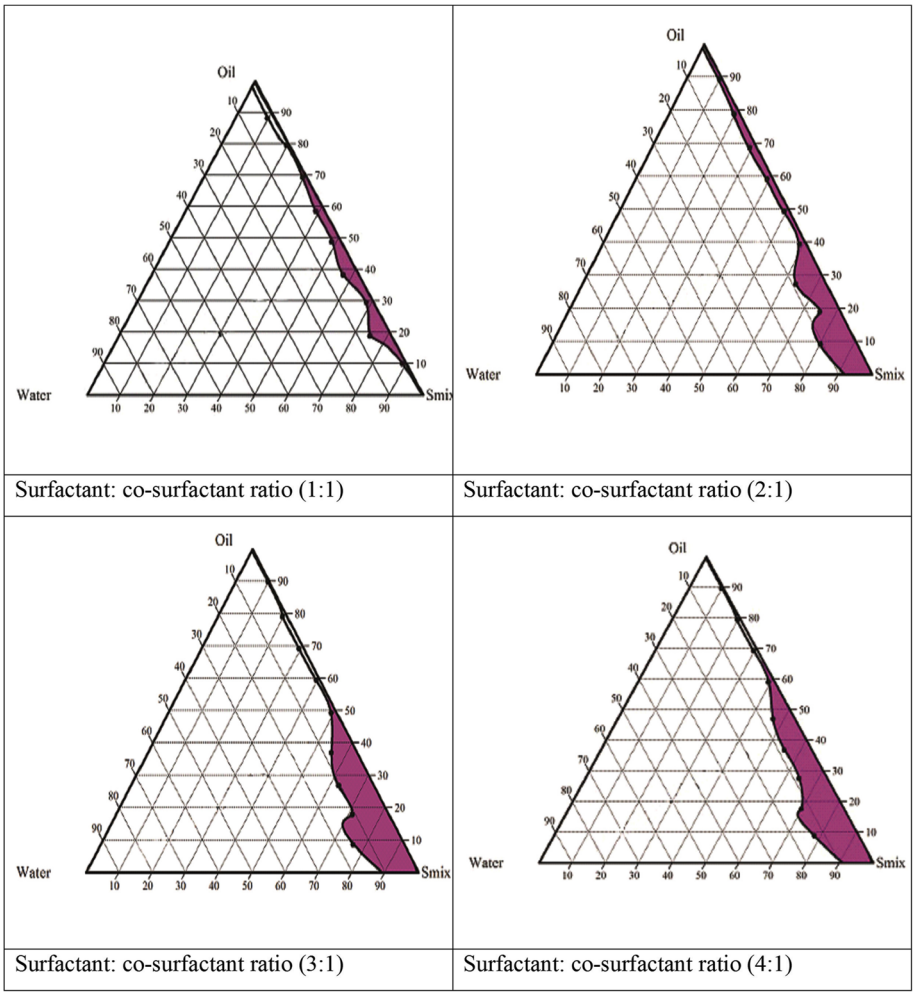

Fig. 2 The pseudo ternary phase diagrams of the oil-surfactant-water system at 1:1, 2:1, 3:1, and 4:1 weight ratio

Abs (λ) = Spectrophotometric absorbance values at wavelength

The value of EE × I is constant.

Evaluation of sunscreen formulation

The microemulsion-containing sunscreen cream formulation was evaluated for pH, tube extrudability, spreadability, viscosity, drug content and in vitro study using various tools and methods.

Texture characterization and spreadability testing

The prepared sunscreen formulation containing microemulsion was characterized for spreadability using CT-3 texture analyser. A cylindrical analytical probe (12 mm diameter) was inserted within the sample at a specific rate (2 mm/s) and at a definite depth (10 mm) at 25 °C. Readings were taken in triplicate for better accuracy.

Table 2 Various evaluation parameters of an optimized microemulsion system

Observations	Results
Average particle (globule) size	208 nm
Polydispersibility index (PDI)	0.342
Zeta potential	− 17.5 mV
Transmittance	90.68%
Refractive index	1.002 ± 0.03
pH	7.01 ± 0.07
Viscosity	82.45 ± 0.07 cps
Drug content (%)	
(a) Lycopene	87.53%
(b) β-carotene	85.08%
(c) Curcumin	90.65%
SPF	36.32
Conductance	0.935 moh/cm

Table 3 Various evaluation parameters of microemulsion-containing sunscreen cream

Observations	Results
Spreadability	17 ± 5 g cm/s
Extrudability	96.58 ± 0.9%
pH	7.1 ± 0.3
Sun protection factor (SPF)	37.65
Refractive index	1.002 ± 0.03
Viscosity	22,341 ± 3 cps
Drug content (%)	
(a) Lycopene	84.33%
(b) β-carotene	83.88%
(c) Curcumin	88.86%

Extrudability study

This study was conducted to find out the extrudability of sunscreen cream formulation when packaged in the tube container. The sunscreen formulation was filled in the standard collapsible tube, sealed properly using crimping machine and cap was fitted. The filled weight of tube was recorded. The tube was clamped between two glass slides and 500 g weight was placed over the glass slides and then cap was removed slowly. The amount of cream extruded was collected and weighed and compared with the initial filled weight of the tube. Finally, the percentage of cream was calculated and graded.

Skin irritation test

The prepared sunscreen formulation containing microemulsion was tested for the skin irritation. Protocols of the study were approved by Institutional Animal Ethical Committee, and with kind permission of the CPCSEA committee, the work was started using three healthy male rabbits. They were kept carefully following the acclimation period of 7 days to ensure their suitability for study. After an acclimation period, the area on the back of each rabbit was shaved carefully before the experiment. The skin surface of the rabbit on its back was divided into three marked areas; at one patch, there was no formulation and on the other two patches, microemulsion and sunscreen cream formulation was applied (0.5 g of each test formulation was applied on each 3 × 3 cm area). The study was carried out for 48 h, and for every 24 h, the animal was observed for irritancy, erythema, inflammation and oedema. The score of primary irritation was calculated for each rabbit.

Results

In the initial study, extraction of plant material was carried out and isolation of lycopene, β-carotene and curcumin was obtained from *Solanum lycopersicum*, *Dacus carota* and *Curcuma longa*, respectively, using cold maceration followed by preparative thin-layer chromatography (TLC). Isolated phytocomponents were tested for identification and quality. Melting point of 184 °C, 171 °C and 181 °C were detected for lycopene, β-carotene and curcumin, respectively, determined by digital melting point apparatus (Veego, model MVP). The melting point was found to be in range and identical to the reported standard melting points. UV-visible spectra and FT-IR spectra confirmed the isolated phytoconstituents based on the various functional groups detected. Maximum absorption spectra (λmax) of lycopene, β-carotene and curcumin were detected at 418, 444 and 460 nm, respectively, after being scanned in UV-visible spectrophotometer in a range from 200 to 800 nm.

Results of globule size analysis showed the average globule size 208 nm (Fig. 1) and conductance of 0.935 moh/cm. The lower value of conductance confirmed the W/O type of emulsion. The microemulsion was tested for pH and average value of 7.1 ± 0.07 was observed. The refractive index is 1.002 ± 0.03. Polydispersibility index (PDI) represents the uniform distribution of globules/particles (> 0.3); the present optimized microemulsion formulation shows an average PDI of 0.342 which has confirmed the uniform distribution of the droplets in the formulation. For better distribution of particles, the zeta potential values of less than − 30.0 mV are genereally not considered due to less repulsive forces which may lead to the formation of agglomerates. An average zeta potential value for optimized microemulsion was found to be − 17.5 mV (Fig. 2) which represents the sign of good dispersibility of microemulsion droplets in the continuous phase and less chances of agglomeration with better stability.

In another study of transmittance, the presence micron-sized globules with uniform distribution was observed when the microemulsion was diluted 100 times and showed 90.68% transmittance with clear appearance whereas without diluted microemulsion has shown

Table 4 Skin irritation study data

Test material[a]	Skin reaction[b]	Mean irritation score		
		12 h	24 h	48 h
Sunscreen cream containing microemulsion	Erythema	0	0	0.2
	Oedema	0	0	0

[a]Test material was applied on rabbit skin
[b]Erythema and oedema; the mean irritation score was the summation of each irritation score divided by the number of animals

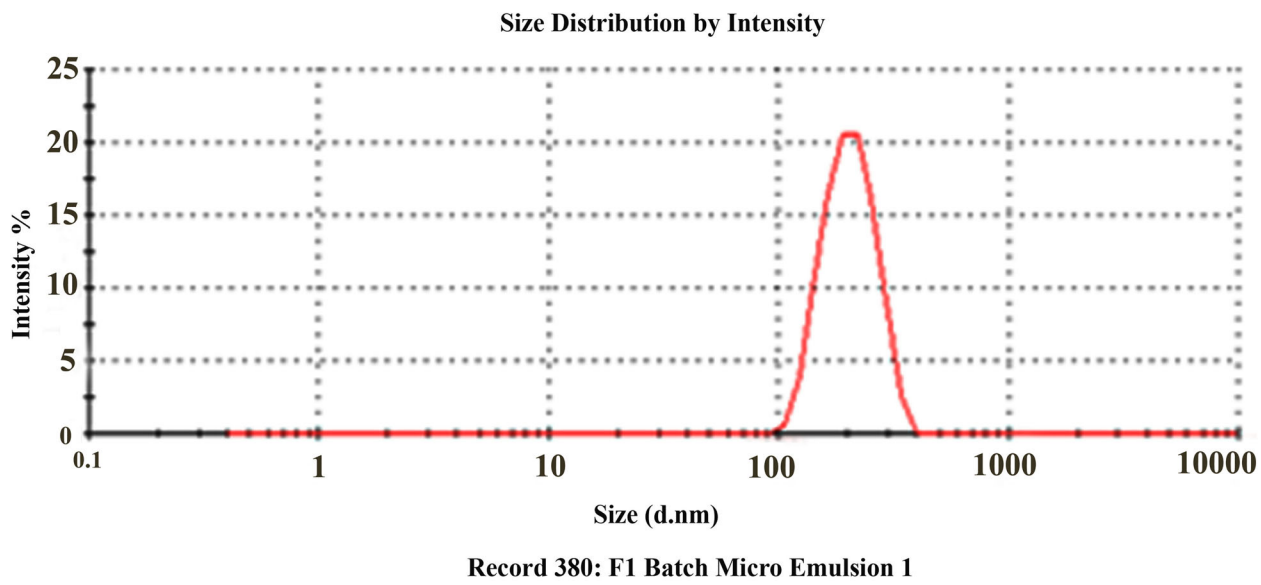

Fig. 3 Size distribution curve of microemulsion system

85.98% transmittance. Further, the sunscreen cream formulation was also evaluated for viscosity, tube extrudability and spreadability. The viscosity of microemulsion was found to be 82.45 ± 0.07 cps, whereas the total content of lycopene, β-carotene and curcumin was found to be 87.53, 85.08 and 90.65%, respectively. The sun protection factor of microemulsion was calculated using Eq. (1) described in the "Methods" section, and it was found to be 36.32. All the results of globule size, PDI, conductance, transmittance, refractive index, pH, viscosity, drug content and sun protectiion factor (SPF) are presented in Table 2.

The extrudability of the prepared sunscreen cream formulation after packaged into standard tube was found to be 96.58 ± 0.9%.

The viscosity of sunscreen cream at 25 °C was found to be 22,341 ± 3 cps which was much higher than the microemulsion preparation. The pH of test sunscreen cream was found to be 7.1 ± 0.3 whereas the percent drug content of lycopene, β-carotene and curcumin was found to be 84.33, 83.88 and 88.86%, respectively (Table 3).

The sun protection factor calculated for the microemulsion-containing sunscreen formulation was found to be 37.65.

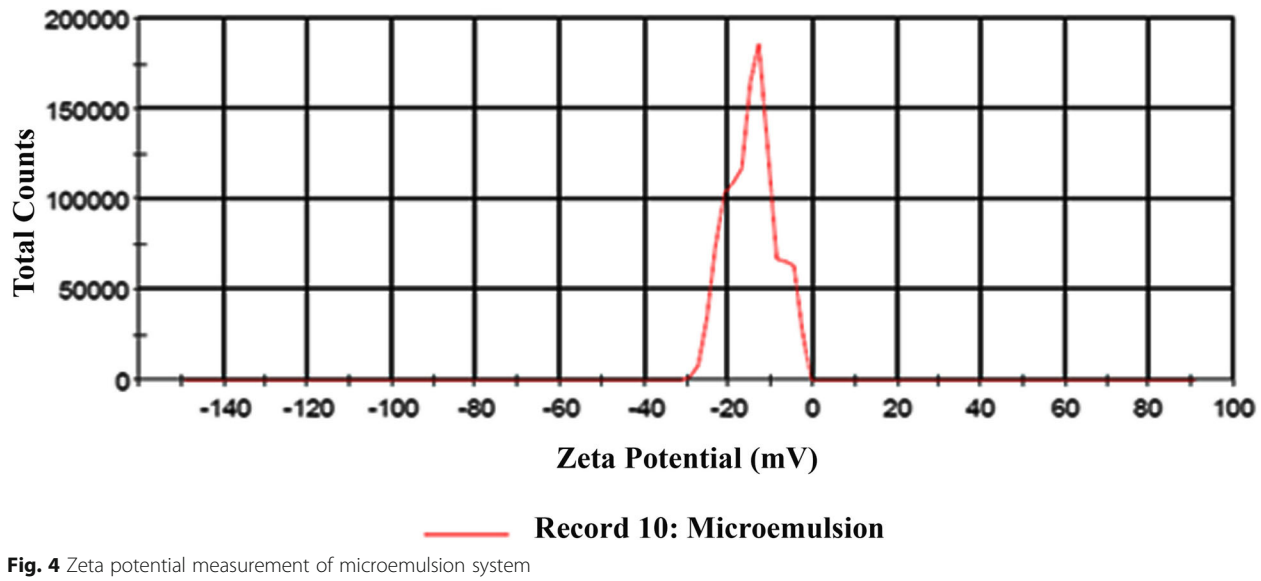

Fig. 4 Zeta potential measurement of microemulsion system

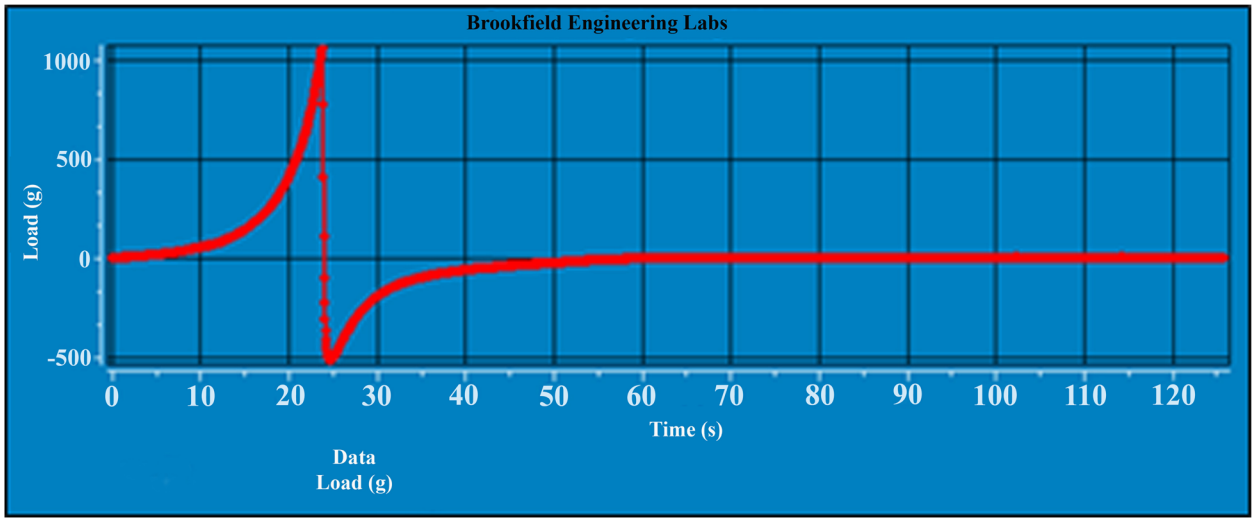

Fig. 5 Texture characterization graph for microemulsion containing sunscreen cream

Skin irritancy test was performed to check the irritation of topically applied microemulsion as well as sunscreen cream formulation. The PII (Primary Irritation Index) when no formulation was applied was found to be 0.166; for microemulsion, it was 0.277; and for sunscreen cream, it was found to be 0.222 (Table 4).

Discussion

In the solubility study of lycopene, β-carotene and curcumin, it has been observed that the maximum solubility of these phytoconstituents was found to be in sesame oil, span 80 to tween 80 (1:1) and isopropyl alcohol. Based on these results of this solubility study, sesame oil, span 80 to tween 80 (1:1) and isopropyl alcohol were selected for the preparation of microemulsion. Results of the solubility study are presented in Fig. 3.

From results of the pseudo-ternary phase diagrams, 2:1 ratio of surfactant to co-surfactant and oil to Smix (2:8) was found to be the best for the development of microemulsion since the maximum microemulsion boundary area was observed as shown in Fig. 4. The maximum microemulsion boundary area represents the formation of microemulsion with micron-sized globules at the interface of oil, water and Smix. This area represents clear, transparent and stable microemulsion with no phase separation up to 72 h when kept on standing in the sealed glass container. Finally, these ratios of components were considered to make an optimized microemulsion system, and microemulsion-containing phytoconstituents were formulated successfully. This optimized microemulsion was characterized for various physiochemical parameters for the confirmation of quality.

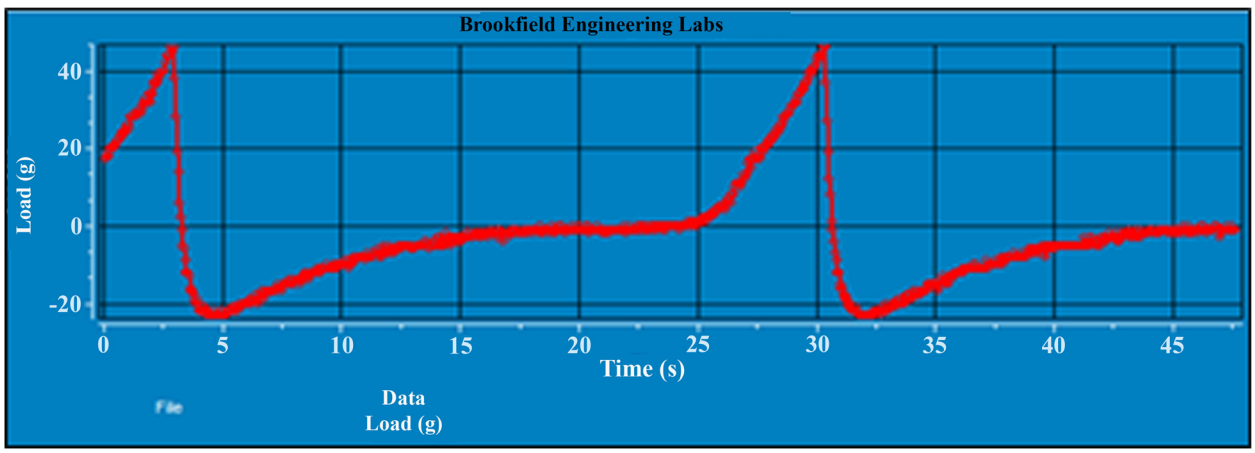

Fig. 6 Spreadability graph of microemulsion containing sunscreen cream

The spreadability of the prepared sunscreen formulation was studied on the CT-3 texture analyser. The area under positive curve is a measure of energy required to deform the sample to a defined depth grade in order of its stability. Higher peak load and work done indicate lower spreadability. Lower peak load value coupled with a lower work done value indicates that the sample is more spreadable. In the case of sunscreen cream formulation, the texture analysis data represents the spreadability of cream (17 ± 5 g cm/s) as shown in Figs. 5 and 6. The negative peak indicates the work done by the probe which was lower than the positive curve which proves that the test formulation possesses good spreadability.

From the above data, it is concluded that the PII (Primary Irritation Index) of both microemulsion and sunscreen cream in the range of 0.0–0.4 and indicating irritancy was negligible.

Conclusion

Prevention from harmful effects of ultraviolet radiation of the sun is on prime importance to everyone by considering cosmeceutical intension and personal external appearance of the individuals. The use of many available synthetic components such as sun protection may be harmful due to various serious issues as discussed in this manuscript. Considering many beneficial effects of phytoconstituents like antioxidant activity and excellent sun protection effect, the present study has focused on the development of microemulsion-based sunscreen cream formulation with excellent SPF values. From the findings of the present research, it has been concluded that stable microemulsion system containing lycopene, β-carotene and curcumin as an important phytoconstituents possessing both antioxidant and ultraviolet radiation protection properties can be formulated successfully as a sunscreen cream formulation.

Abbreviations

UV: Ultraviolet; ROS: Reactive oxygen species; MPKV: Mahatma Phule Krushi Vidyapith; TLC: Thin-layer chromatography; IR: Infrared; IPM: Isopropyl myristate; IPA: Isopropyl alcohol; PEG: Polyethylene glycol; SPF: Sun protecting factor; CF: Correction factor; RH: Relative humidity; ICH: International Conference on Harmonisation

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Authors' contributions

RDB has given her contribution for constructing the idea for the manuscript. SSK has given her contribution for collecting the data and material for this work. PNK has given his contribution for taking responsibility in the construction of the entire part of the manuscript. VVP has given his contribution for making planning as well as organizing and supervising of the course of the article and taking responsibility. MAG has given contribution for guiding the entire team as well as taking effort before submission of the article. All authors have read and approved the final manuscript.

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Availability of data and materials

All data and materials are available upon request

Ethics approval and consent to participate

Institutional Animal Ethics Committee for Animal Experiments of Sanjivani College of Pharmaceutical Education and Research, Kopargaon, approved the study under the protocol SCPER/CPCSEA/IAEC/2016-17/04 and all experiments were conducted in accordance with guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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