Asia-Pacific Journal of Science and Technology: Volume: 29. Issue: 03. Article ID.: APST-29-03-15. Research Article

APST

Asia-Pacific Journal of Science and Technology

https://www.tci-thaijo.org/index.php/APST/index

Published by the Research and Graduate Studies,
Khon Kaen University, Thailand

Development and evaluation of curcumin nano emulsion in moisturizer for antiaging

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Received 6 February 2023
Revised 17 March 2023
Accepted 4 April 2023

Abstract

In this study, an attempt was made to prepare a curcumin nano moisturizer. Curcumin is a powerful antioxidant that neutralizes free radicals and reactive oxygen species. (ROS). Various formulations were prepared by utilizing a pseudo-ternary phase diagram and an appropriate surfactant and co-surfactant mixture (S_{mix}), with olive oil serving as the oil phase. Curcumin and excipients were found to be compatible in FTIR investigations, and droplet dispersion analysis was performed on all formulations. The formulation F3 was found to be optimal, with particle size and zeta potential of mean n=3, 506.30.43 nm, and -31.10.04 mV, respectively. It was characterized and evaluated for viscosity, spreadability, pH, thermodynamic stability studies, robustness to dilution ratio, percent transmittance, drug diffusion studies, and free radical scavenging assay by using DPPH, F3 formulation inhibited 88% of free radicals, which was more than the positive control, ascorbic acid, and it suppressed ROS generation. Short-term stability studies on optimized curcumin nano moisturizer show that it can be stored in a well-closed wide-mouth container for two months at 40±2°C and 75% RH. As a result, the prepared nano moisturizer showed to be a potential anti-aging cosmeceutical candidate.

Keywords: Curcumin, Ternary phase diagram, Thermodynamic stability, Olive oil, Nano moisturizer

1. Introduction

The skin is the biggest organ in the human body. As a result, people are acutely aware of and sensitive to the texture of their skin. Humans have been searching for fair and healthy skin for generations [1]. Skin is an extremely vulnerable organ that can easily injured. Environmental pollution, over exposure to UV radiation, age, and microbes can all cause facial skin disorders. The societal impact of skin ageing is particularly significant. People pay a lot of attention to their skin because of its public visibility and aesthetic appeal. The two types of skin ageing are intrinsic and extrinsic. These variables promote oxidative stress, which produces free radicals, or reactive oxygen species (ROS), in the skin [2]. The development of fine wrinkles is one of the structural changes that occur in chronologically aged skin. Wrinkles (or rhytides) are a powerful and important predictor of aging, as well as a fascinating topic of cosmetic dermatology. Antioxidants protect the skin by neutralising the ROS produced by UV exposure [3,4]. Antioxidants are present at the location of the initial ROS-mediated damage or response. The oxidative stress can be mitigated, and the hazardous chemical reaction can be avoided. During the reaction, the antioxidant is depleted. The skin's antioxidant capacity depletes over time, resulting in skin damage. As a result, topical antioxidants designed to permeate the skin will bind antioxidants to the skin's own pool, increasing protection. Plant polyphenols such as curcumin, quercetin, and gallic acid, among others, are widely employed as primary cosmeceutical components in numerous skin care formulations. Curcumin (diferuloyl methane) is a phenolic phytochemical produced from the rhizome of the herb *curcuma longa* [5]. Although it has been discovered to have numerous therapeutic qualities such as anti-inflammatory, anti-microbial, and anti-oxidant properties, its usage as a functional ingredient is currently limited due to its low water solubility. As a result, it is developed as a nano moisturizer [6,7]. Today, cosmeceuticals are the fastest expanding segment because customers want personal care products that deliver various benefits with low effort, and topical cosmeceuticals are widely used [8,9]. In the current study goal is to formulate a curcumin nano moisturizer for antiaging skin.

Anti-aging drugs prevent wrinkles by maintaining the skin's natural physiological condition [10,11,12]. It also protects against photo aging and hyperpigmentation. Nano moisturizer will be added product variety to the market.

2. Materials and methods

2.1 Materials

Sigma Aldrich in Mumbai provided the curcumin. Karnataka Fine Chemicals in Bengaluru provided olive oil, PEG, and Tween 80. Central Drug House Pvt Ltd in New Delhi provided the solvents and other excipients.

2.2 Methods

2.2.1 Pre formulation studies

The standard calibration curves of curcumin were developed using methanol and Phosphate buffer pH 5.5 with tween 80 as a solvent and a UV-Visible spectrophotometer. The greatest absorption obtained in the UV spectrum was considered as a pure drug λ_{max}. At 421 nm, the absorbance was measured with a UV-Visible Spectrophotometer. Curcumin melting point was determined using Thiele's tube device. Fourier Transform Infrared spectroscopy is more commonly employed for the qualitative identification of chemicals, whether pure or in mixtures. Spectra can give crucial information about the structure of curcumin and its compatibility.

2.2.2 Compatibility studies of curcumin with excipients using phase diagram

For 72 h, a magnetic stirrer at 100 rpm was used to stir 10 mg of curcumin with a calculated amount of natural oils, surfactants, and co-surfactants. The mixture was then filtered. The filtrate was collected, diluted with methanol, and measured the absorbance by using a UV-Vis spectrophotometer at 421 nm [13]. A pseudo-ternary phase diagram comprised of oil, S_{mix} (a mixture of surfactant and co-surfactant), and distilled water was utilized to generate the phase diagram. The titration method was used. S_{mix}: A mixture of surfactants and co-surfactants in various volume ratios. (1:1, 1:2, and 2:1). To achieve the best ratio, nine different combinations of oil and S_{mix} were used: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. One study sought to precisely illustrate the phase boundaries produced in the phase diagram. Titration: After slowly titrating each volume ratio of oil to S_{mix} with distilled water, visual observations were made and recorded. It was not heated during the preparation process. An MS Excel spreadsheet was used to create a phase diagram. Following the plotting of the mixture diagram in Table 1, a pseudo-ternary phase diagram was plotted. The stable phase was prepared by mixing a calculated amount of oil, S_{mix}, and water (5 ml) without heating with a magnetic stirrer at 1200 rpm [14,15].

Table 1 Formulation chart of curcumin nano emulsion.

Formulation code	Curcumin (mg)	Oil conc (%)	Ratio of S_{mix}	Co surfactant	Batch Volume
F1	10	10	1:1	PEG 400	25
F2	10	30	1:1	PEG 400	25
F3	10	10	2:1	PEG 400	25
F4	10	30	2:1	PEG 400	25
F5	10	10	1:1	PG	25
F6	10	30	1:1	PG	25
F7	10	10	2:1	PG	25
F8	10	30	2:1	PG	25

All the materials were accurately weighed and placed in separate beakers, as stated in Table 2. One beaker contains the oil phase, and another contains the water phase, both of which are heated in a water bath at 70°C. In a chill setting, the water phase was progressively introduced to the oil phase while being constantly agitated. The curcumin nanoemulsion and perfume were further added, and the cream was continually mixed to achieve a smooth consistency.

Table 2 Formulation of moisturizer.

Ingredients	B1 (g)	B2 (g)	B3 (g)
Stearic acid	9	8	7
Liquid Paraffin	3.0	2.0	1.0
Lanoline	0.3	0.3	0.3
Glyceryl mono stearate	0.9	0.9	0.9
Glycerin	1.2	1.2	1.2

Table 2 (continued) Formulation of moisturizer.

Ingredients	B1 (g)	B2 (g)	B3 (g)
Propylene Glycol	1.2	1.2	1.2
Isopropyl Myristate	0.6	0.6	0.6
Triethanolamine	0.06	0.06	0.06
Methyl Paraben	0.009	0.009	0.009
Propyl Paraben	0.021	0.021	0.021
Perfume	Q.S	Q.S	Q.S
Distilled water Q.S to	30	30	30

*Batch size = 30 g.

2.3 Characterization of nano emulsion

2.3.1 Thermodynamic stability & robustness to dilution ratio

At 3000 rpm, the formulation was centrifuged. Heat-cool cycles: 6 cycles of temperatures ranging from 4 to 30°C, storage at each temperature for at least 48 h, and formulations visually evaluated for temperature stability. The robustness-to-dilution ratio was calculated by diluting with 100 ml of phosphate buffer (pH 5.5) and distilled water. After 12 h, the diluted nanoemulsion was examined for symptoms of phase separation [16,17,18].

2.3.2 Drug content analysis

About 1 mL of nano emulsion was diluted with pH 5.5 phosphate buffer at drug concentration of 5 µg/mL, and absorbance at 421 nm was measured using a UV-Visible spectrophotometer [19].

2.3.3 Droplet size distribution analysis

In a volumetric flask, the formulation (0.1 mL) was distributed in 50 mL of water, fully mixed by sonication for 15 minutes, and light scattering was measured at 25°C at 90°. A Malvern particle size analyzer was also used to assess droplet size, polydispersity index (PDI), and zeta potential [20].

2.4 In vitro drug diffusion studies & release kinetics

Using the Franz diffusion cell, the in vitro drug diffusion profile of curcumin nanoemulsion was done. The dialysis membrane was immersed in a pH 5 phosphate buffer overnight. On the dialysis bag, around 5 ml of the nanoemulsion was added. Buffer was poured into the receptor chamber using a beaker, making sure that the dialysis bag was dipped completely. After that, the beaker was placed on the magnetic stirrer. During the test, the temperature and speed were kept constant at 37±0.5°C and 100 rpm, respectively. At predefined time intervals, a sample (5 mL) was extracted and replaced with an equivalent volume of the new buffer. (1, 2, 3, 4, 5, 6, and 7 h). The samples were analyzed for curcumin content at 421 nm using a UV-Vis spectrophotometer after suitable dilution. The in vitro diffusion data were fitted with zero-order, first-order, Higuchi, and Korsmeyer Peppa's models to assess the release kinetics and mechanisms of curcumin nanoemulsion [21].

2.5 Formulation optimization

The produced curcumin nanoemulsion was fitted into two factorial statistical designs, with three variables kept constant: oil content, water concentration, and S_{mix} ratio. Using design expert software, the effect of increasing oil concentration and S_{mix} ratio on particle size, zeta potential, and percentage cumulative drug release was investigated.

2.6 Percent transmittance

Percent transmittance of the prepared nano emulsion was determined spectrophotometrically.

2.7 Determination of free radical scavenging activity

The antioxidant activity of curcumin in formulations is determined using the DPPH technique. The investigation employed reagent 2, a 2-diphenyl-1-picrylhydrazyl (DPPH) solution. For the production of the DPPH radical, 10 mg of DPPH was dissolved in 250 mL of ethanol and left overnight in a dark environment. A 0.004% DPPH solution in ethanol and 0.1 ml of the test sample were mixed. The mixture was briskly agitated and

allowed to settle at room temperature for 30 min. The absorbance at 519 nm was used to measure DPPH decolorization [22,23].

2.8 Viscosity & pH measurements

The viscosity of the obtained nanoemulsion formulations was evaluated at room temperature without dilution using a Brookfield viscometer with spindle No S-96. The pH of the formulations was evaluated using a digital pH meter [24,25].

2.9 Spreadability

The spreadability of preparations is determined by using the horizontal glass plate method [26].

2.10 Evaluation of nano emulsion in moisturizer

To achieve homogeneity in the combination, a calculated amount of nanoemulsion F3 formulation was combined with 10 g of Moisturizer. Homogenized at 5000 rpm for 10 min, the nano moisturizer was exposed to several evaluation criteria such as viscosity, pH, drug content, and stability investigations for the final product. The viscosity of the produced nano moisturizer formulations was evaluated at room temperature without dilution using a Brookfield viscometer with spindle No S-96. Digital pH meter was used to determine the pH. To determine the drug content, approximately 1 g of nano moisturizer was diluted with pH 5.5 phosphate buffer and filtered to obtain a concentration of 5 µg/mL, and absorbance was measured using a UV-Visible spectrophotometer at 421 nm; whether the results were statistically significant or not was determined by using the paired t-test.

2.11 Stability study

For two months, the optimized formulation was subjected to stability tests at 40±2°C/75±5% RH. The optimized formulation of curcumin nano moisturizer was kept in a screw-capped wide-mouth container. The product was further evaluated using in vitro for drug diffusion, drug content, pH, and viscosity parameters [27].

3. Results and discussion

3.1 Pre formulation studies

The absorption maxima of curcumin were found to be 421 nm by using methanol with the regression coefficient value of curcumin found to be 0.999 and the slope value was 0.1843. It is also nearest to the reported standard λ_{max} for Curcumin was 425 nm [25]. FTIR spectra of curcumin and its combination with olive oil, PEG-400, and also with tween 80 were shown in Figure 1. From the obtained spectra it was observed that the characteristics significant peaks of curcumin 3510.7 cm^{-1} due to OH stretching, 1429.1 cm^{-1} due to Ar C=C stretching, 1429.1 cm^{-1} due to C=O stretching, 2917 cm^{-1} due to C-H stretching, 1239 cm^{-1} due to C-O stretching. Curcumin is combined with Olive oil, PEG-400, and Tween 80 spectra show almost the same characteristics peaks hence excipients were compatible with an active ingredient.

Olive oil was chosen as the oil phase because it provides higher moisturizing qualities [26]. To maintain monodisperse globules with improved skin penetration, which aids in maintaining homogeneity without phase separation, another crucial factor is the choice of surfactant and cosurfactant. Since tween 80, a non-ionic surfactant has the highest solubility for curcumin and is listed in pharmacopeia's as being non-irritating, it is an excellent option for topical medicinal preparations. Curcumin was more soluble than other co-surfactants like propylene glycol and glycerol, therefore PEG-400 was chosen since it aids in reducing interfacial tension and maintains globule size.

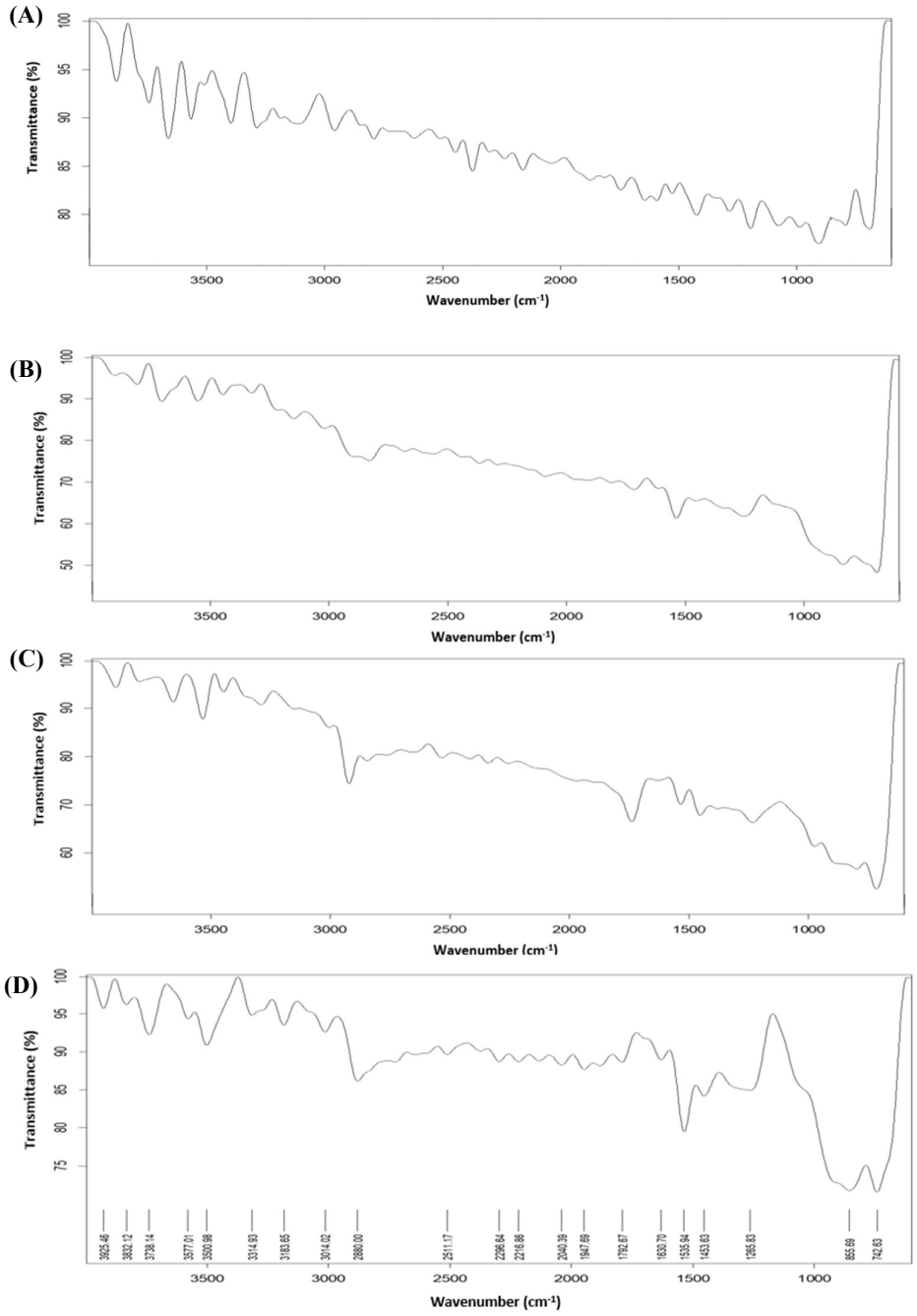

Figure 1 FTIR Spectra of Curcumin and its excipients (A) Curcumin, (B) Curcumin+Tween 80, (C) Curcumin+Olive oil and (D) Curcumin+PEG.

The oil selection is an important criterion in the formulation of nanoemulsions because it influences drug solubility and thus improves drug concentration. Curcumin solubility was determined in various natural oils, with olive oil having the highest solubility and curcumin having the highest solubility in tween 80 and PEG-400. For phase behavior investigations, olive oil, tween 80 (surfactant), and PEG-400 (co-surfactant) were examined in the current study. The shaded area in the ternary diagram represents the nanoemulsion range, but it was discovered that increasing the S_{mix} reduces flowability and that increasing the surfactant ratio in the S_{mix} decreases globule size with good stability, so a 2:1 ratio S_{mix} was chosen and formulations were optimised using software, as shown in Figures 2 and 3.

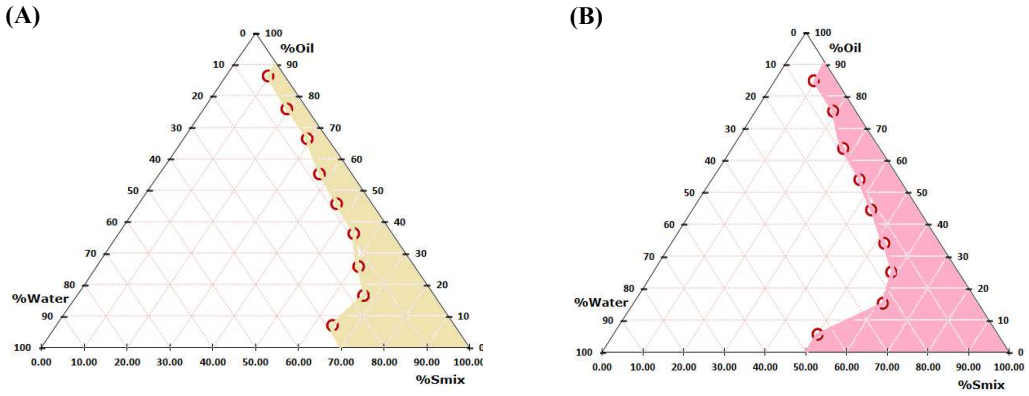

Figure 2 S_{mix} (A) 2:1 and (B) 1:1 (Tween 80 & PEG 400) ratio.

3.2 Pseudo-ternary phase diagram [27]

In the current work, phase behavior investigations were conducted using olive oil, tween 80 (a surfactant), and PEG-400 (a co-surfactant). The range of nanoemulsions is indicated by the shaded area in the ternary diagram; however, it was found that increasing the S_{mix} decreases flowability and that increasing the surfactant ratio in the S_{mix} reduces globule size with good stability, so a 2:1 ratio S_{mix} was chosen. Formulations were then optimized using design expert software while controlling independent variables like oil concentration, the ratio of the S_{mix}, and the water, along with response factors like globule size, zeta potential, and drug release.

3.3 Characterization of nano emulsion

3.3.1 Thermodynamic stability studies & robustness to dilution

The purpose of this stability study is to guarantee droplet integrity while being affected by temperature changes. Formulation F3 didn't experience stability issues like phase separation, coalescence, or sedimentation, so it was thermodynamically stable and confirmed robustness without phase separation after 12 h of visual assessment [28].

3.3.2 Droplet distribution analysis

The entire concept of nano moisturizers is based on their size and stability, which was measured by the variation in light scattering caused by the Brownian motion of the globules, globule size is the most important parameter. The technique of dynamic light scattering was used to investigate structural deportment (DLS). Results as shown in Table 3. Globule size of the optimized formulation F3 was 506 ± 0.45 nm, indicating that it is in the nanometre range as observed from the graph Figure 3 (A).

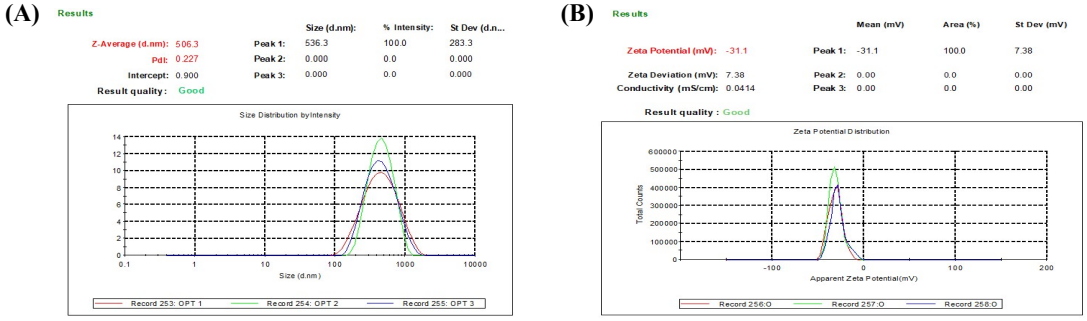

Figure 3 Optimized formulation (F3) (A) particle size distribution and (B) zeta potential.

3.3.3 Zeta potential

Zeta potential is an important tool for assessing stability as it is used to measure the electrostatic charge around droplets as droplet aggregation can occur due to the attraction of the charge. Many studies have suggested and reported that the zeta potential range is stable above 30 mV. The optimized formulation F3 had a zeta potential of

-30±0.32 mV as shown in Figure 3 (B) and remained stable over time as shown in Table 3. No phase separation, turbidity, or cracking was observed. The overall formulation was found to be stable. Thermodynamic stability gives nanoemulsion a long shelf life. The diluted nano moisturizer was stored for 12 h and showed no signs of phase separation.

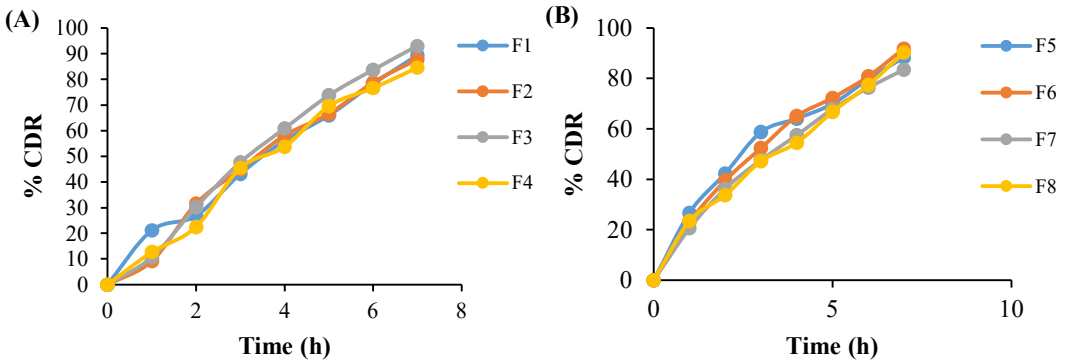

Figure 4 Percentage cumulative drug released profile of formulations (A) F1-F4 and (B) F5-F8.

3.3.4 In vitro drug diffusion studies

In vitro, drug diffusion studies are critical analytical tools for understanding and predicting product behavior at various stages of drug development. Changes in the stratum corneal tight junction properties improve penetration by increasing lipid solubilization or extraction, allowing nano-sized continuous-phase droplets to carry drugs across the skin barrier and into the stratum corneum. Drug release profiles *in vitro* can reveal important information about dosage forms and their behavior. Curcumin nanoemulsion contains water, which hydrates the cellophane membrane. As a result, the drug channels enlarge, and cumulative permeation through the cellophane membrane increases. Figure 4 shows the cumulative drug release of curcumin from all formulations. The optimized formulation F3 shows the highest drug release of 92% at the end of 7 h due to less oil concentration and mono-dispersed nano oil globules containing curcumin. The release kinetic was best fitted to zero order and Higuchi drug release, indicating that formulation was independent of the concentration of curcumin release from the nanoemulsion following zero order, and the mechanism of release was diffusion controlled.

3.3.5 Optimization of formulation

DOE is a useful tool for effectively and methodically choosing experiments that will yield accurate and consistent data. The responses were optimized after producing polynomials relating to the dependent and independent variables. Graphical and numerical analysis utilizing design expert software was used to identify the optimal values of variables based on desirability values. The dependent variables for the 2^3-factorial design that will be fitted to the formulations are the water, S_{mix} ratio, and oil concentration. We will take into account the effects of the independent variables globule size, zeta potential, and cumulative drug release, and reasonable high and low levels should be selected for each of these variables. The maximum composite desirability, as determined by data from the optimization program design expert, was 0.842, as shown in Table 4. F3 formulation that was optimized, it was further concluded.

Table 3 Physicochemical characterization of prepared Nano emulsion.

Formulation	Drug Content* (%)	Globule Size*(nm)	Zeta Potential*	PDI*	Viscosity* (cps)	Spreadability* (cm)	% Transmittance*	pH
F1	82.29±2.72	378±0.33	-33.4±0.32	0.27±0.01	4956±0.66	6211±0.18	20±0.03	5.0
F2	82.44±2.71	650±1.55	-27.9±0.35	0.32±0.02	4873±0.35	9.46±0.15	22±0.04	5.3
F3	88.36±0.86	506±0.45	-30±0.32	0.24±0.02	4875±0.33	13.52±0.25	15±0.05	5.5
F4	81.03±2.67	715±3.37	-29±0.30	0.28±0.01	6137±0.81	10.14±0.21	35±0.03	5.4
F5	83.10±3.90	425±0.42	-28.6±0.25	0.32±0.25	6137±0.81	12.83±0.27	28±0.03	5.2
F6	82.66±1.78	635±2.38	-17.2±0.35	0.29±0.15	5732±0.79	10.25±0.30	18±0.04	5.4
F7	86.49±0.56	412±0.29	-32.6±0.35	0.35±0.13	5843±0.23	11.52±0.44	25±0.05	5.8
F8	81.83±2.32	845±0.52	-15.9±0.3	0.46±0.11	6211±0.18	8.26±0.32	21±0.02	5.2

*Mean±SD (n=3).

Table 4 Optimized solution profile with desirability value.

Sl No.	Conc of oil	Ratio of Smix	Type of Co-surfactant	Particle size (nm)	Zeta potential (mV)	Drug release (%)	Desirability
1	10.369	2:1	PEG 400	506.77	-30.795	95	0.842

3.4 Evaluation of nano emulsion

3.4.1 Percentage transmittance

Using a UV-Visible spectrophotometer, the transmittance of the nanoemulsion formulations was assessed. The results were displayed in Table 2. F3 has a transmittance of 15% among these formulations, which is higher than other formulations. It absorbs less UV and visible light as a result, it may prevent the aging of the skin.

3.4.2 Spreadability and viscosity studies [29]

The rheological features are crucial for operational requirements in the industries of manufacturing pharmaceutical or cosmeceutical topical preparations to pumping, filling, and storage and if it is a cosmetic based on flow properties like appearance, pourability, and soothing to the skin of the finished product are the key parameters for consumers. The spreadability of curcumin nanoemulsion was found to be 13.52±0.25 cm, thus it is easily spreadable over the skin. The viscosity of the curcumin nanoemulsion was found to be 4875±8.33 cps and it lies in the range of 1000-10000 cps which has good flowability and is enough to apply on skin for moisturizing and physically stable for a long duration as shown in Table 3.

3.4.3 pH assessment

The pH of the skin ranges from pH 4-6 because it will help to absorb little quantities of acid or alkali material applied over the skin. Curcumin nano emulsion pH was found to be 5.48±0.02 and it was found to be near to skin pH which improves the partitioning coefficient to release the drug easily and reduce skin irritation.

3.4.4 Free radical scavenging assay

Curcumin has high antioxidant properties; hence it could scavenge free radicals therefore DPPH was a useful marker to identify to evaluate antioxidant activity [30]. The F3 formulation inhibits 88% of DPPH radicals compared to other formulations. The scavenging activity of formulations (F1-F8) was compared with ascorbic acid which inhibits 76% of DPPH radicals thus DPPH scavenging activity confirms curcumin nanoemulsion is sufficient to scavenge the free radicals or ROS helps to prevent the development of wrinkles on the skin as shown in Figure 5.

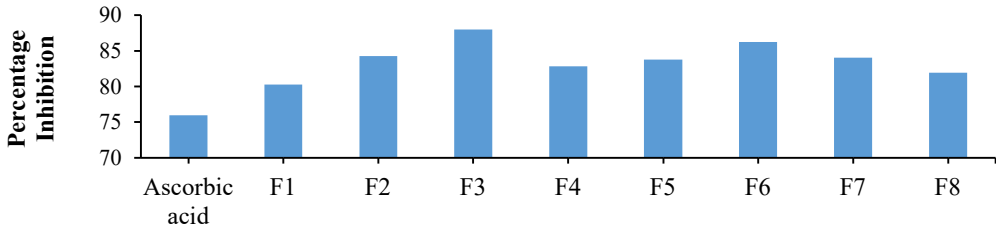

Figure 5 Percentage inhibition of free radicals by Curcumin nanoemulsion (F1-F8) with ascorbic acid as control.

3.5 Evaluation of nano curcumin emulsion in moisturizer

3.5.1 Organoleptic properties

The developed nano moisturizer cream organoleptic qualities, including color, appearance, and odor, were assessed. The moisturizer was determined to be a light-yellow color, has a smooth consistency, free from gritty particles, and has a pleasant aroma.

3.5.2 Spreadability and viscosity studies

The spreadability of curcumin nano moisturizer was found to be 15.30 cm thus it is easily spreadable over the skin. The viscosity of the curcumin nano moisturizer was found to be 306.63± 0.95 cps to 476.67 ± 0.55 cps, it lies in the good flowability range and is enough to apply on the skin for moisturizing due to being physically stable for a long duration.

3.5.3 Drug content

Using UV spectrophotometric measurement, the drug concentration of the nano curcumin moisturizer formulation was determined. Drug content was discovered to be between 88 and 90% as shown in Table 5.

Table 5 Results of Physicochemical parameters of nano curcumin emulsion in moisturizer.

Formulations code	Viscosity* (cps) ± SD	Spreadability*(cm)± SD	pH	Drug content (%)
B1	476.67 ± 0.55	15.36 ± 0.32	5.5	90.0
B2	350.87 ± 0.34	17.12 ± 0.54	5.4	89.0
B3	306.63 ± 0.95	17.76 ± 0.76	5.5	88.0

*n=3± SD.

3.5.4 Paired t test

The data from B1 and B2 were contrasted using the paired t-test. Two-tailed *p* value was found to be 0.4028. This difference is not believed to be statistically significant according to traditional standards. Therefore, B1 is taken into account based on the product's smooth consistency, maximum drug content, and viscosity behavior, which are outcomes as shown in Table 5.

3.6 Stability studies

Stability studies are an important method for developing new products and determining product shelf life. These studies showed that the formulations were stable based on potency, pH, viscosity, and cumulative drug release when stored at 40±2°C and 75±5% RH for 2 months, as shown in Table 6. There is no significant difference after the 2-month short-term stability study was observed. Based on drug concentration, pH, viscosity, and the percentage of cumulative drug released after storage for two months, these analyses showed that formulations were stable. Evaluation after stability studies data were described in (Table 6 and Figure 6).

Table 6 Stability profile of B1 at 40 ± 2°C, 75 ± 5% RH.

Days	Drug Content*(%)	pH*	Drug release*(%)	Viscosity*(cps)
30 days	88.37 ± 0.87	5.48 ± 0.02	91.81 ± 0.72	4865 ± 0.26
60 days	88.25 ± 0.93	5.38 ± 0.02	90.65 ± 0.63	4805 ± 0.22

*Mean ±SD (n=3).

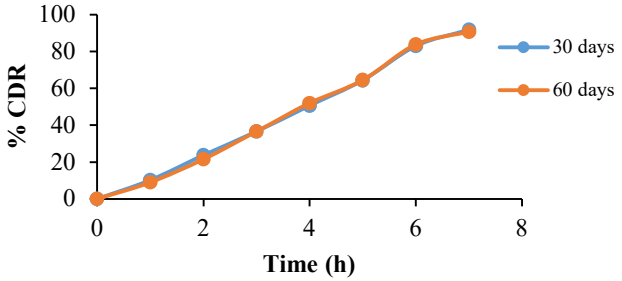

Figure 6 *In vitro* drug released profile of curcumin nano moisturizer (F3) after stability studies at 40±2°C, 75±5%.RH.

4. Conclusion

Curcumin emulsion in moisturizers has been successfully developed and characterized, and it can reduce the production of free radicals. Finally, it was determined that formulation B1 curcumin nano moisturizer could be a promising skin moisturizer for antiaging.

5. Acknowledgements

The authors are grateful to Rajiv Gandhi University of Health Sciences, Karnataka, Bengaluru, for funding under the faculty research grant to obtain all materials and chemicals for the research. We are grateful to the principal and management of Acharya & BM Reddy College of Pharmacy, Bengaluru for providing lab facilities for this research.

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