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Optimization of Span 80-Croduret 50-Propylene Glycol as Emulsifier of Dried Strawberry Juice (*Fragaria vesca* L.) Emulgel and Permeation Test Through Shed Snakeskin Membrane

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ABSTRACT

Strawberry is a natural source of antioxidants with potential to inhibit melanin production in the skin. However, its application in topical formulations is limited by factors such as stability, skin permeability, and effective delivery, necessitating the development of an appropriate delivery system. This has led to the selection of double emulsion due to the water solubility of the active ingredient. To produce a stable emulsion, it is required to combine emulsifier with different hydrophilic-lipophilic balance values. This study aimed to obtain the optimal proportion of emulsifier combinations for formulating an emulgel containing dried strawberry. Antioxidant activity was evaluated using the DPPH assay, while the content of active compounds was quantified using the UV-Vis spectrophotometric method. The optimization of emulsifier proportions was carried out using the simplex lattice design (SLD), with globule size, viscosity, and separation ratio as response parameters. The optimized emulsion system was then incorporated into a hydrogel. Physicochemical stability of the emulgel was assessed based on organoleptic properties, pH, viscosity, spreadability, and phase separation. Permeation studies were conducted using Franz diffusion cells with shed snakeskin membrane as the diffusion barrier. The study successfully demonstrated that dried strawberry juice possesses antioxidant activity, with an IC_{50} value of 0.331 mg/mL. The levels of key active compounds, namely quercetin (23.3% w/w) and anthocyanins (13.23% w/w), supporting its potential use in topical antioxidant applications. The most effective emulsifier system was determined to be a Span 80:Croduret 50:Propylene Glycol ratio of 1:2:1. This emulsifier composition yielded an emulsion with favorable droplet size, viscosity, and stability characteristics. Incorporation into a 1.5% Polygel CA hydrogel resulted in an emulgel formulation with excellent physicochemical stability, as indicated by consistent pH, spreadability, viscosity, and absence of phase separation during storage. Permeation studies using Franz diffusion cells showed that the optimized emulgel was capable of delivering 117.14 μg/cm^2 of flavonoids across shed snakeskin membrane within 5 hours, with a permeability coefficient of 2.84×10^{-5} μg/cm^2 and a flux rate of 6.6×10^{-5} μg/sec, indicating good skin permeation potential.
Keywords: Design Expert; Dried Strawberry Juice; Emulsifier; Permeation Test; Flavonoid Total

INTRODUCTION

Strawberry is a source of natural antioxidants due to the presence of ascorbic acid, polyphenols (Miller et al., 2019), and quercetin-3-β-D-glucoside (Zhu et al., 2015). The total anthocyanin content in strawberry ranges from 200 to 600 mg/Kg, pelargonidin-3-O-glucoside as glycone contains approximately 77-90%, and 6-11% pelargonidin-3-rut as aglycone, while cyanidin-3-glucoside comprise 3-10% as a glycone (Miller et al., 2019). Strawberry can impede skin pigmentation by hindering the formation of melanin through the inhibition of the activity of the tyrosinase enzyme, resulting in a brighter complexion (Zhu et al., 2015). However, the anthocyanin and quercetin content during the production process decreased by 53% for pelargonidin3-O-glucoside (Bursać Kovačević et al., 2009) and 40% for flavonoid quercetin content (Häkkinen et al., 2000). However, its application in topical formulations is limited by factors such as stability, skin permeability, and effective delivery, necessitating the development of an appropriate delivery system. To address the low stability and limited penetration of the active metabolite of strawberry fruit juice, an emulsion system has been developed.

Dried strawberry was formulated into an emulsion to protect and deliver its hydrophilic antioxidants more efficiently into the skin. Although these antioxidants reside in the aqueous phase, the oil phase enhances permeation and emulsion stability. Dried strawberry juice contains bioactive compounds such as flavonoids,

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anthocyanins, and quercetin, which possess antioxidant and anti-melanogenic properties. However, when applied directly or incorporated into a simple aqueous system, these compounds may face stability issues (e.g., oxidation, degradation from light or pH changes), and may have limited permeability through the skin barrier (stratum corneum) (Olayemi et al., 2023).

In this system, topical emulsions optimize the release of active substances from the emulsion, thereby enhancing their effectiveness in topical preparation A double emulsion water/oil/water (w/o/w) also offers several advantages by increasing stability and penetration into skin (Parveen et al., 2011; Olayemi et al., 2023). The emulsion selected as the carrier system was a/m (water/oil), which was dispersed in a gel matrix. To ensure the stability of a/m emulsion preparations, suitable emulsifier such as span 80, cremofor, and propylene glycol are employed. Moreover, these emulsifiers also function as humectants, emollients, and co-solvents (Rowe et al., 2013).

The low viscosity of water/oil emulsions contributes to their dispersion in aqueous media (hydrogel matrix) to increase viscosity, stability, absorb active components into skin and enhance the appearance of the preparation. Hydrogel matrices such as HPMC, carbopol, alginic acid, xanthan gum, and cellulose are polymers commonly used in topical preparations (Alam et al., 2012). This is because the hydrogel matrix inhibits the oxidation reaction of active components caused by environmental influences and provides greater stability by protecting against the degradation of these components, along with the oil phase (Korać et al., 2014).

Most strawberry-derived antioxidants are hydrophilic and thus primarily reside in the aqueous phase of the emulsion. However, the oil phase plays a supportive role in facilitating skin penetration by: Softening the stratum corneum, enhancing diffusion of active compounds through the lipid matrix of the skin, and increasing the occlusive effect, which helps in retaining skin hydration and promoting penetration. While it is true that many antioxidants from strawberries are water-soluble, the skin is a lipophilic barrier, making it difficult for water-based actives to penetrate effectively. The emulgel, combining the benefits of both emulsion and gel systems, ensures sustained release, user-friendly application, and enhanced delivery of antioxidants into deeper layers of the skin (Mishra et al., 2023).

The Hydrophile-Lyphophile Balance (HLB) value of emulsifier ranges from 1 to 20, where values between 1-10 are lipophilic, and 10-20 are hydrophilic. For example, Span 80, croduret 50, and propylene glycol have HLB values of 4.3, 15.4, and 3.4, respectively. The proportion of emulsifier combination can be determined by the Simplex Lattice Design (SLD) method. SLD is optimization method that provides the optimal composition of the ingredients in the mixture by using minimum comparisons (Bolton & Bon, 2003). Therefore, this study aimed to obtain the optimal composition of the 80-croduret 50-propylene glycol as emulsifier to ensure the stability of the water/oil emulsion of dried strawberry. The double emulsion system was also employed to stabilize and release the active ingredients of dried strawberry.

This research contributes valuable insights into the development of natural antioxidant-based topical formulations by demonstrating the feasibility of using dried strawberry juice as an active ingredient in emulgel systems. This study advances formulation science by integrating systematic emulsifier optimization through simplex lattice design (SLD) and introduces a novel approach for enhancing the topical bioavailability of plant-derived antioxidants. The results may serve as a foundation for the future development of safe, stable, and effective phytocosmeceutical products, particularly for skin protection and pigmentation control.

MATERIALS AND METHODS

Materials

Fresh strawberry was harvested in Banyuroto Village, Sawangan, Magelang, Central Java, Indonesia. The materials used in the experiment included Span 80 (Bratachem, Indonesia), Isopropyl myristate p.a quality (Merck KGaA, Germany), pharmaceutical propylene glycol (Bratachem), croduret 50 ss (CRODA Inc, English), all solvent is pro analysis grade, DPPH reagent (Sigma USA Inc), quercetin standard (Sigma USA Inc), buffer components (Merck KGaA, Germany); shed snakeskin (snake keeper, Yogyakarta), cellophane membrane (Spectrapor membrane tubing MW cutoff 6000-8000).

Equipment: Stirrer 100-2000 rpm (Stuart Overhead Stirrer), spectrophotometer UV-VIS (Genesys 10 UV Scanning), Franz-type diffusion apparatus (Pearmea Gear, ITB, Bandung, Indonesia), Viscometer Brookfield cones and plates (DV-I Prime), Digital microscope (Olympus CX-41), Centrifuge 600-6000 rpm (5804R), Climatic chamber, Moisture Balance (Ohaus MB23, Germany), Freez-Drying (alpha LD plus).

Table I. The double emulsion formula of dried strawberry juice using emulsifier combination

System	Ingredients	Percentage (%)	Function
Active ingredients	Dried strawberry juice	1.0	Active substance
	PEG 400-HCl 1% mix solvent	12.0	Solvent for dried strawberry juice
Water in oil emulsion system	Benzoic acid	0.1	Preservatives
	Span 80	8.0	Mix emulsifier
	Croduret 50 ss		
	Propylene glycol		
	Isopropyl myristate	18.9	Oil phase
Hydrogel matrix	Polygel Ca	1.5	Hydrogel agent
	Triethanolamine	1.5	Alkaline agent
	Tween 80	2.0	Emulsifier
	Buffer pH 5.4	55.0	Solvent

Methods

Plant Material Preparation

The fresh fruit farms were identified at the Plant Taxonomy Laboratory, Faculty of Biology, Universitas Gadjah Mada, Yogyakarta, Indonesia, for analysis purposes. The fruits were gently washed and blended before freeze-drying. Dried samples were analyzed for moisture content using a Moisture Balance (Ohaus MB23, Germany), placed into plastic tubes, and stored at -10°C.

Antioxidant Activity

Strawberry-dried juice weighing 500 mg was reconstituted in 25 mL of ethanol 96% p.a to a final concentration of 20.0 mg/mL. This stock solution was serially diluted from 0.1 to 1.0 g/mL. DPPH in ethanol 96% (0.4 mM) was combined with 2.0 mL of test samples to a final volume of 5.0 mL. Ethanol 96% was used as the negative control, and quercetin was used as the positive control. The reaction mixtures in triplicate, were incubated for 30 min at 25°C, and absorbance was measured at 517 nm. Scavenging of DPPH radical was evaluated by comparing the results of the negative control group (dissolved sample without DPPH). The IC50 values were calculated to determine the concentration of sample required to scavenge 50% DPPH free radicals. Subsequently, DPPH bleaching activity was expressed as IC50 in mg/mL for extracts or fractions. The lower the IC50 value, the higher the antioxidant activity (Smith, Reeves, Dage, & Schnettler, 1987).

Flavonoid and Anthocyanins Content

Flavonoid and anthocyanins were measured using a Spectrophotometer UV-VIS method. For anthocyanins, the samples were dissolved using 0.1% HCL and 96% ethanol at a ratio of 8:2. The solution was filtrated using Whatmann paper no. 1 and centrifuged for 10 min at 3000 rpm. Subsequently, 1 mm of supernatant was transferred into a measuring flask of 50.0 mL and mixed with 0.025 M KCl buffer at pH 1 and 0.4 M CH3COONa buffer at pH 4.5. The absorbance of the solution was measured at the maximum wavelength of 530 nm for anthocyanins and 700 nm as a reference (Tonutare et al., 2014). For Flavonoid, a total of 500 mg dried strawberry juice was weighed and dissolved with 96% p.a ethanol in a 5.0 mL measuring flask, shaken for 30 seconds, and filtered. A total of 1.0 mL filtrate was taken into a 50.0 mL measuring flask and 96% ethanol was added. The absorbance of the solution was measured at the maximum wavelength of quercetin, and 96% p.a ethanol solution as a blank. External standards with a purity of 99.5% from Sigma Aldrich were used for calibration.

Optimization of Emulsifier

Dried strawberry juice weighing 1.0 grams was dissolved in a mixture of 12.0 mL of a PEG 400 and 0.1% HCl (8:2) and filtered. The filtrate was dispersed in a water/oil emulsion formula, as shown in Table I. The polygel Ca, solvent, and TEA was homogenized using a stirrer at 650 rpm, followed by the addition of w/o emulsion to the mixture. Subsequently, stirring was carried out for 10 minutes until w/o/w emulgel formed.

Design Expert 7.1.5 software. A counterplot diagram will be obtained based on the mathematical equation for each response (Table II). Counter plot diagrams of each response parameter are then made diagram superimposed counterplots to determine the optimum area.

Stability Test of Optimum Formula

The optimum formula of dried strawberry emulgel was stored at -4°C for 24 hours and transferred to 45°C for 24 hours. This cycle was repeated six times and observed for organoleptic,

Table II. The proportion of emulsifier combination based on SLD and the parameter response for optimum formula

Run	Mix emulsifier			Respons for optimum proportion		
	Span 80	Croduret 50 ss	Propylene glycol	Diameter of globule (mm)	Viscosity (log P.as)	Separation ratio
1	2.00	2.00	4.00	1.59	-0.53	0.56
2	2.00	4.00	2.00	2.86	-0.63	0.92
3	3.00	2.00	3.00	4.24	-1.42	0.60
4	3.33	2.33	3.33	5.22	-0.54	0.74
5	3.00	3.00	2.00	9.69	-0.45	0.67
6	2.00	4.00	2.00	4.09	-0.54	1.00
7	4.00	2.00	2.00	3.03	-1.28	0.94
8	2.00	3.00	3.00	5.20	-1.34	0.84
9	2.33	2.33	3.33	4.77	-0.80	0.75
10	4.00	2.00	2.00	5.61	-1.34	1.00
11	2.33	3.33	2.33	3.94	-0.29	0.90
12	3.00	3.00	2.00	8.34	-0.97	0.59
13	2.00	2.00	4.00	4.09	-0.45	0.60
14	2.67	2.67	2.67	6.51	-0.37	0.50

pH, viscosity, spreadability, thickness, and active substance content in dried strawberry emulgel (Ermawati and Jannah, 2023).

Transport through Shed Snakeskin Membrane

The experiments were conducted in one independent vertical Franz cell with a nominal volume of the acceptor compartment of 25 mL and a diffusion area of 2.5 cm^2. For the donor compartment, 1.0 g of formulation was initially set, and the experiments were carried out in triplicate at 37 ∘ C and 100 rpm for 5 h. The samples were evaluated at different time points and data analysis was performed by comparing the releasing efficiency (PE) values. The assays were performed using buffer solutions at pH 7.4, involving two types of membrane, namely cellophane membrane with molecular weight cut-off at 12 kDa and shed snakeskin. Subsequently, releasing efficiency was defined in terms of the mass flux (J), which described the change of drug permeation. In this study, the mass flux ($mol.cm^{-2}\cdot h^{-1}$) was determined using the AUC of permeation profile recorded at a specific time interval and was related to the rectangular area (R) described by 100% of permeation process at the same time interval (5 hours). Mass flux calculated using the equation below:

$$\text{Flux (J)} = \frac{\int_0^t dt}{y\ 100^t} \text{ x } 100\% \quad \text{......} (1)$$

where y_{100} is the AUC value, assumed with permeation of 100% in a time interval *t*, and *y* value of the permeated drug during the same time interval.

Data Analysis

The values of permeation efficiency were compared by one-way ANOVA. The Student's *T*-test was employed to determine the differences between the data test and the recommendation of SLD. A confidence level of 95% was adopted and the data were presented as mean ± standard deviation.

RESULTS

The identification results showed that strawberry plants used in this study were harvested from Banyuroto, Magelang, Indonesia from Familia: *Rosaceae*, Genus: *Fragaria*, and Species: *Fragaria vesca* L. The identification was carried out to ensure the correctness of the species used. Based on the analysis, the moisture content contained in dried strawberry fruit was found to be 13.46%.

In this study, the IC50 value of dried strawberry juice using the DPPH method was 0.331 mg/mL. A previous investigation of the antioxidant activity of strawberry juice extract reported a value of 0.238 mg/mL (Zhu et al., 2015). The equation of the standard curve of quercetin was determined of y = 0.0675x-0.004 and the average concentration of total flavonoid total was 23.3%w/w. The results of the maximum wavelength in 0.2% HCl and 96% ethanol mixed solvents were 271 nm and 496 nm, respectively. Pelargonin-3,5-diglucoside in HCl 0.1%-ethanol mixed solvent had a wavelength of 269 nm and 505 nm, while cyanidin-3 glucoside had 275 nm and 523 nm (O'Neil et al., 2013). The dominant

pigment in strawberry was pelargonin-3-diglucoside with a percentage of 77-90%. Based on the results, the maximum wavelength of dried strawberry fruit had anthocyanin content close to pelargonin-3,5-diglucoside. Furthermore, the Tonutare et al. (2014) equation obtained an average anthocyanin content of 13.23% for dried strawberry fruit as pelargonin-3,5 diglucoside.

The mathematical equation for the viscosity response showed an interaction between span 80, croduret 50, and propylene glycol. This interaction increased the viscosity of dried strawberry fruit emulsion, with propylene glycol exhibiting the most influential effect among other emulsifiers. The interaction between span 80 and propylene glycol reduced the viscosity of the emulsion (Ermawati et al., 2022). The phase separation response showed that the interaction between croduret 50 and propylene glycol improved the stability of the emulsion. However, the interaction of the three emulsifier components did not affect emulsion stability. The interaction between span 80 and croduret 50 reduced the globule diameter of the w/o emulsion, while the interaction of the three emulsifier components had no significant effect.

Based on the composition obtained from the analysis results with Design Expert 7.1.5 software, one optimum formula was selected. This formula had emulsifier composition ratio of span 80, croduret 50, and propylene glycol at 1: 2: 1, with a desirability value of 0.822. The desirability value expressed the closeness between the optimization processes and the target to be achieved, ranging from zero to one. A desirability value close to one indicated that the response variable selected for formula optimization can reach the optimum point by the desired target. Meanwhile, a value close to zero indicated that optimization is difficult based on the selected response variable.

Stability Test of Emulgel Optimum Formula

Dried strawberry juice emulgel color faded to pale during temperature treatment. This occurred due to an increase in pH caused by temperature, thereby affecting the red color of the active substance, which was relatively stable at low pH (Gössinge et al., 2009). Temperature treatment also affected the viscosity and spreadability of dried strawberry fruit emulgel. At high temperatures, the consistency of span 80 and croduret 50 changed from thick to liquid, resulting in decreased viscosity and increased spreadability of emulgel (Table III).

The standard curve equation for calculating total flavonoid content in emulgel is y = 0.0763x + 0.0017 with a correlation coefficient (r), exceeding 0.99. The average flavonoid total content of dried strawberry emulgel optimum formula was 15.3%w/w, indicating an approximate 40% decrease after formulation in emulgel system. This was consistent with previous study, where the total flavonoid (quercetin) content decreased by 40% after formulation (Häkkinen et al., 2000). The decrease in the levels of active substances was due to the influence of temperature, the pH of emulsifier, and the oxidation of span 80 group with oxygen.

Transport Through Membrane

The standard curve equation for total flavonoid calculated as quercetin in phosphate buffer at pH 7.2 was given as y = 0.0548 x - 0.0071. This equation was used to determine the total flavonoid content released from the optimized formula of dried strawberry juice emulgel base. The cumulative total flavonoid content of the optimum formula, which was transported for 5 hours test, was 117.14 μg/cm^2 of a total of 2.24 mg of dried strawberry juice in formulas. The permeability value of shed snakeskin membrane was 2.84x10^{-5} cm/second and a flux value of 6.6x10^{-5} μg/cm^2. Furthermore, it was discovered that Isopropyl Myristate can change the structure of fat in the stratum corneum. These changes resulted in reduced path length drug penetration and increased skin permeability, facilitating the diffusion of active substances into skin (Tsai et al., 2010). Apart from being emulsifier, propylene glycol also functioned as an emollient to form gaps on the sides of the stratum corneum, making it easier for active substances to penetrate skin (Carrer et al., 2020). Based on these results, the combination of emulsifier that was used met the requirements and enabled the release of the active ingredient for 300 minutes. However, it was not stable enough to maintain the concentration of the active ingredient during storage (Figure 2).

DISCUSSIONS

The fading of the red color of strawberry was caused by several factors, such as the glycosidase enzyme, which affected anthocyanins, the water content, and carbon dioxide (Giampieri et al., 2014). The ascorbic acid content in strawberry also affected anthocyanin dyes due to the influence of oxygen and nitrogen from the environment, with loss of catechins, as well as increasing browning and polymeric color (Giampieri et al., 2014). Furthermore, anthocyanin levels in emulgel preparations decreased by more than 50%. Several other parameters affect the anthocyanin yield, such as temperature, incubation time, sample-to-buffer ratio, and solvent type.

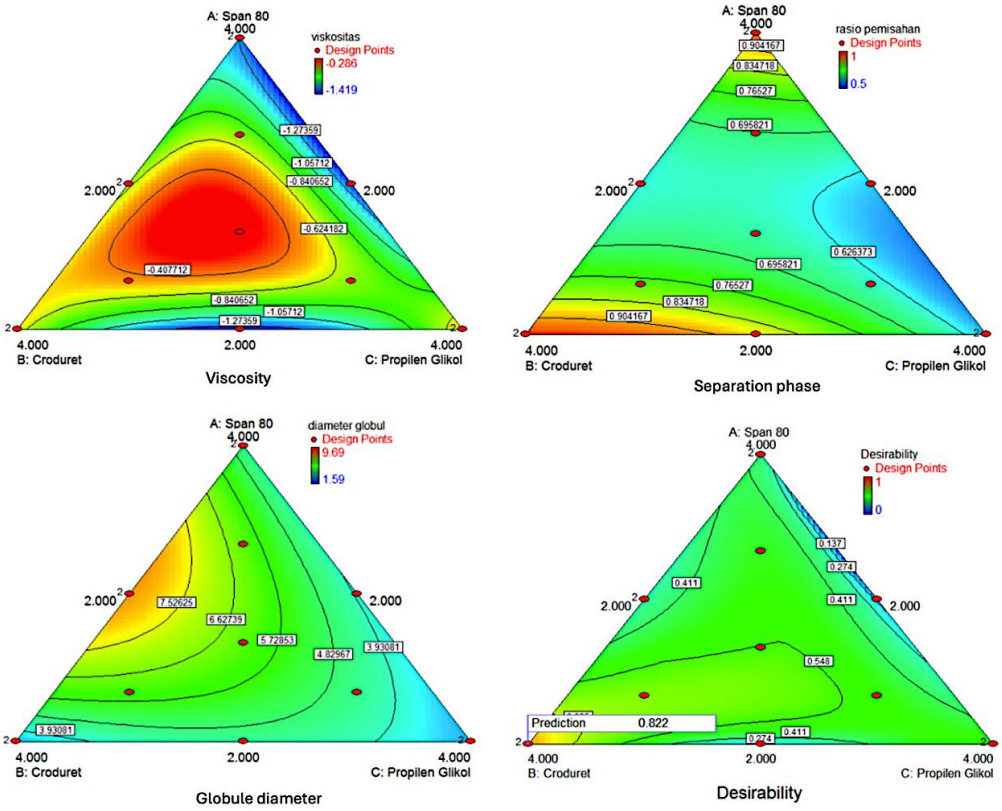


Figure 1. Contour and Superimposition Plot of Emulsifier Mixtures Based on Response Parameters Using SLD

Table III. The stability test result of the Dried Strawberry Emulgel Optimum Formula

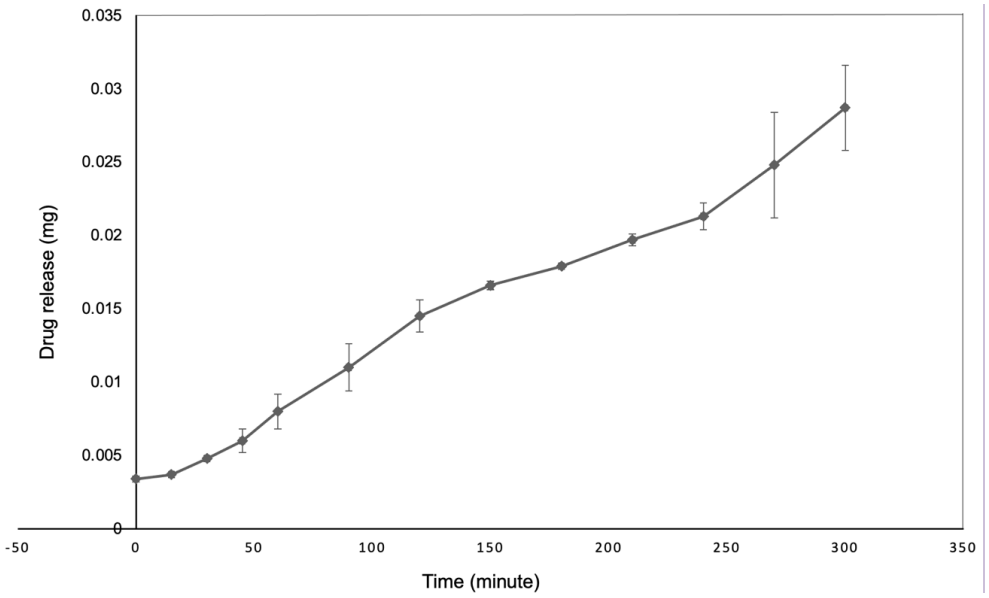
Parameter	Before	After
Viscosity	142±0.26	110±0.20
pH	6.52±0.05	6.82±0.06
Spreadability	3.60±0.30	4.30±0.20
Adhesion strength	1.87±0.12	2.05±0.07

*The averages and standard errors of 3 independent experiments with triplicate samples

Acidified solutions help anthocyanins to penetrate through the cell membrane and be released into the extraction buffer. Low concentrations of HCl or other strong acids, are recommended and 0.1% HCl were used in this experiment. The pH of the solution may also affect the extraction yield and the stability of anthocyanins in the solution. A pH of 1 to 3 prevents the formation of the colorless anthocyanins.

Phase separation occurred when the emulsion was stored at low temperatures due to crystallization in the continuous phase, which caused damage to the film interface. However, storage at high temperatures reduced the interfacial tension and viscosity. Storage at room temperature was considered optimal for emulsion stability, as it balanced the hydrophilic and lipophilic properties. Temperature changes can alter the distribution coefficient of emulsifier between the two phases and cause migration of emulsifier (Liberman et al., 2007).

This research contributes valuable insights into the development of natural antioxidant-based topical formulations by demonstrating the feasibility of using dried strawberry juice as an active ingredient in emulgel systems. The optimized emulsifier combination and hydrogel matrix not only ensured physicochemical stability but also facilitated effective transdermal delivery of flavonoids. This study advances formulation science by integrating systematic emulsifier optimization through simplex lattice design (SLD) and introduces a novel approach for enhancing the topical bioavailability of plant-derived



The averages and standard errors of 3 independent experiments with triplicate samples

Figure 3. Profile of the cumulative amount of flavonoid transported across shed snakeskin membrane of dried strawberry juice emulgel optimum formula per unit time

antioxidants. The results may serve as a foundation for the future development of safe, stable, and effective phytocosmeceutical products, particularly for skin protection and pigmentation control.

CONCLUSION

The study successfully demonstrated that dried strawberry juice has antioxidant activity, with an IC_{50} value of 0.331 mg/mL. Quantitative analysis revealed of key active compounds, namely quercetin (23.3% w/w) and anthocyanins (13.23% w/w), supporting its potential use in topical antioxidant applications. Through optimization using SLD, the most effective emulsifier system was determined to be a Span 80 : Croduret 50 : Propylene Glycol ratio of 1:2:1. This emulsifier composition yielded an emulsion with favorable droplet size, viscosity, and stability characteristics. Incorporation of the optimized emulsion into a 1.5% Polygel CA hydrogel base resulted in an emulgel formulation with excellent physicochemical stability, as indicated by consistent pH, spreadability, viscosity, and absence of phase separation during storage. Furthermore, permeation studies using Franz diffusion cells showed that the optimized emulgel was capable of delivering 117.14 µg/cm^2 of flavonoids across shed snakeskin membrane within 5 hours, with a permeability coefficient of 2.84×10^{-5} µg/cm^2 and a flux rate of 6.6×10^{-5} µg/sec, indicating good skin permeation potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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